MICROWAVE-ASSISTED SYNTHESIS OF MONOMERIC AND POLYMERIC AMIDES:

KINETICS AND MECHANISTIC CONSIDERATIONS

Inaugural-Dissertation

zur

Erlangung des Doktorgrades der

Mathematisch-Naturwissenschaftlichen Fakultät

der Heinrich-Heine-Universität Düsseldorf

vorgelegt von

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Dezember 2006

Aus dem Institut für Präparative Polymerchemie
der Heinrich-Heine Universität Düsseldorf

Gedruckt mit der Genehmigung der
Mathematisch-Naturwissenschaftlichen Fakultät der
Heinrich-Heine-Universität Düsseldorf

Referent: Prof. Dr. H. Ritter

Koreferent: Prof. Dr. C. Staudt

Tag der mündlichen Prüfung: 24.01.2007

Psalm 23

A psalm of David.

1 The LORD is my shepherd, I shall not be in want.

2 He makes me lie down in green pastures, He leads me beside quiet waters,

3 He restores my soul. He guides me in paths of righteousness for his name's sake.

Alla mia famiglia

Contents

Abstract

The use of microwave irradiation has become, over the years, a well-established technique to promote and enhance chemical reactions. A proof of it is the increasing number of publications concerning the application of microwaves (MW) in all fields of the chemical sciences.

Microwaves are electromagnetic waves that can be placed between infrared radiation and radio frequencies with wavelengths ranging from 1 m to 1 mm. The corresponding frequencies range between 300 MHz and 300 GHz. Being this range extensively used for telecommunications purposes, in order to avoid interferences, almost all commercially available microwave reactors for chemical use, as well as household and industrial microwave ovens, operate at the frequency of 2.45 GHz (12.2 cm). The main advantages of MW assisted chemistry are shorter reaction times and higher selectivity compared with syntheses performed under conventional heating. Most of these enhancements can be described as thermal effects mainly due to homogeneous heating or superheating easily realized, for example, using highly polar reaction media. The possible existence of so called “specific” microwave effects that could rationalize specific synthetic pathways observed in microwave and not under conventional heating is still subject of debate and controversy.

The chiral (R)-*N*-(1-phenylethyl)-methacrylamide was synthesized directly from methacrylic acid and (R)-*N*-1-phenylethylamine through microwave irradiation in a solvent-free medium. Kinetic comparison between reactions carried out either under MW or conventional thermal heating evidenced the higher selectivity of the MW accelerated reaction. Under the applied conditions, the desired amidation was clearly preferred to the Michael addition side-reactions. The addition of a radical initiator to the starting mixture led, in a single step, to the formation of optically active polymers containing both methacrylamide and imide moieties.

The synthesis of the corresponding chiral acrylamide, prepared in MW by direct conversion of acrylic acid with (R)-*N*-1-phenylethylamine, without solvent or any activating reagent, was not possible to perform by conventional heating in oil-bath. In the latter case only polymeric and decomposition products were obtained. The performed kinetic measurements showed high selectivity and conversion to the amide after only a few minutes of reaction time. The irradiation of the educts mixture, in presence of AIBN, led also in this case to polymeric structures containing imide units. The applied MW power resulted to have a clear influence on yield and molecular weight distribution of the obtained optically active polymers.

Acid functionalized polyethylene, containing about 10 mol % of acrylic acid units, was reacted in microwave and, as a comparison, in oil-bath with dissimilar amines to give copolymers

bearing amide groups. The MW-assisted reactions showed increased conversion for most of the investigated amines. In the case of a few amines, a better conversion was obtained for the runs in oil-bath. Considering that the reactivity of the amines depends mainly on their nucleophilicity and basicity, it was attempted to correlate an experimental reactivity index (based on FT-IR analyses) with the order of basicity and nucleophilicity of the amines. For the MW runs an excellent linear correlation (R=0.97, SD=0.68) was obtained comparing basicity and reactivity. On the other hand the oil-bath reactions correlated very well (R=0.97, SD=1.13) with a nucleophilicity scale obtained by theoretical calculations. The correlation of reactivity-basicity observed in microwave has to be related to the strong microwave-absorbing capacity of ionic species (ammonium salts). Under conventional thermal heating, the amidation reaction is mainly ruled by the nucleophilicity. A reactivity behavior based on dissimilar parameters cannot be rationalized only invoking purely thermal effects. Specific microwave effects have to be considered.

The synthesis of N-benzensulfonamide maleimide was performed in bulk through the microwave-assisted reaction of maleic anhydride with *4*-amino-benzenesulfonamide. The product was obtained in a good yield in very short reaction time (2 min). The same reaction was also performed in oil-bath showing the superiority of the microwave-assisted approach. The monomer was polymerized under MW irradiation in N,N-dimethylformamide (DMF) solution using benzopinacol as a free radical initiator. Qualitative investigations of the pH dependent solubility of the polymer were also performed.

The imide-containing diol, 2-hydroxy-*N*-(2-hydroxypropanoyl)-*N*-(1-phenylethyl)propanamide, was synthesized by microwave activation of a stoichiometric mixture of lactic acid and (R)-*N*-1-phenylethylamine. 20 minutes of irradiation were sufficient to reach a conversion of 90 % whereas the oil-bath reaction needed 60 minutes to provide 70 % of the desired product.

Preliminary investigations of the free radical polymerization of methylmethacrylate (MMA), methacrylic acid (MA), dimethylaminoethylmethacrylate (DMAEM) and zinc methacrylate (ZMA) in tetrahydrofuran (THF) solution using AIBN as an initiator were performed in MW and in oil-bath. For MMA and ZMA no benefits could be obtained from the MW approach. In the case of the copolymer MA/DMAEM appeared the experimental evidence of a negative MW effect dependent on the applied power. A possible rationalization is proposed in terms of power influence on the acid-base equilibrium. Anyway, more detailed investigations are required to better elucidate this unexpected occurrence.

Preface and aim

Amides are well known chemical compounds that find a wide range of applications in our daily life. Proteins, the structural base of all organisms, are actually biopolymers containing amide bonds (peptide bonds). The secondary structure of them, so important in term of metabolism regulation, is mainly due to the possibility of amides to form strong hydrogen bonds. Polyamides like Nylon® or Kevlar® are largely used thermoplastics with excellent mechanical properties and chemical resistance. Finally, the amide group is a versatile building block for organic synthesis.

Amides are mostly prepared from amines and acid chlorides or carboxylic acids, in the latter case using coupling agents like *N*,*N′*-dicyclohexylcarbodiimide or other chemical activation methods. All these approaches require the use of solvents (usually chlorinated) and basic reactants (sodium hydroxide, triethylamine) as an acid scavenger and/or to increase the electrophilicity of the carboxylic containing reagent. Biocatalytic synthetic strategies using enzymes like amidase, lipase or hydrolase are also performed, though on a smaller scale, aiming to more environment-friendly processes. Anyway, real “green” pathways should avoid the use of solvents and acid chlorides providing products in high yield and high purity. Same considerations can be made for the synthesis of monomeric imides, precursors of materials with improved thermal and mechanical stability.

The peculiarities of microwaves are being more and more exploited to provide chemists with easier approaches to the synthesis of different kind of organic compounds and polymeric materials. Even simple and well-established organic transformations are still object of studies to completely understand the real nature of microwave effects.

The aim of this work is to study microwave-induced synthetic pathways for addition-elimination reactions (amidation, imidization), applied to both, monomer and polymer synthesis and polymer modifications. Amide and imide formation is investigated, under microwave conditions and as comparison under classical thermal heating, with the idea to evaluate, with kinetic measurements and mechanistic considerations, the occurrence of effects that could not be described as purely thermal. Missing yet fully accepted theories to rationalize these effects, the detailed analysis of relatively simple systems is a valuable effort in this direction.

1 Microwave Chemistry

1.1 Introduction

Microwaves are electromagnetic radiations with frequencies ranging from 300 MHz to 300 GHz (wavelength 1 – 0.001 m) (Figure 1.1). 2.45 GHz (12.2 cm wavelength) is the frequency allotted by an international commission for domestic or industrial ovens.[1] Microwaves represent a non-ionizing radiation that influences molecular motions such as ion migration or dipole rotations, but not altering the molecular structure.

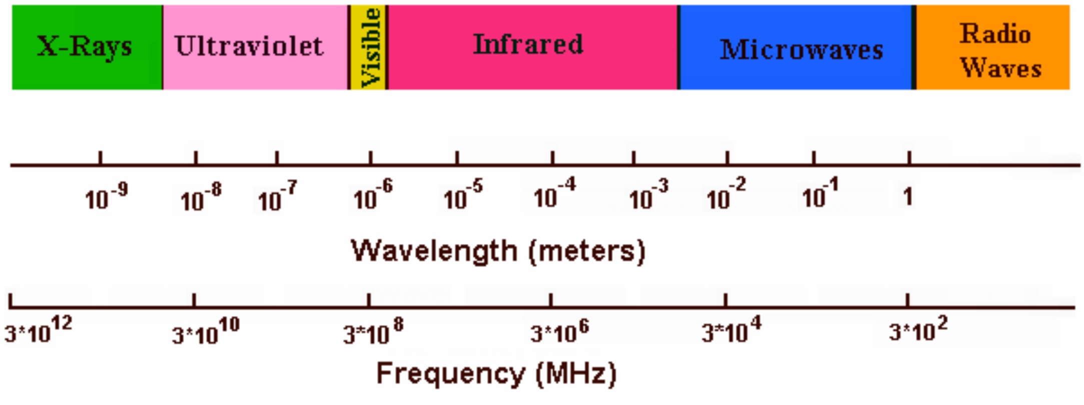
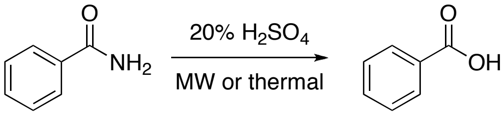


Figure 1.1 Schematic representation of the electromagnetic spectrum.

In 2.45 GHz microwaves the oscillation of the electric field of the radiation occurs about $4.9 \cdot 10^9$ times per second; the timescales in which the field changes is about the same as the response time (relaxation time) of permanent dipoles present in most organic and inorganic molecules are.[2] This fact represents a fundamental characteristic for an efficient interaction between the electromagnetic field of microwaves and a chemical system. The absorption of microwaves causes a very rapid increase of the temperature of reagents, solvents and products. Moreover, in the case of solutions containing salts or strong acids and bases the energy can also be dissipated through ionic conduction, causing heating or overheating of the solvent (together with a possible increase of the pressure when the reaction is carried out in closed vessels).

During the Second World War, the magnetron was designed by Randall and Booth and used for RADAR (Radio Detection And Ranging). It was soon recognized that microwaves could heat water in a very effective manner, and microwave-heating appliances became available in the United States from the 1950's. These devices were widespread by the 1980's, and it was around this time that the application of microwave heating upon chemical reactions began to develop. The first work concerning microwave accelerated organic reactions was published in 1986 by the group of Richard Gedye (Scheme 1.1).[3]



thermal: 1h, 90% yield (reflux)
MW: 10min, 99% yield (sealed vessel)

Scheme 1.1 Hydrolysis of benzamide. First published example of microwave-assisted organic chemistry.

1.2 Microwave Heating

Although microwaves are best known for their use in the domestic oven, they are also used in a wide array of heating applications, from industrial-scale processing,[4] through medical use,[5] to synthesis in the research laboratory.[6] This is due to various differences in the way a material is heated by microwaves, and the high efficiency that can result from heating only the target rather than maintaining an oven at elevated temperatures.

Conventional heating is normally carried out in an oven, which is an inefficient process. The oven walls, and everything contained within the oven is heated along with the sample. The heat slowly penetrates the material mainly through conduction, resulting in a temperature gradient from the outside in. Microwaves cause heating by acting directly on the sample and cause an inverted temperature profile (Figure 1.2).[7]

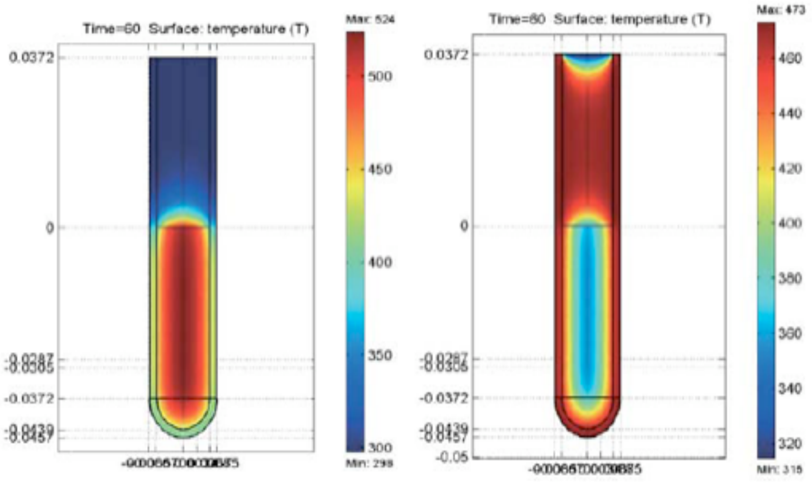


Figure 1.2 Comparison between the temperature gradient obtained by thermal heating (right) and microwave irradiation (left).

When microwaves penetrate a material it absorbs some of the their energy. The absorbed amount will vary depending on the properties of both the microwaves and the material itself. Because the microwave is losing energy as it travels through the material, it will at some point have lost all its energy and become extinct. After this point, any heating cannot be due to the direct interaction of microwaves with the material, but instead is due to conduction from the regions that have interacted with the microwave radiation. Another point to note is that the shape of the sample can affect the power distribution through refraction and diffraction of the microwave radiation. As microwaves are macroscopic, with a wavelength of 12.2 cm at 2.45 GHz, there is also the problem of positioning the sample inside a cavity. As the cavity is usually of similar dimension to the wavelength of the microwaves, standing waves will occur, resulting in an inhomogeneous field. Thus, samples at different positions in the cavity will experience different microwave field strengths and will heat at different rates. In domestic microwave ovens, this effect is commonly countered either with a turntable, or a mode-stirrer. A mode stirrer is a rotating metal paddle that reflects the microwaves in different directions. Although these methods produce a more equal exposure to the microwaves over time, they are not ideal for scientific purposes. Instead a cavity with a single standing wave should be used, with the sample positioned in the maximum field strength position.

1.2.1 Dielectric heating

A dielectric material is one which contains either permanent or induced dipoles which when placed between two electrodes acts as a capacitor, *i.e.* the material allows charge to be stored and no dc conductivity is observed between the plates.

The permittivity of a material, ε, is a property that describes the charge storing ability of that substance irrespective of the sample's dimensions. The permittivity is frequency dependent and for a polar liquid generally shows a marked decrease as the frequency of the electromagnetic radiation increases from 10^6 (radio frequencies) to 10^{12} Hz (infrared frequencies).

When a dielectric material is placed in a static electric field, it will align itself with the field to minimize free energy and a finite time, known as the response time, is required for this to occur. If the field is oscillating there are three possibilities.

At low frequency the dipoles are able to remain aligned with the field as the response time is much smaller than the period of the perturbation.

At high frequency the response time is much greater than the period, the dipoles are unable to react to the changing field, and remain static.

However, at intermediate frequencies where the response time is of the same magnitude as the period of the electric field, the dipoles experience a force that causes a rotation (Figure 1.3).

Figure 1.3 Schematic representation of molecular rotation induced by microwaves.

The precise frequency, at which this phenomenon occurs, reflects the frequency of the rotations of the molecules, which in turn depends on the size and on the intermolecular forces. For polar molecules with molecular weights less than a few hundred the frequency range falls in the microwave region (300 MHz–300 GHz). The rotation of the dipoles and displacement of charge is equivalent to an electric current (I), known as the Maxwell displacement current.

For an ideal dielectric there is no lag between the orientation of the molecules and the variations of the alternating voltage, the displacement current is 90° out-of-phase with the oscillating electric field. In this case no heating occurs because there is no component of the current in-phase with the electric field and the product E × I is zero (Figure 1.4 a).

When the rotation lags behind the electric field oscillations there is a phase displacement δ and the current acquires a component $I \times \sin\delta$ in phase with the electric field (Figure 1.4 b). In this way, resistive heating occurs in the medium that causes energy to be absorbed from the electric field.[8]

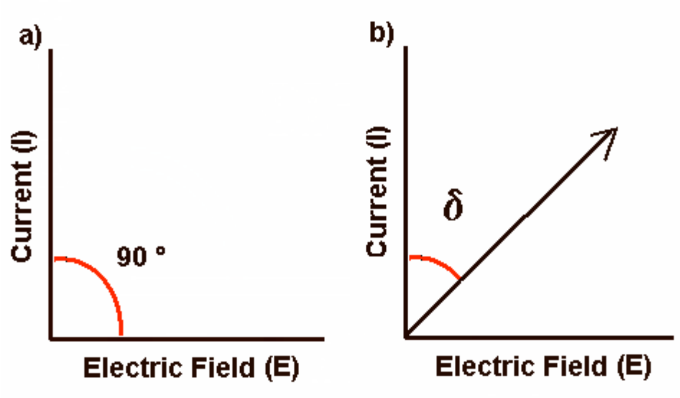


Figure 1.4 Phase diagrams for (*a*) an ideal dielectric; (*b*) a dielectric that experiences a phase displacement (δ).

The complex dielectric constant (ε*) completely describes the dielectric properties of a homogeneous material. It can be expressed as the sum of two parts (Eq. 1.1), where ε' is the real part (the dielectric constant) and ε" is the loss factor which reflects the conductance of the material.

$$\varepsilon^* = \varepsilon' + \varepsilon'' \qquad (1.1)$$

The dielectric constant (ε') describes the ability of the molecule to be polarized by the electric field. At low frequencies this value will reach a maximum, as the maximum amount of energy can be stored in the material. The dielectric loss (ε") measures the efficiency with which the energy of the electromagnetic radiation can be converted into heat. The frequency dependence of ε' and ε" and their magnitudes control the extent to which a substance is able to couple with microwave radiation The ratio of the dielectric loss and the dielectric constant defines the (dielectric) loss tangent (tan δ) which is related to the ability of a material to convert electromagnetic energy into heat energy at a given frequency and temperature (Eq. 1.2).

$$\tan\delta = \frac{\varepsilon''}{\varepsilon'} \tag{1.2}$$

A reaction medium with a high tan δ value is required for efficient absorption and, consequently, for rapid heating. In general, in function of tan δ, substances can be classified as high (tan δ > 0.5), medium (tan δ 0.1–0.5), and low microwave absorbers (tan δ < 0.1).[9]

Another important parameter is the penetration depth (Dp) defined as the depth at which the microwave power has fallen to 1/*e* of its incident value; it is dependant on the wavelength and the properties of the material. If a material has a small penetration depth, then all of the power will be lost near the surface of the material, and a similar temperature profile to that of a conventionally heated object will result. If the material has a large penetration depth, heating will occur deeper within the material and leads to an inverted temperature profile. An approximate relationship for penetration depth when ε” is small, is given by (Eq. 1.3):

$$Dp \propto \lambda_0 \cdot \sqrt{\frac{\varepsilon'}{\varepsilon''}} \tag{1.3}$$

where λ_0 is the wavelength of the microwave radiation.[1]

1.2.2 Conduction heating

Another form of heating is caused by the conduction of charged particles such as electrons or ions. Because the time scale of movement for electrons and ions is much shorter than that of microwave radiation, they will couple in phase with the electric field (Figure 1.5).

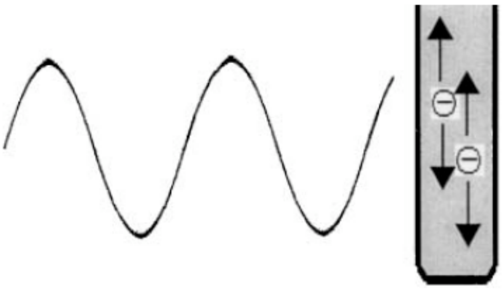


Figure 1.5 Schematic representation of ions coupling with microwaves.

Conduction heating is the most common mechanism for heating of all solids, and can be sensitive to temperature. Alumina, for example, has a conductivity that rises with temperature, as the number of electrons thermally excited into the conduction band increases. This can lead to the phenomenon known as thermal runaway. As the temperature rises in the solid, more electrons are excited into the conduction band and more of the microwave energy is absorbed, resulting in a greater heating effect. This positive feedback can lead to a very rapid temperature rise.[10]

1.3 The Temperature Issue

The measurement of temperature under microwave heating is a difficult proposition. As microwaves heat materials differentially depending on their dielectric constant, the introduction of a temperature-measuring device that has a dielectric loss is unsatisfactory. A number of solutions to this problem have been proposed.

1.3.1 "Atypical" thermometers

A conventional thermometer works through conduction of heat. When a thermometer is brought into contact with a material that is of a different temperature, it will assume the temperature of that material as long as the volume of the material is much greater than that of the thermometer bulb. The expansive liquid is commonly either mercury or alcohol, both of which couple with microwaves. If these are placed in a sample within a microwave field, they will not only give a measure of the temperature, but also that of the heating effect upon the expansive liquid within the thermometer. It is possible to use a thermometer where the expansive liquid used has a very low dielectric loss tangent such as xylene.[11] Measuring the pressure of a gas in a constant volume has also been demonstrated as a viable method.[12] Anyway, the necessary volume of sample for these probes prevents them from being used in a small system. Their size will also cause them to demonstrate a time lag in reporting an accurate temperature and will report a temperature average over their contact with the samples. Calibration of this kind of thermometers is also a non-trivial exercise.

1.3.2 Fluoroptic thermometers

All temperature probes rely on a property of a material that varies with temperature. Fluorescent decay has been shown to do this and temperature probes that use this phenomenon are commercially available. A fiber probe is used to illuminate a temperature sensitive phosphor that is attached to the end of the probe. This material fluoresces and the light is transmitted back along the probe to a detector. The time for this to occur is measured and compared with a calibration profile to obtain the temperature.[11] Whilst this method is commonly seen as the ‘gold standard’ of temperature measurement in a microwave, it is not without drawbacks. The probes are not very durable and have a restricted maximum working temperature. It has also been shown that where an intense illumination source is present, temperature measurements may not be accurate.[13]

1.3.3 Infrared pyrometers

A hot body loses energy by emitting radiation. The energy of the radiation that is emitted is a function of the temperature. For a perfect emitter, known as a black body, the relationship is given by the Stefan-Boltzmann law (Eq. 1.4):

$$J^* = \sigma \cdot T^4 \qquad (1.4)$$

Where J^* is the energy flux density, σ is the Stefan-Boltzmann constant and T is the thermodynamic temperature. For real (non-black-body) emitters, this is only an approximation, but instruments that measure the infrared emission of a sample can give a temperature reading. Optical measurements such as these have the advantage that the instrument does not have to be in contact with the sample. However, as it is only possible to observe radiation from the outside of samples, only the temperature of the surface can be measured. This temperature may not accurately represent the bulk temperature due to surface cooling, different dielectric properties between the reaction mixture and the vessel, or the inverse temperature profile that microwave heating can establish.

An attempt has been performed in trying to compare the accuracy of different thermometers showing the differences that it is possible to observe (Table 1.2).

Table 1.2. Comparison of attempts to use a *p*-xylene thermometer, a fluoroptic sensor and an IR pyrometer for measuring the temperature of superheated boiling solvents during microwave irradiation.[14]

Solvent	bp (°C)	*p*-xylene thermometer (°C)	fluoroptic sensor (°C)	IR pyrometer (°C)
H_2O	100	104	104	105
MeOH	65	78	84	84
2-PrOH	82	87	100	108
THF	66	79	81	103
CH_3CN	81	97	107	120

1.3.4 Thermocouples

In 1821 the physicist Thomas Seebeck discovered that a potential difference existed between two ends of a metal bar, where a thermal gradient existed in the bar. A thermocouple exploits this effect and consists of two dissimilar metal wires, joined together by welding. A potential difference exists between these two wires, which varies with temperature. Because of the thermocouples small size, fast response, flexibility, ruggedness and low cost they are probably the most favored method of temperature measurement for both conventional and microwave heating. Anyway, it is not possible to insert wires into a microwave cavity without interference to the microwave field and inducing currents in the wires. A partial solution to the problem is to use a shielded thermocouple, where the two wires are enclosed within a cover made of a material that does not absorb microwaves. These can be obtained with diameters as small as 0.2 mm. If they are inserted into a cavity whereby the thermocouple is aligned with the direction of microwave travel, the interference will be reduced as the amount of material aligned with the electrical and magnetic field directions is minimized.[15] If a shielded thermocouple is introduced into the cavity in another orientation with the exterior attached to the cavity wall, and therefore grounded, the thermocouple will not be subject to induced currents. However, this will affect the shape of the cavity and may lead to localized heating, or even arcing. For certain temperature ranges however, thermocouples are the only option.

1.4 Microwave Reactors

Microwave reactors are available on the market in a variety of designs. However, the underlying principles of operation are very similar. Microwaves are generated inside a cavity by the alternating current from domestic power lines at frequency of 60 Hz and stepped up to 2450 million Hz. This is accomplished by a device called magnetron that operates at 4000 to 6000 volts inside the reactor. A magnetron is a thermionic diode having an anode and a directly heated cathode. As the cathode is heated, electrons are released and are attracted towards the anode. The anode is made up of an even number of small cavities, each of which acts as a tuned circuit. The gap across the end of each cavity behaves as a capacitance. The anode is therefore a series of circuits that are tuned to oscillate at a specific frequency or its overtones. A very strong magnetic field is induced axially through the anode assembly and has the effect of bending the path of the electrons as they travel from the cathode to the anode. As the deflected electrons pass through the cavity gaps they induce a small charge into the tuned circuit, resulting in the oscillation of the cavity. This process of oscillation continues until the oscillation has achieved sufficiently high amplitude. It is then taken off the anode via an antenna. Of the total of the electrical line power used by the magnetron, generally 1200 - 1500 W, around a half is converted into electromagnetic energy. The residue is converted into heat that must be dissipated through air or water cooling.

The microwaves are transmitted from the magnetron to the microwave cavity or applicator through a waveguide. A waveguide is a channel of different shapes made of metal sheet. The minimum frequency that can be propagated is related to the dimensions of the rectangular cross section through the expression $c/f=2d$ where c is the speed of light, f the cut-off frequency and d the larger of the dimensions of the rectangular section of the waveguide.

The common household microwave reactors do not provide any reliable control over the emitted power neither are equipped with temperature or pressure sensors for the reproducibility of the experimental conditions. Despite the variety of cavities available, there are in reality only two basic types: single-mode (often referred to as monomode), and multimode.

Specialized microwave reactors for chemical synthesis both monomode and multimode are commercially available from such companies as CEM,[16] Milestone,[17] Biotage,[18] Anton Paar,[19] and Plazmatronika.[20] They are equipped with built-in magnetic stirrers and direct temperature control by means of an IR pyrometer, shielded thermocouple or fiber-optical temperature sensor, and continuous power feedback control, which enable to heat reaction mixture to a desired temperature without thermal runaways. In some cases, it is possible to work under reduced pressure or in pressurized conditions within cavity or reaction vessels.

1.4.1 Single-mode reactors

The essential characteristic of single-mode cavities is the deliberate creation of a standing wave pattern inside the cavity (Figure 1.6). To obtain this, the dimensions of the cavity must be carefully controlled to correspond in some systematic way to the characteristic wavelength of the microwaves. Just as the resonant frequency of a standing wave on a violin string is a function of the length of the string, so too is the maintenance of that standing wave determined by the stability of the string dimensions.

For 2.45 GHz microwaves, the length of a single full wave is 12.2 cm. A single-mode cavity for 2.45 GHz microwaves must be dimensioned such that a whole-number multiple of the full or half wavelength fits inside the confines of the cavity. There are specific positions inside the single-mode cavity where items to be heated must be placed. The intensity of the field is greatest at the peaks of the standing wave, and actually goes to zero at the nodes of the standing wave. There are positions in the single-mode cavity (the nodes) where no heating will occur. Only in the volume of the peak envelopes can transfer of microwave energy to a target absorbing material occurs. This substantially limits the physical dimensions of objects (such as reaction vessels) that can be placed in a single-mode cavity and be heated effectively. Anything placed inside a single-mode cavity can disrupt the standing wave pattern. For this reason, it is quite uncommon for single-mode cavities to be designed to accept more than one target object (such as a vessel) to be heated at a time.

The main advantages in using single-mode cavities are the high field homogeneity that is possible to achieve and the elevated energy density. Anyway, a final consequence is the fact that there is no practical way to scale up processes because the dimension of a standing wave cavity cannot be extended indefinitely. Single-mode cavities do not lend themselves to simultaneous processing of multiple targets (such as reaction vessels) The only possibility is to use an automatic sampler that provides a new reaction vessel when the reaction is completed or a system that pumps in the cavity the educts mixture and pumps out the products in a kind of semi-continuous (batch flow) fashion. However, even in this way, thinking on industrial or pilot scale, the achievable productivity remains low.

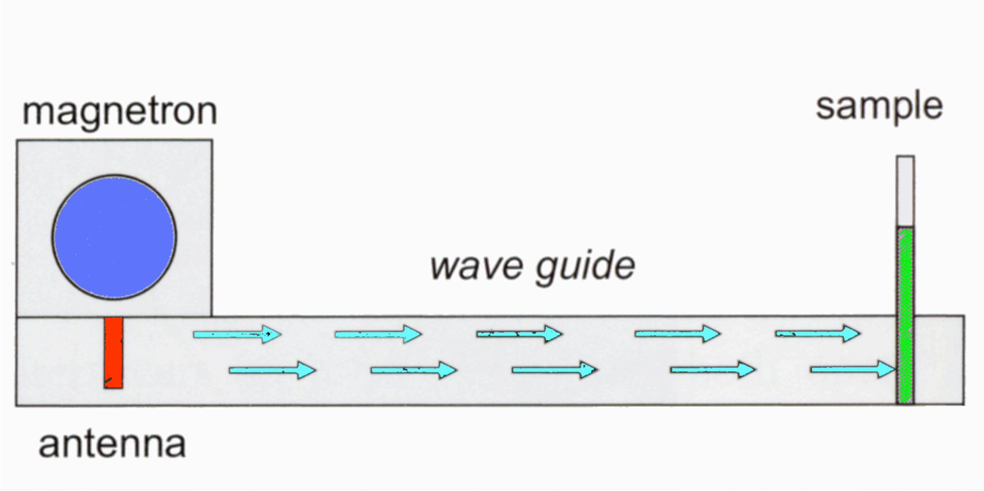


Figure 1.6 Schematic representation of single-mode microwave reactor.

1.4.2 Multimode reactors

The essential characteristic of multimode cavities is the deliberate avoidance and/or disruption of any standing wave pattern inside the cavity. The engineering goal is to produce as much chaos inside the cavity as possible (Figure 1.7).

There are two principal approaches to achieving this goal. First, the dimensions of the cavity must be carefully controlled to avoid whole-number multiples of the microwave full or half wavelength. Second, some means must be employed to physically disrupt any standing waves that may form as a consequence of items placed in the cavity. This is best performed with a mechanical mode stirrer, typically a periodically moving metal vane that continuously changes the instantaneous field pattern inside the cavity. The shape of the vane and its movement is such that the microwave field is continually stirred, and therefore the field intensity is homogeneous in all directions and all locations throughout the entire cavity.

In a multimode reactor, microwave-absorbing materials placed anywhere inside the cavity will, in fact, absorb microwaves anyway experiencing a lower electric field strength than can be obtained in a monomode reactor.

In a properly designed multimode cavity, there is no specific position inside the cavity where items to be processed must be placed. The field homogeneity is obtained by continuously stirring of the waves everywhere and in all directions so that every position in the cavity is like every other position. In this way nothing placed inside the cavity will permanently affect the distribution of the field intensity. This means that there are no limitations on the size and shape of the objects placed inside the cavity. This also means that multiple objects (for example, multiple reaction vessels) can be processed simultaneously. A major concern in using multimode reactors for organic synthesis is the possibility of “hot and cold spots”. It means a field pattern with high and low field strength that could create localized superheating. Mode stirrers cause the microwaves to move around in the cavity, reducing most of the differences in hot spots and cold spots. When performing reactions in parallel, or with larger sample sizes, the presence of these multiple areas of energy is not as significant; the samples move around and are large enough to effectively absorb the existing microwave energy. Anyway, at the moment, the multimode approach seems to be the most indicate for practical scale-up of processes.

A multimode cavity can, in theory, be infinitely extended in every dimension. Additional field intensity to fill that extended cavity can easily be had by simply adding additional magnetrons to the system. In this way it is also possible to increase the achievable energy density to levels comparable to those obtainable in single-mode applicators.

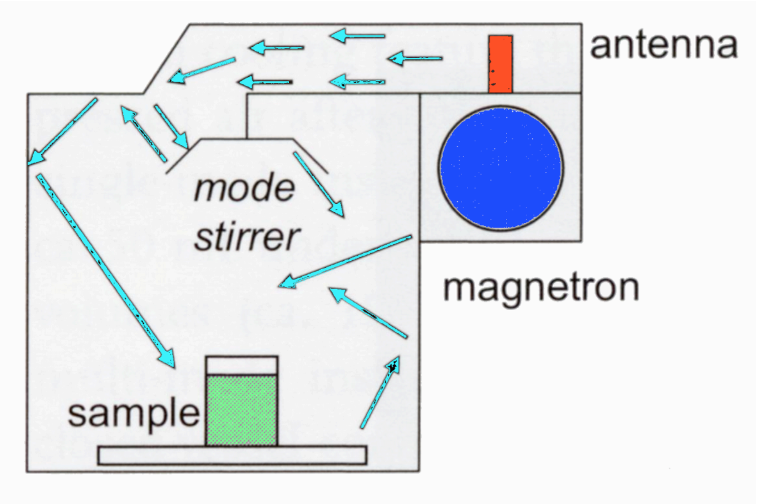


Figure 1.7 Schematic representation of multimode microwave reactor

1.5 Microwave Effects

Microwave-assisted syntheses are characterized by the strong accelerations produced in many reactions as a consequence of the peculiarity of the dielectric heating, which cannot be reproduced by classical thermal heating. Higher yields can be afforded, milder reaction conditions and shorter reaction times can be used and many processes can be improved. Even reactions that do not occur by conventional heating can be successfully performed using microwaves.

Several attempts[1,21] in the rationalization of the causes of such effects have led to definition of two main outcomes of the microwave interactions with the matter: thermal and non-thermal (also referred as “specific”) microwave effects.

1.5.1 Thermal microwave effects

Thermal effects are strictly correlated to the possibility to achieve, under microwave irradiation, very high temperature in very short time. Especially in the case of working in pressurized vessels, it is possible to superheat solvents or neat reagents well above their boiling points obtaining an increased reaction rate. This is easily understandable by simply considering the Arrhenius law that correlates the rate constant (*k*) of a reaction with activation energy (Ea) and temperature (T) (Eq. 1.5).

$$k = A\exp(-Ea/RT) \tag{1.5}$$

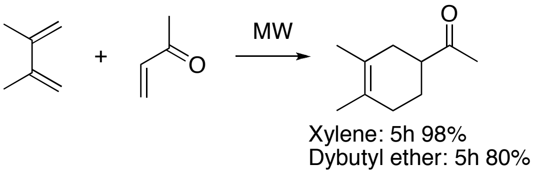
As pointed out by Mingos and Baghurst,[1] a typical first-order transformation that requires 68 days to reach 90% conversion at 27 °C, will show the same degree of conversion within 1.61 seconds when performed at 227 °C.

The presence of “hot spots” as a consequence of the inhomogeneity of the applied field, resulting in the temperature in certain zones within the sample being much higher than the macroscopic temperature, could account for this kind of effects. Also in the case of solid-supported reactions or reactions between solids or in presence of microwave susceptors it is possible to observe such overheating that is thought to be the cause of purely thermal effects.

Most of the results presented in the early days of microwave-assisted chemistry are uncertain due to a lack of reproducibility or comparison with thermal reaction in conditions not always well controlled. Replicating those reactions in more recent times, has led to an almost general confidence that most of the accelerations observed could be simple attributed to the impossibility to reproduce, by conventional heating, the exact temperature reached by dielectric heating. The debate on the existence of specific interactions on a molecular level between matter and microwaves that could account for unexpected selectivity or at least not reproducible (in oil-bath) products distribution is still open.

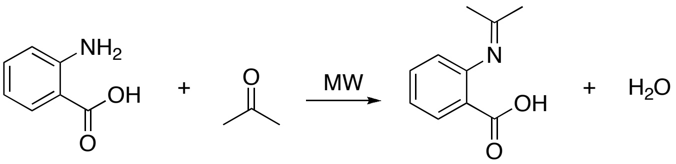
1.5.2 Specific microwave effects

Specific-microwave effects should be classified as accelerations that cannot be rationalized by purely thermal/kinetic effects. Nonthermal effects essentially result from a direct interaction of the electric field with specific molecules in the reaction medium. It has been argued that the presence of an electric field leads to orientation effects of dipolar molecules and hence changes the pre-exponential factor A or the activation energy (entropy term) in the Arrhenius equation.[22,23] Loupy has published a tentative rationalization of non-thermal effects [24] considering the reaction medium (polar and apolar solvents and solvent-free reactions) and the reaction mechanism, i.e., the polarity of the transition state (isopolar and polar transition states) and the transition state position along the reaction coordinate. According to this, specific microwave effects should increase in apolar solvents and solvent-free reactions, and when it is possible to observe an increasing in polarity passing from the ground state to the transition state. Also the high selectivity observed for competitive reactions has been attributed to the polarity of the transition state. It has been stated [24] that the synthetic pathway leading to the most polar transition state is the favorite one in microwave due to stabilization obtained by direct interaction on molecular level. In connection to the influence of the reaction medium, Berlan et al. showed that the acceleration of the nonsymmetric Diels-Alder reaction between 3-buten-2-one and 2,3-dimethylbutandiene was more apparent in xylene than in the more polar dibutylether (Scheme 1.2).[25]



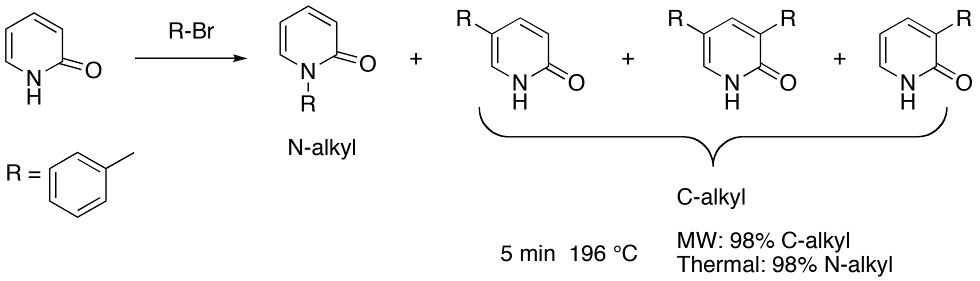
Scheme 1.2 Nonsymmetric Diels-Alder reaction.

Bimolecular reactions between neutral reactants that lead to charged transition states, for example amine or phosphine alkylation or addition to a carbonyl group have been reported to show strong not purely-thermal microwave effect. An example is the reaction of anthranilic acid with amides or ketones (Scheme 1.3). The mixture of reactants adsorbed on an inert support, led to the addition compound in 70% yield after 30 min.[26] The thermal reactions required 24 h to afford only poor yield.



Scheme 1.3 Enamine formation under solid-state microwave irradiation.

Very few results on selectivity effects are available due to a lack of strict comparisons between microwave and thermal activation.[23] Among them is interesting the case of the regiospecific benzylation of 2-pyridone under solvent-free conditions and in absence of base (Scheme 1.4).[27]



Scheme 1.4 Selective benzylation of 2-pyridone

This result could be justified assuming that the transition state leading to C-alkylation is more polar than that responsible for the N-alkylation.

Non-thermal effects may also arise from interactions between the microwave field and the material, similar to thermal effects. In this regard, thermal effect strongly interferes with possible non-thermal effects and these cannot be easily separated in mechanistic studies.

Finally, various authors have proposed that specific effect could instead derive from changes in thermodynamic parameters under microwave irradiation.[23,28]

1.6 Microwave Processing Techniques

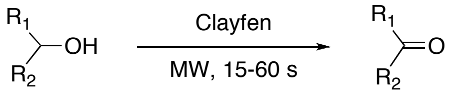
Most of the early published microwave chemistry has been performed using domestic microwave ovens. The main reason for using a device intended for heating food items to perform syntheses is that they are readily available and inexpensive. The use of domestic ovens might be the main reasons why microwave-assisted organic synthesis has not attained fast popularity during the first ten years. The lack of control in domestic ovens when performing synthesis has led to a vast number of incidents, including explosions, being reported. Aided by the availability of diverse types of dedicated microwaves reactors, nowadays a variety of different processing techniques can be utilized.

1.6.1 Solvent-free reactions

To avoid the problems connected with the use of household microwave ovens, the most used approach in the early days has been to omit the solvent from the reaction and perform the reactions on solid supports. These can be either almost transparent to microwave such as various clays, aluminum oxides and silica or strong absorber like graphite, that can additionally be doped with catalysts or reagent.

The solvent-free technique has been claimed to be particularly environmentally friendly, since it avoids the use of solvents and offers a simpler method of workup. By altering the characteristics of the solid support, it is possible to strongly influence the outcome of the reaction.

Many reports have showed the easiness and feasibility of this synthetic approach. For example, Varna and Dahija have developed a method in which montmorillonite K 10 clay-supported iron(III) nitrate (so called clayfen) is used as support for the oxidation of alcohols to carbonyl compounds (Scheme 1.5).[29] It is noteworthy that, quantitative conversions where obtained within 15-60 s of irradiation and in the case of primary alcohols (R_1 = H) no carboxylic acids could be detected.



Scheme 1.5 Oxidation of alcohols with iron(III) nitrate supported on Montmorillonite K 10 clay

The main concern with solid-state reactions is that it may be very difficult to obtain a good temperature control at the surface of the solids. This would inevitably lead to problems regarding reaction predictability, reproducibility and controllability. There are, however, still benefits from using solvent-free approaches, which include improved safety by avoiding low boiling solvents that would otherwise cause undesirable pressure increases during heating in closed systems.

1.6.2 Phase-transfer catalysis

Microwave unique property to heat substances in function of their dielectric properties, has been largely exploited in promoting reactions where the reactants are situated in two separate phases, for example liquid-liquid or solid-liquid.[30] In liquid-liquid phase-transfer catalysis (PTC), because the phase are mutually insoluble, ionic reagents are typically dissolved in the aqueous phase, while the substrate remains in the organic phase. Strauss performed a Hoffmann elimination using a two-phase water/chloroform system (Figure 1.8).[31] The reaction proceeds nicely under microwave irradiation, the temperatures of the aqueous and organic phases being 110 and 50 °C, respectively, due to differences in the dielectric properties of the solvents. This difference avoids the decomposition of the final product. Comparable conditions would be difficult to obtain by traditional heating methods.

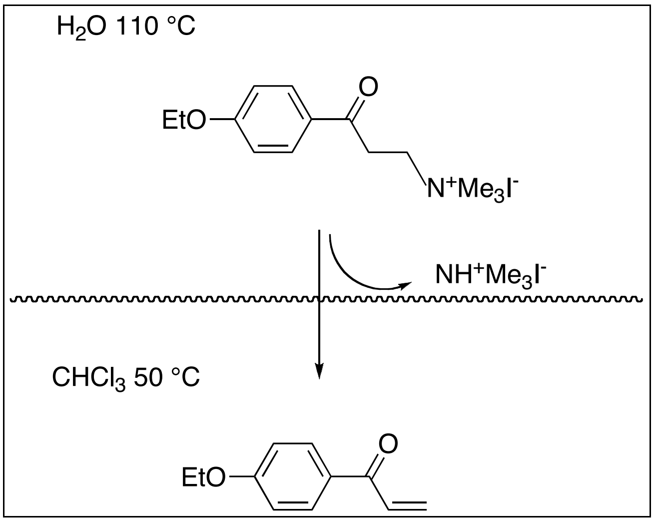


Figure 1.8 Hoffman elimination performed in a two-phase system water/chloroform.

In solid-liquid PTC, ionic reagents may be used in their solid state as a suspension in the organic medium. Phase-transfer catalysts, typically quaternary ammonium salts or cation-complexing agents facilitate transport of the anions from the aqueous or solid phase to the organic phase.

A related example is the alkylation of potassium acetate with alkyl halides in the presence of Aliquat 336 as a catalyst (Scheme 1.6).[32]

$$CH_3COOK + nC_8H_{17}Br \xrightarrow[\text{MW, 160 °C, 5 min}]{\text{neat, Aliquat 336}} \underset{98\%}{CH_3COOnC_8H_{17}}$$

Scheme 1.6 *O*-Alkylation of potassium acetate under MW-PTC conditions.

1.6.3 Reactions using solvents

Microwave-assisted syntheses can be carried out using standard organic solvents under either open- or sealed-vessel. Polar solvents, such as DMF, N-methylpyrrolidone (NMP), ethanol, are good microwave absorbers and will heat efficiently. On the other hand, less polar or non-polar solvents such as toluene, dioxane and tetrahydrofuran (THF) are more or less transparent to the microwave irradiation and will not heat in the pure form. However, most chemical reactions contain enough polar or ionic substances to efficiently absorb microwave energy and generate heat. When the dielectric properties of the sample are too poor to allow efficient heating by microwave irradiation, the addition of small amounts of polar or ionic additives, with large loss tangent values, can significantly overcome this problem and enable adequate heating of the entire mixture. Fluid salts or ionic liquids, consisting entirely of ions, absorb microwave radiation in a highly efficient manner and are particularly attractive additives because they are relatively inert and stable at temperatures up to 200 °C, have a negligible vapor pressure and dissolve to an appreciable extent in a wide range of organic solvents. Energy transfer between the polar molecules that couple with the microwave radiation and the non-polar solvent bulk is rapid and often provides an efficient means of using non-polar solvents as thermal sink to dissipate the excess of energy not directly absorbed which, raising up the temperature, could lead to decompositions or uncontrollable side-reactions. The possibility to perform microwave reactions under reflux (open-vessel), due to the availability of dedicate monomode an multimode reactors, has given a rapid relaunch to the use of solvents that have been previously avoided for the risk of explosions. In fact, under reflux, the systems are at atmospheric pressure and flammable vapors cannot be released into the microwave cavity. The temperature, however, cannot be increased by more than 10-20 °C above the normal boiling point of the solvent and only for a limited time. Although this particular superheating effect will, of course, speed up the reactions to some extent, it will not result in the same effects that can be achieved at much higher temperatures. Among others, the main advantage is that the bulk temperature is fixed by the boiling point of the solvent so that it is accurately measurable. The reactions that most benefit of open-vessel conditions are all kind of reactions where a volatile compound is developed as a product or co-product and so can be easily removed from the reaction ambient.

Reactions performed under pressure in sealed-vessel also benefit from the rapid heating rates of microwave dielectric heating. This technique offers a simple method of performing rapid syntheses and is the most versatile of other approaches. Different kind of dedicated reaction vessels are available on the market allowing to reach pressure up to 200 bar and to pre-pressurize the system with inert or reactive gases.

1.7 References

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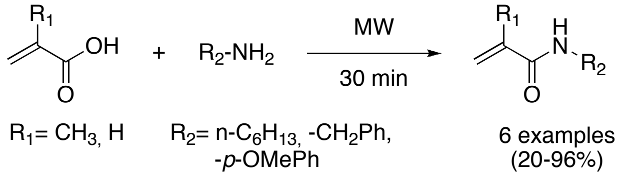
2 Synthesis and Polymerization of Chiral (Meth)acrylamides

2.1 Introduction and Literature Survey

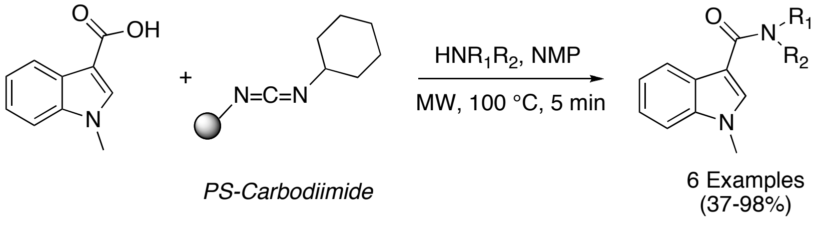
A series of monomers were reported to be successfully synthesized and polymerized by means of microwave (MW) activation.[1-4] Among them, the simple amide bond formation was described to take place starting from aliphatic acids and primary and secondary amines[5] or from esters and amines in the presence of potassium *tert*-butoxide.[6]

In this connection, Ritter et al. published preliminary results about the formation of (meth)acrylamides directly from (meth)acrylic acid and different amines (Scheme 2.1).[7]

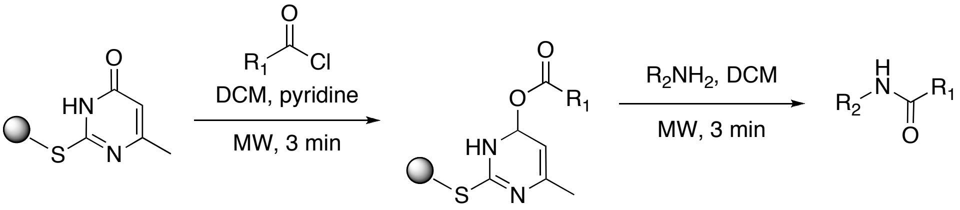


Scheme 2.1 Direct synthesis of (meth)acrylamides without activation of educts.

Polymer supported reagent like polystyrene-bound carbodiimide (Scheme 2.2),[8] or polystyrene-bound acylation agent (Scheme 2.3),[9] were also conveniently used to synthesize amides and amide libraries.



Scheme 2.2 Synthesis of amide library utilizing polymer-bound carbodiimide.

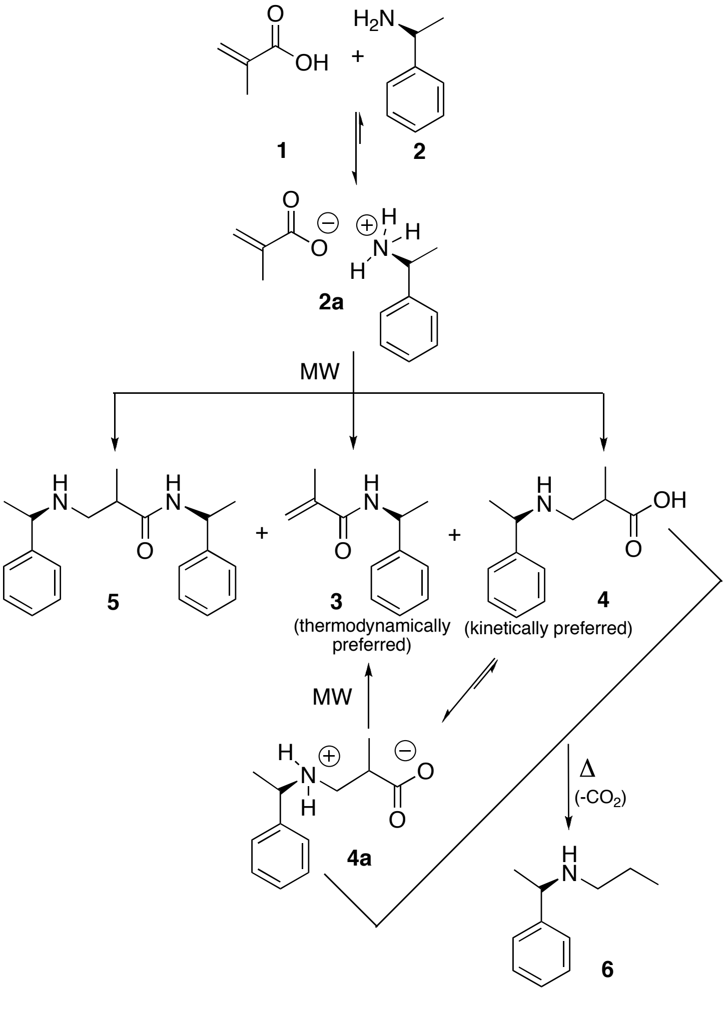


Scheme 2.3 Amide synthesis utilizing a reusable polymer-supported acylation reagent.

The synthesis of chiral synthetic polymers is a topic of special interest due to their applications as chromatographic supports,[10] catalysts[11] and materials with ferroelectric and nonlinear optical properties.[12] The optical activity of the polymer can be tuned by choosing an appropriate chiral initiator or by starting from a chiral monomer. Asymmetric synthesis and polymerization of prochiral monomers are also ways available for synthesizing such optically active polymers.[13]
The polyacrylamide family of polymers and copolymers is a highly versatile group used in a multitude of applications including clarification of drinking water[14-16] flocculants for wastewater treatment,[17,18] oil recovery,[19] soil conditioning,[20] agriculture,[21,22] and biomedical applications.[23-25] However, the neurotoxicity of the acrylamide monomers has led to some concerns and even reluctance to accept polyacrylamides as safe materials particularly in situations where the polymer is in direct contact with bodily fluids (e.g., renal dialysis, blood filtration, etc.) or where the polymer is used in making therapeutic products. There are lingering concerns regarding the possibility that residual acrylamide is present in the polymeric materials and whether polyacrylamides can degrade back to the monomer.

2.2 Bulk Synthesis and One-Pot Polymerization of (*R*)-*N*-(1-phenylethyl)methacrylamide

(*R*)-*N*-(1-phenylethyl)methacrylamide (**3**) was synthesized by MW irradiation of an equimolar mixture of methacrylic acid (**1**) and of the optically active (*R*)-*N*-(1-phenylethyl)amine (**2**) (Scheme 2.4).



Scheme 2.4 MW accelerated bulk synthesis of the chiral methacrylamide **3** without any educts activation.

In shorter reaction times compared with the conventional synthetic routes and in the absence of solvent, the amide was obtained in very good yield (> 90%) and without racemization (Table 2.1).

Table 2.1 MW accelerated synthesis of the methacrylamide **3**.

Compound	MW Power (W)	Time (min)	Yield (%)	$[a]^{25}_D$ (°)
2	-	-	-	+30
3	140	15	93	+61

The results obtained under MW irradiation were compared with those of the reactions carried out under normal thermal heating, trying to reproduce, as far as it was possible, equivalent conditions of temperature and heating rate. The temperature was monitored using an infrared (IR) pyrometer that measures the temperature on the outside of the reaction vessel. This latter does not really reflects the temperature inside the reaction mixture due to different interactions between MW, the glass vessel and the reaction mixture and to the short reaction time that does not allow the system to reach a thermal equilibrium. The use of a more accurate fiber-optic thermometer was avoided because, attempting to evaluate the accuracy of this device, it was not possible to find a clear correspondence between the measured temperature and the boiling points of several solvents, at least in the needed temperature range. To overcome this situation, a calibration curve of the infrared pyrometer with an external digital thermometer was plotted (Figure 2.1).

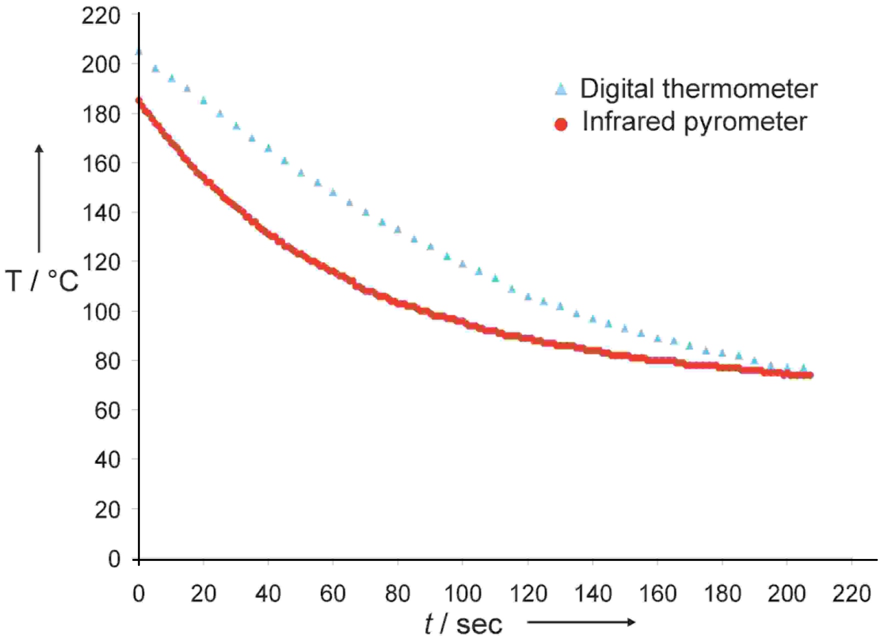


Figure 2.1 Calibration curve for the infrared pyrometer.

The calibration curve was built up irradiating the salt **2a** in a test tube in the same conditions (power and cooling air pressure) used for the synthesis of **3**. When the temperature showed by the IR-pyrometer reached the value of about 190 °C, the MW irradiation was stopped without stopping the cooling stream yet. A preheated digital thermometer was then put in contact with the reaction mixture and the temperature was sampled each 5 sec until almost constant value.

In this way it was possible to evaluate the "real" temperature inside about 20 °C higher (200 °C) than the one showed by the pyrometer at the same time (180 °C). Although it is not really possible to reproduce by conventional heating the effects of the dielectric heating derived from MW, a comparison was realized performing the reaction in a Differential Scanning Calorimeter (DSC) that allows reproducing nearly the same heating profile observed in MW (Figure 2.2). The heating rates were reproduced like those observed in MW except for the segment 102 °C - 194 °C where 150 °/min was the maximum rate allowed by the DSC. The heating rate in MW, in the same temperature segment, was about 180 °/min. Moreover, the very small volume of the DSC crucible assures a homogeneous heating of the bulk of the reaction mixture allowing negligible convection currents or volumetric heating effects and making the system more similar to the heating effect that is produced in the MW.

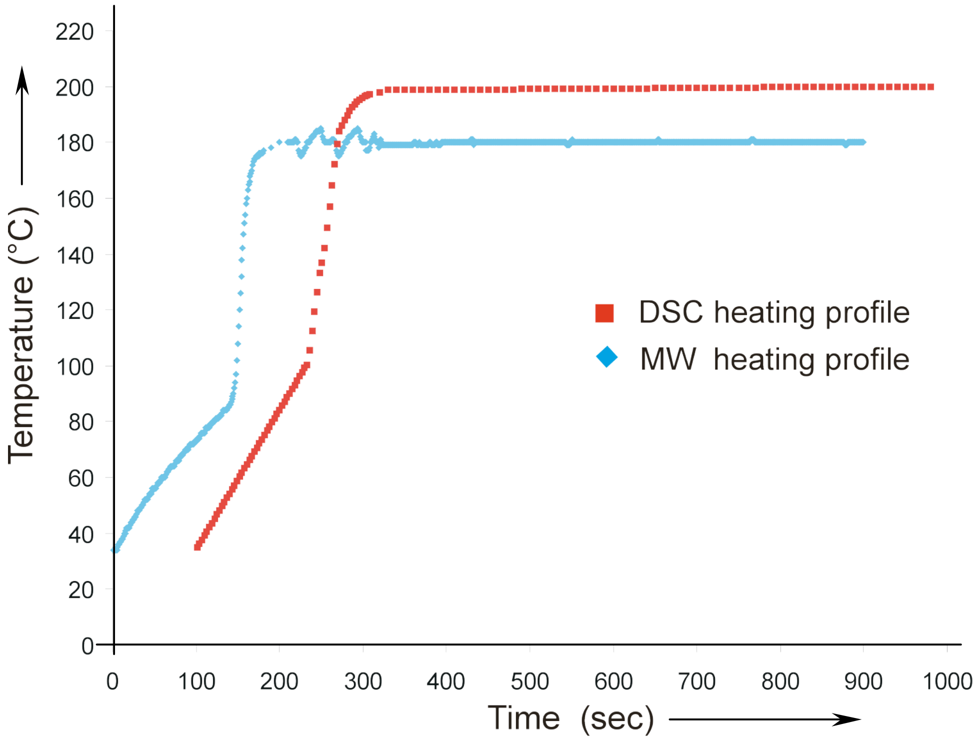


Figure 2.2 Comparison between the heating profile observed in MW and that reproduced in DSC.

From Figure 2.3 it is possible to observe that after 15 min of irradiation the conversion in the desired amide reached the maximum value of 93 % while the conversion of the reaction carried out by thermal heating was only 12 % after the same period of time. This is an evident proof of the enhanced condensation rate obtained using MW irradiation.

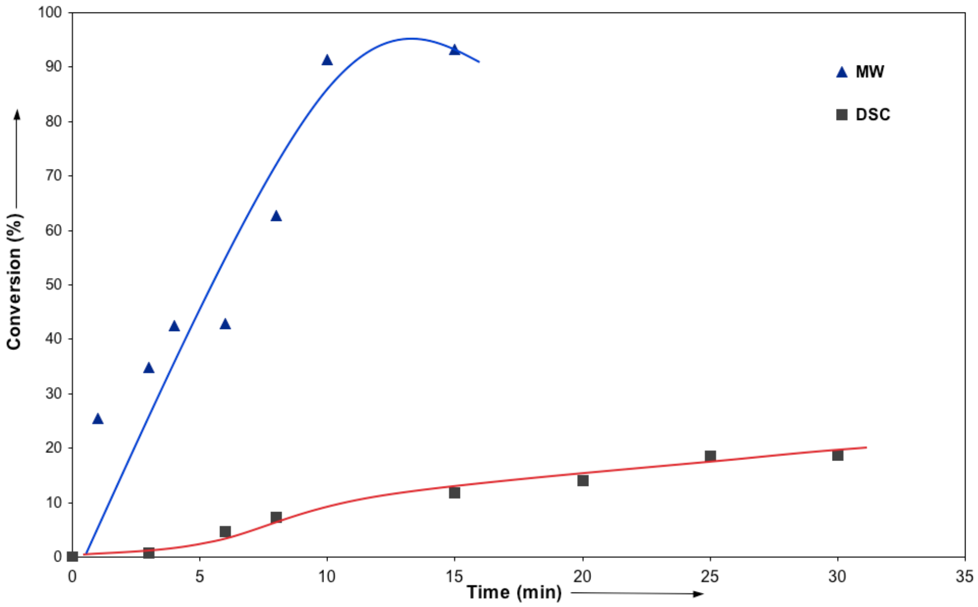


Figure 2.3 Comparative kinetic plots of methacrylamide **3** formation under MW irradiation (▲) and in DSC (■). The plotted curves are only visual aids and not to be meant as fitting curves.

The reaction was followed by FT-IR spectroscopy. As expected, after MW irradiation, the typical absorption bands of amides were detected at 3331 (NH), 1649 (I amide band), 1611 (conjugated C=C), 1522 cm^{-1} (II amide band). The final structure of the synthesized monomer was proven by ^{1}H- and ^{13}C-NMR spectroscopy (Figure 2.4).

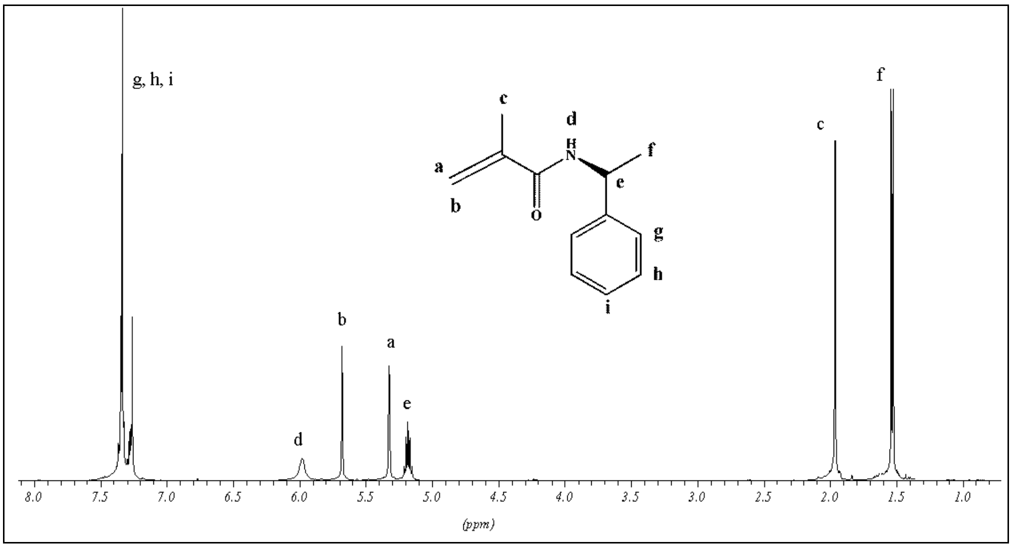


Figure 2.4 ^{1}H-NMR spectrum ($CDCl_3$) of **3** prepared by MW irradiation.

The detailed study of both reactions led to the identification of the side-products 2-methyl-3-(1-phenyl-ethylamino)-propionic acid (**4**) and 2-methyl-*N*-(1-phenyl-ethyl)-3-(1-phenyl-ethylamino)-propionamide (**5**) as a result of a Michael addition reaction on the starting acid **1** and the formed amide **3**, respectively. Surprisingly, for the reaction carried out by thermal heating it was possible to identify the presence of (1-phenyl-ethyl)-propyl-amine **6** (Figure 2.5) as a result of the decarboxylation of **4** definitively enabled by the high temperature (200°C). Nevertheless there was no evidence of the same side-product in MW (Figure 2.6).

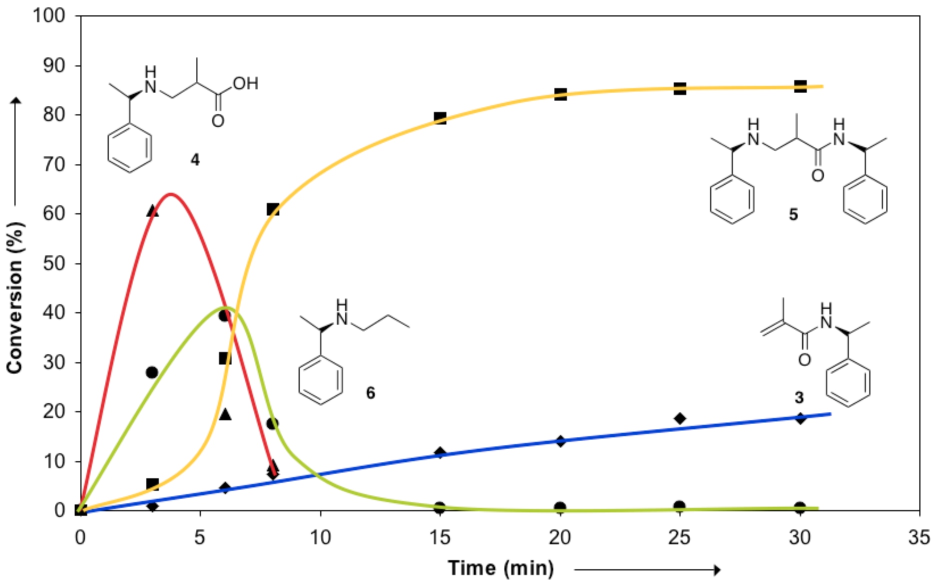


Figure 2.5 Kinetic plots of the amide synthesis under conventional thermal heating conditions (DSC). The plotted curves are only visual aids and not to be meant as fitting curves.

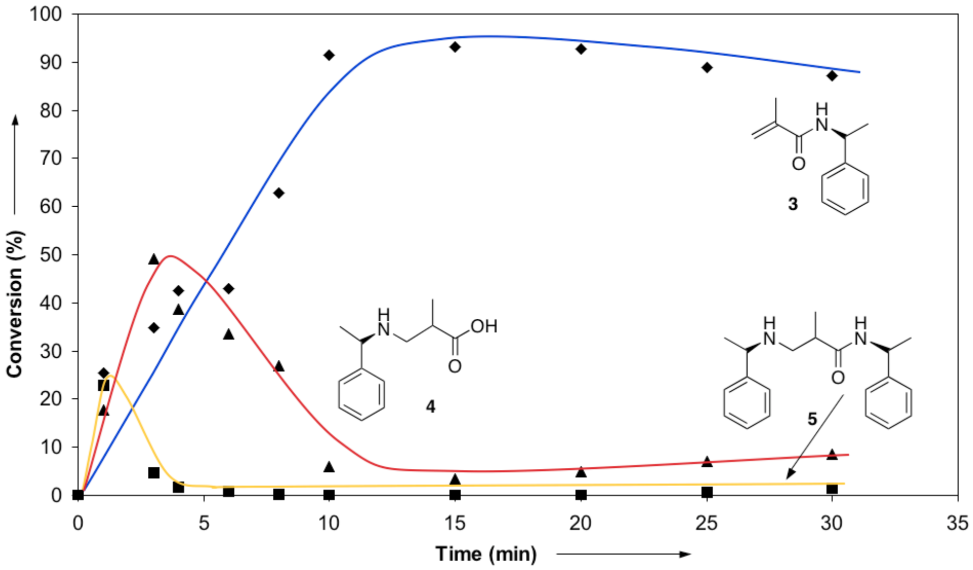
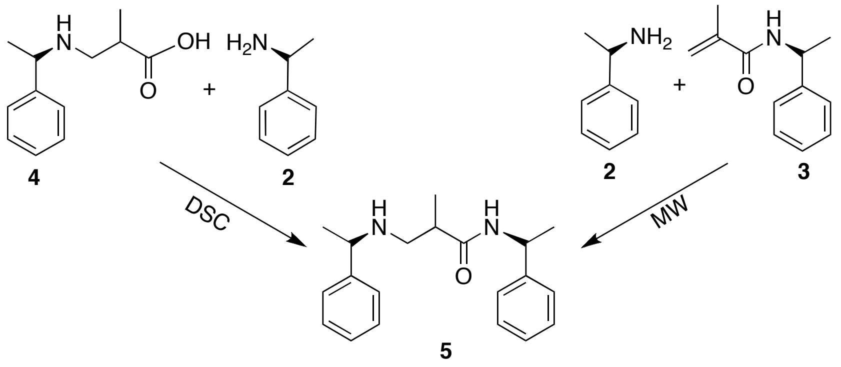


Figure 2.6 Kinetic plots of the amide synthesis under MW irradiation. The plotted curves are only visual aids and not to be meant as fitting curves.

From the kinetic data, obtained by GC-MS measurements, it was possible to observe that in both reaction conditions, **4** was the main formed Michael addition compound during the first 5 min of reaction time (Figure 2.5 and Figure 2.6).

After this time, due to the reversible character, its amount decreased progressively and, in the case of MW irradiation, the desired amide **3** became the main product. In contrast, during classical thermal reaction, there was a competition between the appearance of compounds **5** and **6**. For longer reaction time, up to 30 min, the dominant compound became **5**; **6** disappeared progressively due to its volatility at the reaction temperature. By this comparison, it is reasonable to assume that the compound **5** can be formed through two different pathways: Michael addition reaction or amidation according to Scheme 2.2. It is possible to presume that under the applied MW conditions, the very high stability of amide **3** is the driving force for the rapid decomposition of the product **4** via a retro-Michael reaction. Therefore, the high selectivity in **3** consumes almost all free amine allowing compound **5** to be formed only in considerably low amount, 3.4 % after 15 min of irradiation (Figure 2.6), preferentially by Michael addition of the amine **2** on the amide **3**.

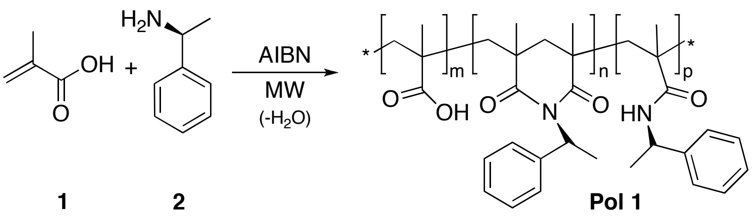


Scheme 2.5 Different pathways for the formation of the compound **5** under MW irradiation and under conventional thermal heating (DSC) conditions.

In classical thermal heating conditions, compound **4** decomposes in a very lower amount than the former case; its presence can lead to the formation of **5** by condensation with amine **2** still available in the system.

The high selectivity in the formation of amide **3** can be related to the fact that under MW irradiation, when competitive reactions are involved, the mechanism occurring via the hardest transition state is favored.[26] In this case the transition state associated to the amide **3** is harder, due to its lower polarizability, than that associated to the Michael addition compound **4**. Moreover, the mixture of the educts is a salt (**2a**, see scheme 2.4) and also the kinetically preferred intermediate **4** is in equilibrium with the zwitterion **4a**. Both species possess high dipole moments and can be considered strong microwave absorbers.[27]

The MW irradiation of the bulk mixture of **1** and **2** in the presence of AIBN (5 mol-%) as a free radical initiator led to a one-pot condensation and polymerization. Three different structural units could be observed in the resulting polymer (Scheme 2.6).



Scheme 2.6 MW assisted condensation reaction and one-pot polymerization.

In the ^{1}H-NMR spectrum of the polymer **Pol 1**, it was detected a signal at 10.3 ppm deriving from the carboxylic groups and a signal at 7.8 ppm related to the N-H proton of the amide structure. The signal at 5.6 ppm was attributed to the presence of imide moieties consequent to an intramolecular dehydration favored by the high temperature of reaction and by the formation of a six-membered ring. Besides, the FT-IR spectrum showed a signal at 1721 cm^{-1} (Figure 2.7), attributed to the stretching of the imidic C=O.

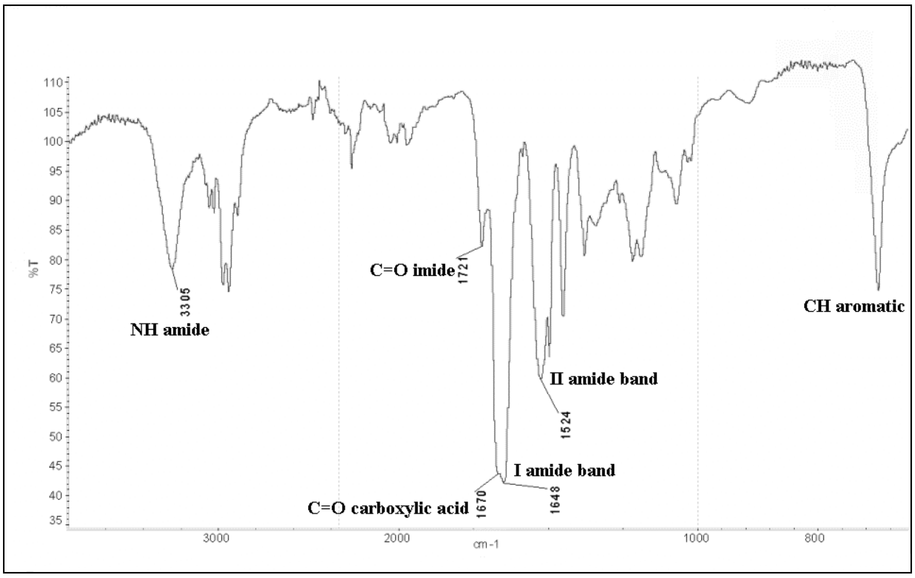


Figure 2.7 FT-IR spectrum of the polymer **Pol 1**.

During the transformation from monomer to polymer it was also observed a large increase of the absolute value of the specific rotation (Table 2.2).

Table 2.2 Properties of the poly(methacrylamide) synthesized by MW irradiation of methacrylic acid **1** and (*R*)-*N*-1-phenyl-ethylamine **2** in the presence of 5 mol-% of AIBN

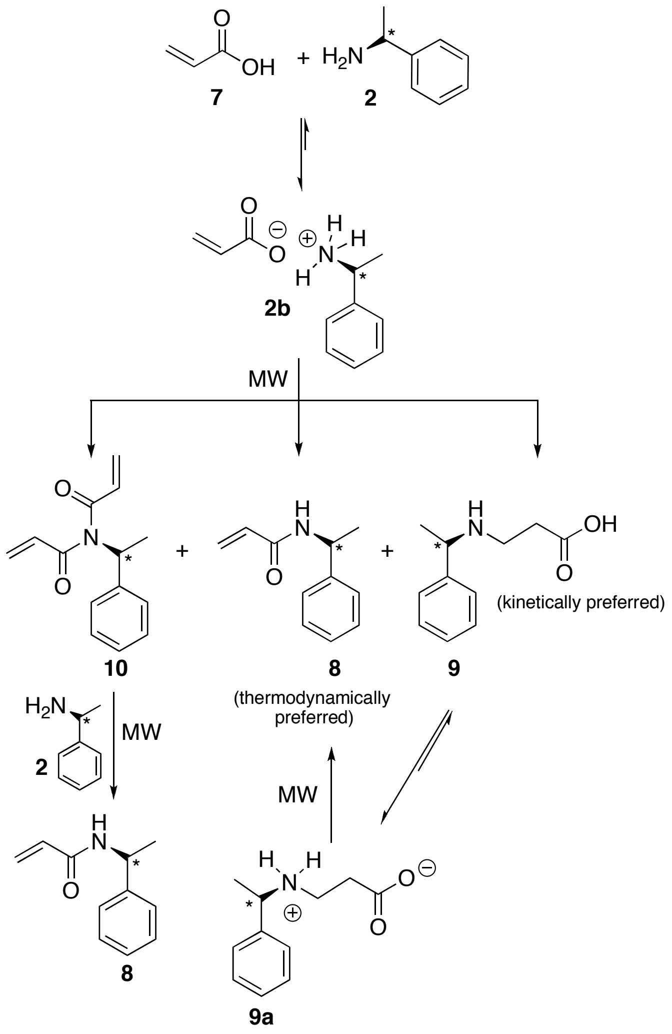
Polymer	M_w (·10^{-4}) (g/mol)	M_w/M_n	$[a]^{25}_D$ (°)	% m ^{a}	% n ^{a}	% p ^{a}	Yield (%)
Pol 1	9.6	2.98	+110	10	65	25	30

(a) Estimated by integration of the ^{1}H-NMR peaks at 10.42, 5.71 and 4.81 ppm; m = acid units, n = imide units, p = amide units.

A similar behavior has been already reported by Ritter et al. in a work concerning optically active poly(methacrylamides) containing methionine groups.[28] Despite of the bulky side group, the radical polymerization by MW irradiation afforded optically active polymers with relatively high molecular weights and low polydispersity index. The low yield obtained for **Pol 1** could be attributed to the low reactivity of methacrylamide in general due to steric effects.

2.3 Direct Synthesis and Polymerization of (*R*)-*N*-(1-phenylethyl)acrylamide

The direct synthesis of the chiral acrylamide (*R*)-*N*-(1-phenylethyl)-acrylamide (**8**) was achieved by MW irradiation of an equimolar mixtures of acrylic acid (**7**) and chiral (*R*)-*N*-1-phenylethylamine (**2**) (Scheme 2.7). A high yield (> 90%) in absence of solvent was attained in only a few minutes (up to 15) of reaction time. Numerous attempts to perform the same synthesis analogously by conventional thermal heating only led to the almost complete polymerization of the acrylic acid-amine salt after only about 2 minutes of reaction in all cases. In contrast, no polymerization was observed in MW even after longer reaction time, up to 30 minutes. In all the experiments no inhibitor was added to the reaction mixture to prevent thermal polymerization. It is possible to assume that the formation rate of **3** in MW is much higher than the thermal polymerization rate of the acrylic acid (**7**). Under the applied conditions, being **3** more thermally stable than **7**, no thermal polymerization could be observed.



Scheme 2.7 MW assisted synthesis of (*R*)-*N*-(1-phenylethyl)acrylamide (**8**).

The detailed study of the reaction through the kinetic data obtained by GC-MS measurements led to identification of the side-products 3-(1-phenyl-ethylamino)-propionic acid (**9**) and N-acryloyl-N-(1-phenyl-ethyl)-acrylamide (**10**) (Figure 2.8).

The adduct **9a** is the kinetically preferred product of a Michael addition reaction on the starting acrylic acid (**7**) in the betaine form. The monomer **10** can be derived by a further condensation of the preformed amide **8** with a molecule of acrylic acid **7**. The reversibility of the first addition reaction lead to the conversion of **9** into the thermodynamically more stable amide **8**. Moreover, after 4 min (Figure 2.8) the imide **10** is consumed in the reaction medium. It can be assumed that **10** reacts with the free amine **2** to give again the desired amide **8**.

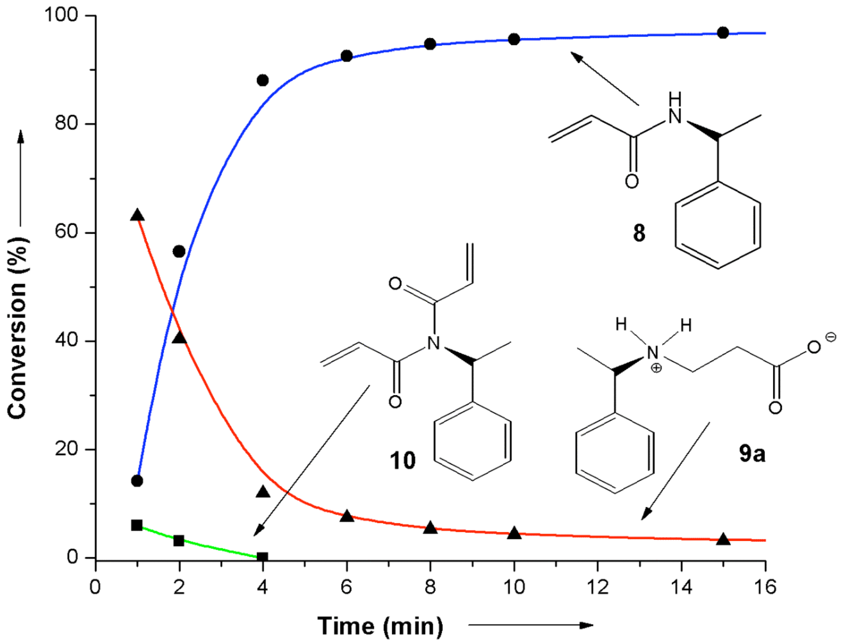
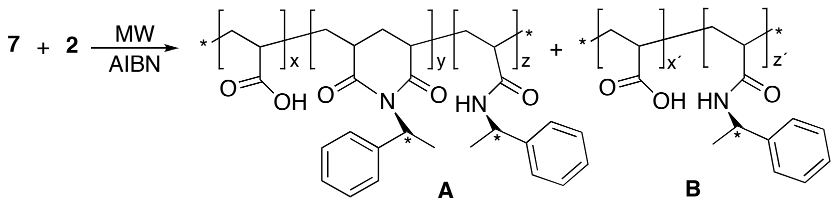


Figure 2.8 Kinetic plots for the synthesis of **8** under MW irradiation. The plotted curves are only visual aids and not to be meant as fitting curves.

The FT-IR spectroscopic analyses showed the typical absorption bands of the amide **8** at 3329 (ν_{NH}), 1648 (I amide band), 1614 (conjugated C=C), 1520 (II amide band) cm^{-1}; the final structure of the synthesized monomer was also proven by use of ^{1}H- and ^{13}C-NMR spectroscopy.

The one-pot polymerization reactions were performed by MW irradiation, at different power, of a mixture of the educts **7** and **2** in the presence of AIBN (5 mol-%) as a free radical initiator. The reaction temperature was maintained nearly constant at 100 °C as shown by the internal IR-pyrometer. For comparison, a polymerization of the same reagents mixture was carried out in a preheated oil-bath at 194 °C. This temperature was evaluated as the closest (± 10 °C) to the real temperature inside the MW using an experimental setup analogous to that used for the synthesis of the corresponding methacrylamide. ^{1}H-NMR spectra of the obtained polymers suggest the presence of blends containing two different copolymeric structures (Scheme 2.8).



Scheme 2.8 MW-assisted one-pot polymerization.

A signal at 10.61 ppm could be attributed to free carboxylic groups belonging to the structure **A**. A signal at 8.22 ppm was attributed to N-H proton of the amide structure and seemed to consist of two different signals partially overlapped; that could justify the assumption of two different amide units (Figure 2.9). A signal at 5.82 ppm was referred to the presence of imide moieties in accordance with the structure **A** (Scheme 2.8). Thus, an intramolecular dehydration, favored by the high temperature, could have led to the formation of the imide ring. Although the most probable structure is a six-membered ring it was not possible to exclude the possibility of larger structures. As a further confirmation, the FT-IR spectra showed a sharp band at 1719 cm^{-1} attributed to the stretching of the imidic carbonyl group (Figure 2.10). The ^{1}H-NMR signal at 12.20 ppm was attributed to the free carboxylic groups regarding to the structure **B**.

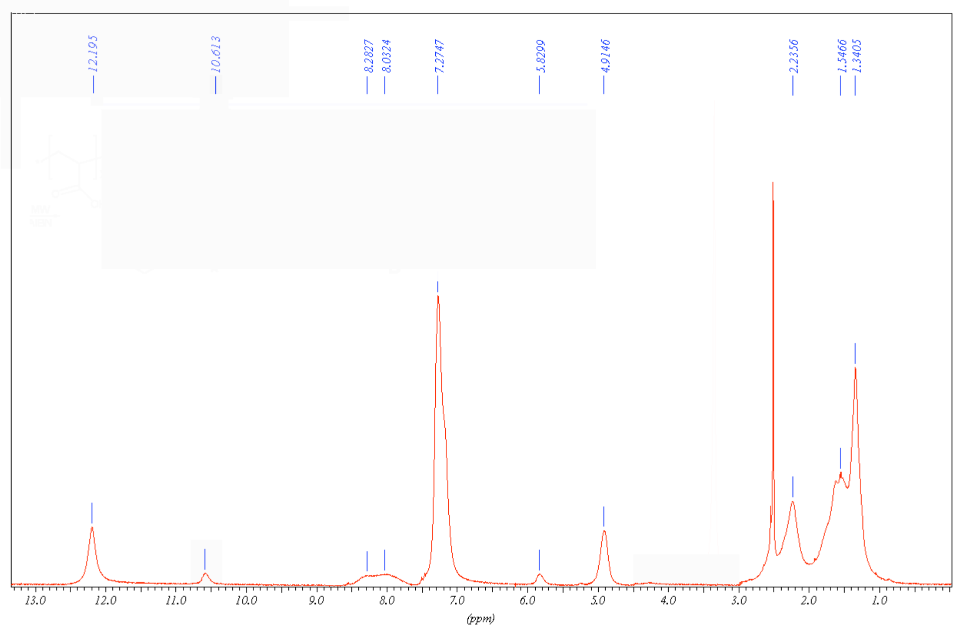


Figure 2.9 ^{1}H-NMR spectrum of the polymer **P1** in DMSO-d$_6$.

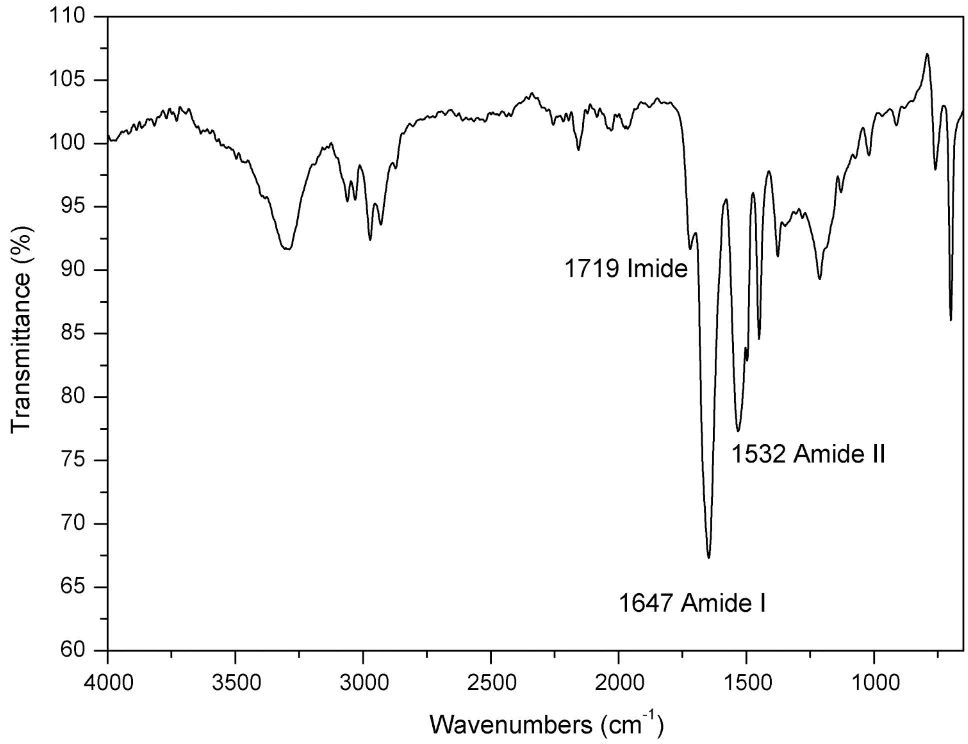


Figure 2.10 FT-IR spectrum of the polymer **P3**.

In Table 2.3 is reported the ratio between the integrals of the signals at 12.20 and 4.91 ppm (attributed to the CH proton of the amide unit in both structure). This proton ratio (**PR**) is indicative of the relative proportion of the structure **B** in the blends. For **P1** and **P6** this ratio seems to indicate a larger proportion of the structure **B** compared to the structure **A**.

Table 2.3 Properties of the poly(acrylamides)

Polymer	MW Power (W)	% m [a)]	% n [a)]	% p [a)]	PR [b)]	Tg (°C) Tg1	Tg (°C) Tg2	$M_w/10^3$ (g/mol)	D	$[\alpha]^{20}_D$ (°)	Yield (%)
P1	5	2	15	83	1.2	45	143	7.1	2.1	88	52
P2	20	2	8	90	0.05	120		87.2	3.1	161	65
P3	50	1	8	91	0.12	135		49.9	2.1	153	68
P4	100	4	14	82	0.15	143		48.4	1.3	143	74
P5	130	3	14	83	0.16	137		22.6	2.1	87	80
P6 [c)]	-	2	5	93	1.1	33	142	1.9	2.2	142	40

a) Estimated by integration of ^{1}H-NMR peaks at 10.61 ppm, 5.82 ppm and 4.91 ppm; m = acid units, n = imide units, p = amide units.

b) Proton ratio (PR) estimated by the ratio between the integrals of ^{1}H-NMR peaks at 12.20 ppm and 4.91 ppm.

c) Polymer prepared by thermal heating in oil-bath.

The polymer **P1** was obtained by irradiation at the lowest MW power (5 W) while the polymer **P6** was prepared by thermal heating. Therefore, it is possible to assume that the reaction conditions obtained with a very low MW power are very close to those obtainable by normal thermal heating. For the other prepared polymers (**P2** - **P5**), the **PR** increased with the applied MW-power, assuming always values below 0.2, that identify the structure **A** as the main molecular system in the blend.

It was possible to evaluate the relative percentages of the different structural units (amide, imide, acid) in the blends by integration of the corresponding ^{1}H-NMR signals. As shown in Table 2.3, the amide structure was present in a large proportion, the percentage of imide structure varied from 5 % (**P6**) to 15 % (**P1**), and the carboxylic acid residue (of the structure **A**) was only found in very little amounts. Nevertheless, the spectral data (^{1}H-NMR and FT-IR) did not permit a complete quantitative elucidation of the chemical structure.

Thermal characterization by DSC measurements were carried out to clarify the structural hypotheses and to confirm the presence of blends (Figure 2.11).

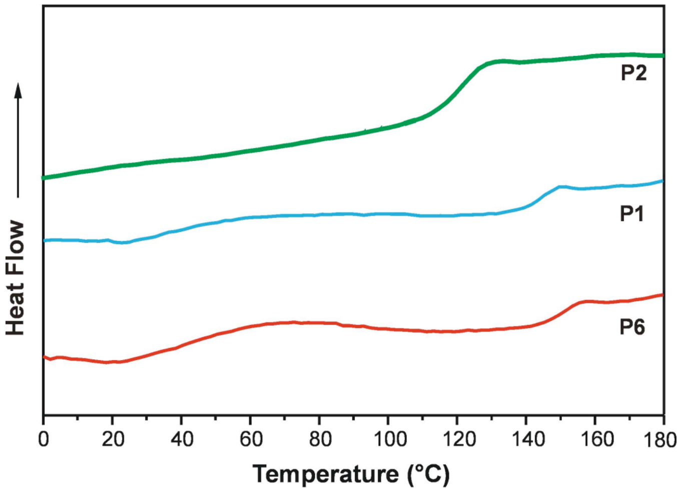


Figure 2.11 DSC traces of the polymers P2, P1 and P6. Third scan at a heating rate of 10 °C/min.

All the polymers, except **P1** and **P6**, showed only one glass transition temperature (Tg) ranging from 120°C (**P2**) to 143°C (**P4**) (see Table 2.3).

Two Tg values were observed for **P1** and **P6**. The highest one for both, respectively 143 °C and 142 °C is in agreement with the glass transition temperatures identified for the other polymers. The lowest Tg, at 45 °C for **P1** and 33 °C for **P6**, accounts for the presence of the structure **B**, a copolymer presumably very rich in acid units.

A possible explanation is that this low value could be due to the very low contribution from hydrogen bonding towards the rigidity of the polymer as against poly acrylic acid where the higher Tg of 106 °C [29] is due to strong H-bonds making it highly rigid. On the other hand, in a random copolymer (Scheme 2.8, structure B), the hydrogen bonding entity is notably reduced which is reflected in the lower Tg.[30]

Despite **PR** showed the presence of a blend for all the polymers, only for **P1** and **P6** two different Tg values were observed. Henceforth, it can be considered that **PR** values around or even below 0.2 indicate a very low percentage of the copolymer **B** in the blend. Under these conditions it is hardly possible to identify two diverse glass transitions. The GPC analyses revealed a correlation between the applied MW-power and the average molecular weight (M_w) values. The latter increased with decreasing MW-power, reaching a maximum value of $8.72 \cdot 10^4$ g/mol for **P2** corresponding to a MW power of 20 W. The polymer **P1** did not follow this trend showing a M_w of $7.1 \cdot 10^3$ g/mol. This behavior has to be again attributed to the fact that, at a very low MW-power (5 W), the polymerization behavior is very close to that observed for the classical thermal heating. In fact, **P6** showed a M_w in the same order of magnitude ($1.9 \cdot 10^3$ g/mol). The polydispersity index (**D**) was generally high, anyway in agreement with the values expected for a normal free radical polymerization (see Table 2.3).

The one-pot free radical polymerization by MW irradiation afforded optically active polymers with relatively high yields in 30 minutes reaction time. It was possible to find a regular increase in yield with increasing MW power. A maximum yield (after purification) of 80% was achieved for **P5** corresponding to a MW power of 130 W. Even under a power of only 5 W, a 52% yield was obtained for the polymer **P1**, while the yield for **P6** (prepared by classical thermal heating in oil-bath) was only 40%. Passing from the monomer to the polymer, it was also observed, as in the case of the poly(methacrylamide), a large increase of the absolute value of the specific rotation.

In conclusion, MW irradiation accelerates considerably the process of condensation and it is more selective as compared with classical thermal heating. Although there are still controversies about the existence of a so-called "specific" microwave effect, the final results in terms of conversion and selectivity in the methacrylamide **3**, observed in the MW and not in the thermal run for the same reaction under nearly the same conditions of temperature and heating rate, can not be attributed only to the exceptional strong heating effect due to the MW. In the case of the acrylamide **8**, the reaction mixture heated in oil-bath was almost completely polymerized after only 2 minutes. From the experimental data, it is strongly understandable that highly polar intermediates (zwitterions and salts) interact directly on a molecular level with the electromagnetic field associated to the MW.

The MW assisted radical polymerization of the educts afforded, in a single step, optically active polymers or blend of polymers containing acid, amide and imide units. The composition and structure were largely dependent from the applied MW power. These materials are expected to be suitable for optical resolution or in catalysis for organic asymmetric synthesis.

2.4 Experimental

All the syntheses carried out under MW irradiation were performed under power control to assure a constant energy transfer in the time. The monomers (**3** and **8**) were prepared in open system while the polymers (**Pol 1**, **P1-P5**) in closed system. The syntheses in DSC were conducted by heating the sample with the following program:

RT-102°C: heating rate 30 °/min
102°C-194°C: heating rate 150°/min
194°C-200°C: heating rate 6°/min
Isotherm at 200°C for the remaining reaction time (until 27 min).

2.4.1 Synthesis of (R)-*N*-(1-phenylethyl)-methacrylamide (3) under MW irradiation

1.42 g (16.5 mmol) of methacrylic acid (**1**) was added to 2 g (16.5 mmol) of (*R*)-1-phenylethylamine (**2**) in a pressure-resistant test tube. The formed salt, **2a**, was placed in the microwave reactor and irradiated at 140 W for 15 min maintaining a constant temperature of 180 °C (IR-pyrometer) by cooling with compressed air at room temperature. The crude product was dissolved in diethyl ether and washed with 5% HCl solution (30 mL) and 5% $NaHCO_3$ solution (30 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated under vacuum to afford a yellowish solid that was recrystallized in hexane to get a white solid. The yield, determined by gas-chromatography (GC), was 93%. The yield after recrystallization was 90%.

mp=91-92 ºC; $[\alpha]^{25}_{D} = 61$ (*c* = 10 mg/cm^3 in THF) ; FT-IR (diamond): 3331 ($\nu_{N\text{-}H}$), 1649 ($\nu_{C=O}$, I amide band), 1611 ($\nu_{C=C}$), 1522 cm^{-1} ($\delta_{N\text{-}H}$, II amide band); ^{1}H-NMR (500.13 MHz, $CDCl_3$): δ=7.36-7.34 (m, 5H, *Arom*), 5.99 (s, 1H, -N*H*), 5.69 (s, 1H, CH^aH^b=C), 5.34 (s, 1H, CH^aH^b=C), 5.19 (q, 1H, -NH-C*H*-Arom), 1.97 (s, 3H, $CH_2=CCH_3$), 1.55 ppm (d, 3H, Arom-CH-CH_3); ^{13}C-NMR (125.77 MHz, $CDCl_3$): δ=167.47, 143.15, 140.22, 128.73, 127.42, 126.20, 119.37, 48.81, 21.65, 18.69 ppm.

2.4.2 Synthesis of (R)-*N*-(1-phenylethyl)-methacrylamide (3) under conventional thermal heating in DSC

1.42 g (16.5 mmol) of methacrylic acid (**1**) was added to 2 g (16.5 mmol) of (*R*)-1-phenyl-ethylamine (**2**) in a test tube. 10 mg of the obtained salt **2a** were transferred in an aluminum pan, placed in the DSC and heated with the temperature program previously reported. The products obtained were identified by comparison their GC-MS spectra with those obtained by MW irradiation of the same educts.

2.4.3 Synthesis of the polymer Pol 1

1.42 g (16.5 mmol) of methacrylic acid (**1**), 2 g (16.5 mmol) of (*R*)-1-phenyl-ethylamine (**2**), and 0.135 g (0.83 mmol) of AIBN were mixed in a pressure-resistant test tube. The tube was sealed, placed in the microwave reactor and irradiated at 140 W for 30 min maintaining a constant temperature of 120 °C (IR-pyrometer) by cooling with compressed air at room temperature. The obtained raw mixture polymer was dissolved in acetone and precipitated into methanol. The polymer was recovered by centrifugation and dried under vacuum. The yield was 30%. FT-IR (diamond): 3300-3000 ($\nu_{N\text{-}H}$ amide, $\nu_{C=O}$ carboxylic), 1711 ($\nu_{C=O}$, imide), 1651 ($\nu_{C=O}$, I amide band), 1520 cm^{-1} ($\delta_{N\text{-}H}$, II amide band); ^{1}H-NMR (500.13 MHz, $(CD_3)_2SO$): δ= 10.42 (-COO*H*), 7.81 (-N*H*-), 7.32 (*Arom*), 5.71 (CH_3-C*H*-Arom imide), 4.81 (CH_3-C*H*-Arom amide), 1.46 (CH_3-CH-Arom), 1.24 (CH_3-C(CH_2)C=O), 1.05 ppm (CH_3-C(CH_2)-C=O); T_g = 160 ºC; $[\alpha]^{25}_{D} = 110$ º (*c* = 10 mg/cm^3 in THF).

2.4.4 Synthesis of (R)-*N*-(1-phenylethyl)-acrylamide (8)

Acrylic acid (**7**) (1.2 g, 16.5 mmol) and (R)-*N*-1-phenylethylamine (**2**) (2 g, 16.5 mmol) were mixed in a pressure-resistant test tube provided with a magnetic stirring bar. The tube was placed in the CEM monomode microwave and irradiated at 50 W for 15 min maintaining a constant temperature of 150 °C (IR-pyrometer) under effective cooling by compressed air. The obtained crude product was dissolved in diethyl ether and washed with 5% HCl solution (30 mL) and 5% $NaHCO_3$ solution (30 mL). The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under vacuum to afford a yellowish solid that was recrystallized with hexane to get a white solid. The yield, determined by gas-chromatography (GC), was 92%.
mp=72-73 ºC; FT-IR (diamond): 3329 ($\nu_{N\text{-}H}$), 1648 ($\nu_{C=O}$, I amide band), 1614 ($\nu_{C=C}$), 1520 ($\delta_{N\text{-}H}$, II amide band) cm^{-1}; ^{1}H-NMR (500.13 MHz, $(CD_3)_2SO$): δ = 8.12 (s, 1H, -N*H*), 7.33-7.26 (m, 5H, *Arom*), 6.48 (dd, 1H, CH_2C*H*-C=O), 6.12 (dd, 1H, C*H*H=C cis), 5.65 (dd, 1H, CH*H*=C trans), 5.04 (q, 1H, -NH-C*H*-Arom), 1.48 (d, 3H, Arom-CH-CH_3) ppm; ^{13}C-NMR (125.77 MHz, $CDCl_3$): δ =166.51, 142.43, 130.81, 129.13, 128.34, 127.42, 126.20, 48.81, 23.13 ppm; $[\alpha]^{25}_D$ = 15 º (*c* = 10 mg/cm^3 in THF).

2.4.5 Synthesis of the polymers P1-P5

The general synthetic procedure is given for **P1** as a typical example.
Acrylic acid (**7**) (1.2 g, 16.5 mmol), (R)-*N*-1-phenylethylamine (**2**) (2 g, 16.5 mmol) and AIBN (0.135 g, 0.83 mmol) were mixed in a pressure-resistant test tube provided of a magnetic stirring bar. The tube was sealed with a silicon septum, flushed with nitrogen for 10 minutes and irradiated at 5 W for 30 min in the microwave reactor. The reaction mixture was dissolved in dimethylsulfoxide (DMSO) and purified by precipitation in a 5% HCl solution. The polymer was recovered by filtration and dried under vacuum. The yield after purification was 52%.
FT-IR (diamond): 3305 ($\nu_{N\text{-}H}$), 1721 ($\nu_{C=O}$, imide), 1675 ($\nu_{C=O}$, carboxylic), 1648 ($\nu_{C=O}$, I amide band), 1524 ($\delta_{N\text{-}H}$, II amide band) cm^{-1}; ^{1}H-NMR (500.13 MHz, $(CD_3)_2SO$): δ = 12.20 (-COO*H*), 10.61 (-COO*H*), 8.22 (-N*H*-), 7.26 (*Arom*), 5.82 (CH_3-C*H*-Arom imide), 4.91 (CH_3-C*H*-Arom amide), 2.28 (-CH_2-C*H*C=O), 1.60 (CH_3-CH-Arom), 1.31 (-CH_2-CHC=O) ppm;
Tg1 = 45 ºC; Tg2 = 143 ºC; $[\alpha]^{20}_D$ = 88 º (*c* = 10 mg/cm^3 in THF).

2.4.6 Synthesis of the polymer P6 by thermal heating in oil-bath

Acrylic acid (**7**) (1.2 g, 16.5 mmol), (R)-*N*-1-phenylethylamine (**2**) (2 g, 16.5 mmol) and AIBN (0.135 g, 0.83 mmol) were mixed in a pressure-resistant test tube provided of a magnetic stirring bar. The tube was sealed with a silicon septum, flushed with nitrogen for 10 minutes and placed in a preheated oil-bath at the constant temperature of 194°C for 30 minutes. The reaction mixture was dissolved in DMSO and precipitated in a 5% HCl solution. The polymer was collected by filtration and dried under vacuum. The yield was 40%.

FT-IR (diamond): 3312 ($\nu_{N\text{-}H}$), 3000 ($\nu_{O\text{-}H}$) 1706 ($\nu_{C=O}$, carboxylic), 1630 ($\nu_{C=O}$, I amide band), 1527 ($\delta_{N\text{-}H}$, II amide band) cm^{-1}; ^{1}H-NMR (500.13 MHz, $(CD_3)_2SO$): δ (ppm) = 12.20 (-COO*H*), 10.61 (-COO*H*), 8.22 (-N*H*-), 7.26 (*Arom*), 5.82 (CH_3-C*H*-Arom imide), 4.91 (CH_3-C*H*-Arom amide), 2.28 (-CH_2-C*H*C=O), 1.60 (CH_3-CH-Arom), 1.31 (-CH_2-CHC=O);
Tg1 = 33 ºC; Tg2 = 142 ºC; $[\alpha]^{25}_D = 142$ º (*c* = 10 mg/cm^3 in THF).

2.5 References

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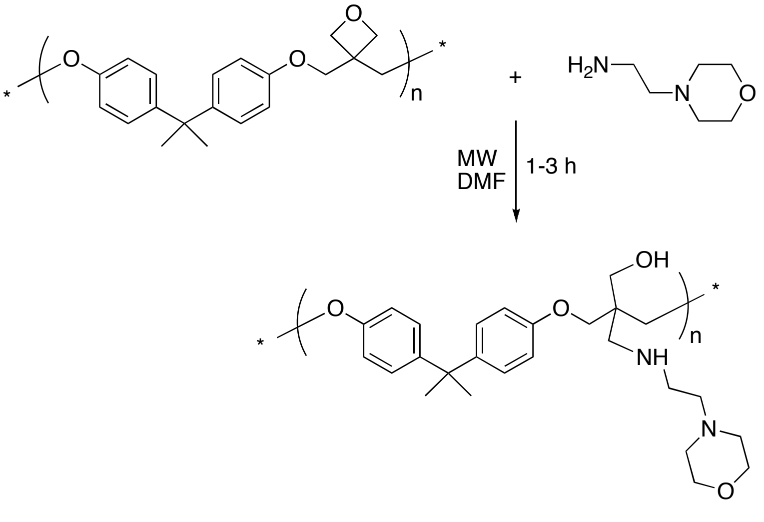
3 Amidation of Poly(ethylene-*co*-acrylic acid)

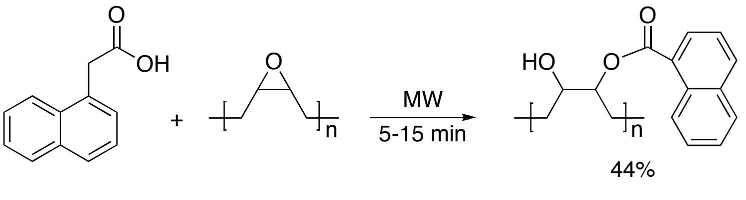
3.1 Introduction and Literature Survey

The modification of preformed polymers is a widely used method to obtain new materials with improved mechanical or chemical properties. Microwave (MW) irradiation was used to improve and accelerate different kind of polymer analogous reactions. Hurduc et al.[1] investigated the modification of oxetane based polymers with 4-(2-aminoethyl)morpholine (Scheme 3.1). The highest degree of conversion under MW reached 27% while in several syntheses under conventional conditions the conversions of oxetane rings were always lower and achieved maximum value of 18%.



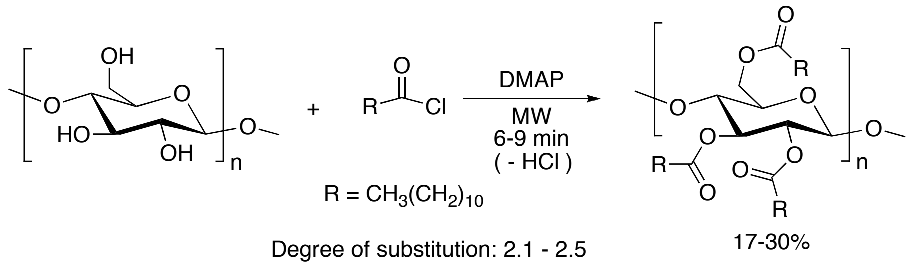
Scheme 3.1 Modification of oxetane based polymers with 4-(2-amino-ethyl)morpholine.

The ring opening reaction of naphthyl acetic acid with epoxidized liquid natural rubber (ELNR) (Scheme 3.2) was studied by Huy and coworkers.[2]



Scheme 3.2 Reaction between α-naphthyl acetic acid and epoxidized liquid natural rubber.

Applying dodecanoyl chloride in presence of *N*,*N*-dimethylaminopyridine (DMAP) under MW conditions, Krausz et al.[3] demonstrated that the esterification of cellulose can be achieved within 6–9 min (Scheme 3.3).



Scheme 3.3 Esterification of cellulose with dodecanoyl chloride under microwave conditions.

The surface oxidation of polyethylene (PE) under solid-state conditions with potassium permanganate was studied by Mallakpour.[4] After a reaction time of 90 s, FT-IR analyses revealed the presence of hydroxyl as well as vinylic functional groups on the polymer surface whereas hydroperoxy groups were not detected.

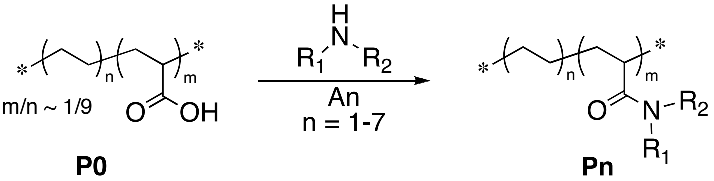
Modification of polyolefins bearing carboxylic groups is a method to obtain materials with improved interfacial properties. For example, the neutralization of the polymer-attached carboxylic groups with metal bases can produce polyelectrolytes with increased stiffness and resilience at room temperature.[5] Polymeric products obtained by reaction of acid-functionalized polyethylene or maleic anhydride grafted polystyrene with aliphatic diamines at elevated temperature simply achieved by classical thermal heating have been described.[6]

In this connection, the reactions and the relative reactivity of different amines with the carboxylic groups of poly(ethylene-*co*-acrylic acid) in microwave were investigated. As comparison, the same polymer analogous reactions were also performed under conventional thermal heating.

Poly(ethylene-*co*-acrylic acid*)* is one of the most easily processible ethylene copolymers. It founds many applications in industrial and commercial environments due to the fact that can be pigmented, painted or plated, and can be UV-stabilized for exterior applications. It is generally used in molded or extruded parts requiring unique combinations of flexibility and tensile strength, low temperature impact and adhesion. It is produced by the high-pressure polymerization of ethylene and acrylic acid in the presence of free radical initiators. This method of polymerization produces a branched, random ethylene acrylic acid copolymer. The carboxyl groups on adjacent molecules interact and form a weak cross-linked network through hydrogen bonding. This produces copolymers with excellent toughness whose total property package is dependent on the acid content, molecular weight and the extent of short and long chain branching. The carboxyl groups disrupt the linearity of the polyethylene backbone. This interferes with chain alignment and reduces the total crystallinity, as in the case of other ethylene copolymers, such as ethylene-vinyl acetate or ethylene methyl acrylate copolymers. As a result, it has lower melting point, stiffness and tensile yield strength in proportion to the acid comonomer content. In addition, the carboxyl functionality contributes to improved adhesion and toughness, with good adhesion to foil, paper, glass, aluminum, and other metals. The degree of adhesion is related to the acid comonomer content, as well. The acid functionality allows the polymer to form very strong bonds to polar substrates that withstand a variety of aggressive environments and also improves resistance to grease and oils.

3.2 Results and Discussions

Acid-functionalized polyethylene (**P0**), containing about 10 mol% of acrylic acid units, was reacted in MW and, as a comparison, in oil-bath with various amines (**An**, Table 3.1) to give copolymers bearing amide groups (Scheme 3.4). The reactions were performed in sealed vials using a ten-fold excess of amine that acted also as a pseudo-solvent for the reaction mixture.

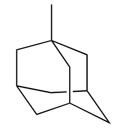
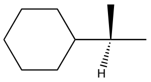
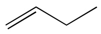
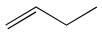
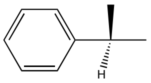
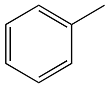


Scheme 3.4 Polymer analogous amidation of acid-containing polyethylene.

The compositions of the synthesized polymers (**Pn**) were determined semiquantitatively by FT-IR spectroscopic analyses. Due to the poor solubility of the samples, it was not possible to carry out NMR studies.

The FT-IR spectra of **Pn** showed the characteristic amide I and amide II (for primary amides) bands at about 1648 and 1540 cm^{-1} due to the stretching vibration of the carboxylic group and to the bending vibration of the N-H group respectively. A typical infrared spectrum in the range between 1800 and 1400 cm^{-1} is reported in Figure 3.1 where **P0** is the commercial polymer. **P6 MW** and **P6 OB** are the polymers obtained after reaction with (R)-*N*-1-(phenylethyl)amine in microwave and in oil-bath, respectively.

Table 3.1 Properties of the amines used in the reaction with poly(ethylene-*co*-acrylic acid).

Amine	**R_1**	**R_2**	**pKa** [a)]	**E_a** [b)] **(eV)**	**Nucleophilicity (a.u.)**	**Conductivity** [c)] **(μS·cm^{-1})**
A1	$CH_3(CH_2)_7$—	H	10.21	2.2576	7	219.1
A2		H	10.71	2.3076	5	- [d)]
A3		H	10.46	2.2902	6	104.5
A4			9.16	2.4352	2	82.1
A5	$CH_3O(CH_2)_2$—	$CH_3O(CH_2)_2$—	9.08	2.4307	3	67.7
A6		H	9.73	2.3675	4	134.9
A7		H	4.64	2.5186	1	35.7

a) Calculated using the program MarvinSketch by ChemAxon Ltd.

b) Calculated using the semiempirical model AM1 with the software PC Spartan '04 by Wavefun.

c) Conductivity of the DMF solutions of the ammonium salts with dodecanoic acid.

d) Adamantylamine was not soluble in DMF at the needed concentration.

Even working with a large excess of amine, the conversion was never quantitative and in all cases it was still possible to identify a stretching vibration of the unmodified carboxylic acid at about 1705 cm^{-1}. The inverse of the ratio between the intensities of this band and of the band at about 1464 cm^{-1}, that belongs to the methylene scissoring of the polyethylene backbone (internal standard), was taken as a reactivity index (RI) (Table 3.2).

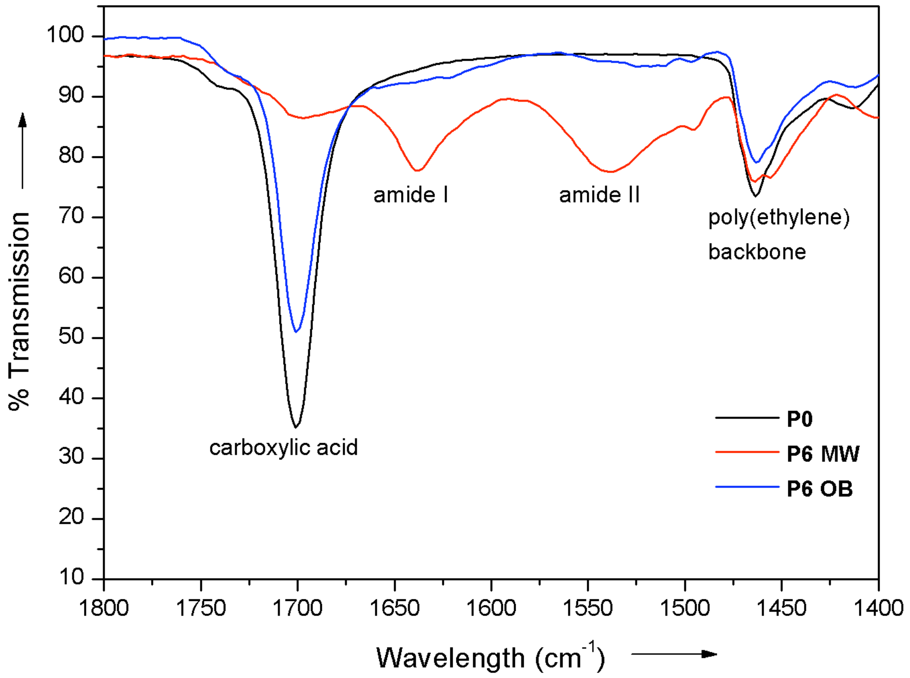


Figure 3.1 FT-IR spectra comparison in the range between 1800 and 1400 cm^{-1}.

Table 3.2 FT-IR absorption for the carboxylic acid band, ratio between its intensity and the intensity of the band due to the methylene scissoring of the polyethylene backbone, reactivity index (RI).

Polymer	Carboxylic acid ν C=O (cm^{-1})	Ratio (Acid / PE backbone)	Reactivity Index RI
P1MW	1699	0.21	4.93
P1OB	1702	0.11	9.75
P2MW	1710	0.17	5.96
P2OB	1697	0.15	6.50
P3MW	1690	0.08	12.5
P3OB	1687	0.12	8.62
P4MW	1702	0.77	1.29
P4OB	1703	1.64	0.61
P5MW	1703	1.14	0.87
P5OB	1703	1.09	0.91
P6MW	1696	0.54	1.84
P6OB	1701	2.59	0.38
P7MW	1701	2.81	0.35
P7OB	1701	3.09	0.32

The semi-quantitative evaluation of the relative reactivity of the amines was based on this parameter. Figure 3.2 shows a comparison between the reactions performed in MW and in oil-bath.

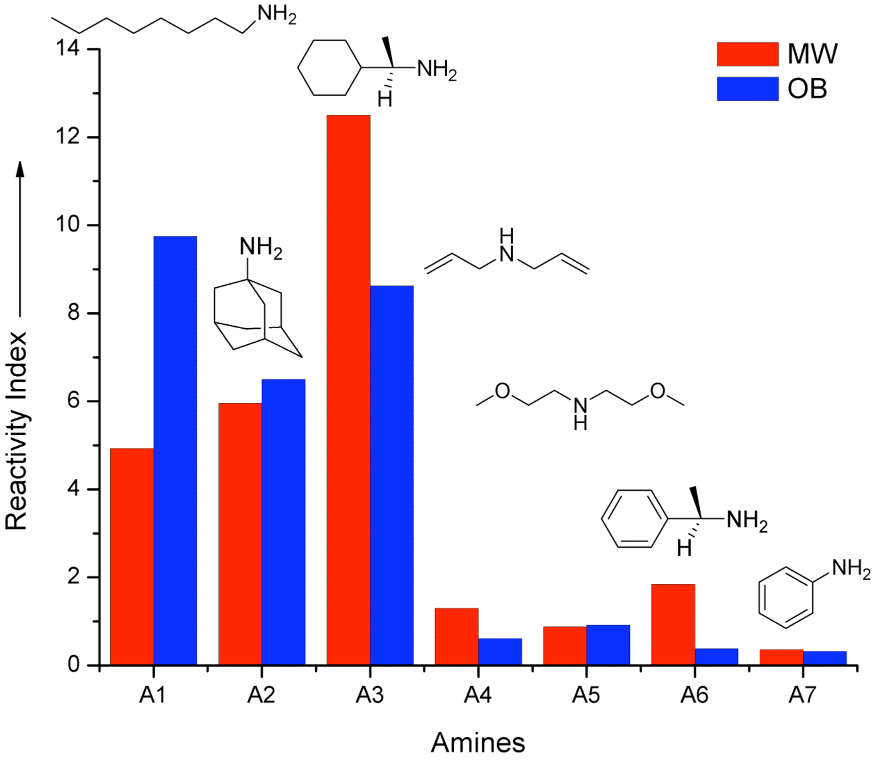


Figure 3.2 Evaluation of the relative reactivity of the amines in microwave (MW) and in oil-bath (OB) respectively.

As expected, the MW-assisted reactions typically showed increased conversion for most of the investigated amines. Surprisingly, in the case of octylamine, adamantylamine and (*R*)-1-phenylethylamine **(A1**, **A2** and **A6** respectively) a better conversion was obtained in oil-bath.

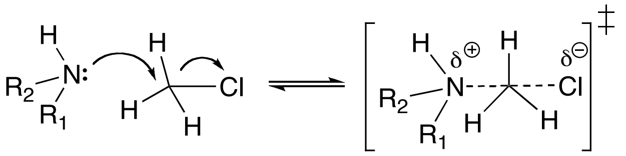
The reactivity of the amines depends mainly on their nucleophilicity and basicity. The former is responsible for attacking the electron-deficient carbon of the acyl group to form the amide, while the latter is involved in the acid-base reaction that leads to ammonium salts. In general, secondary alkyl amines are stronger bases than primary amines owing to the electron donating property of the alkyl groups. Aromatic amines are the weakest bases in the lot due to the lower availability of the lone pair delocalized by conjugation with the phenyl ring. Apparently, the basicity of amines follows the order: secondary > primary > aromatic. Anyway, the presence of electron-donating (increasing basicity) or electron-withdrawing (decreasing basicity) groups has a strong influence on this trend.

On the other hand, the nucleophilicity decreases in the order: primary > secondary > aromatic, a combination of steric and electronic effects being responsible for this trend.[7]

For example, the low reactivity showed by aniline is simply due to its low basicity and low nucleophilicity.

For a better understanding of the results described above, it was attempted to correlate the experimental reactivity index of the amines with their order of basicity and nucleophilicity. To define a basicity scale we used pKa values obtained by computational evaluations using the software Marvin Sketch 4.0.3 (Table 3.2).[8]

These values showed absolute agreement with the experimental values reported in the literature.[9] Unfortunately, experimental data were hardly obtainable for a few of the amines. The definition of a nucleophility scale requires, on the other hand, a more theoretical approach. With this aim, it was evaluated the activation energy (E_a) for a S_N2 displacement model reaction that also involves, as in our experimental case, a rate-determining nucleophilic attack (Scheme 3.5).



Scheme 3.5 Model reaction used for theoretical evaluation of the nucleophilicity scale.

Theoretical calculations,[11] performed using the semiempirical method AM1,[12] were used to obtain E_a as the difference between the transition state energy (E_{TS}) and the ground state energy (E_{GS}) (Table 3.2). All the geometries for the transition states were fully optimized without symmetry constraint (Figure 3.3).

Vibrational analyses were also performed for all transition states to confirm whether an optimized geometry corresponded to a transition state with only one imaginary frequency.

While the obtained values are by no means ultimate or absolute, they can serve as a yardstick for comparison within the series of amines. Using the E_a scale we defined an arbitrary nucleophilicity scale attributing the lowest nucleophilicity to the amine involved in the model reaction with the highest E_a (aniline) and vice versa (Table 3.3).

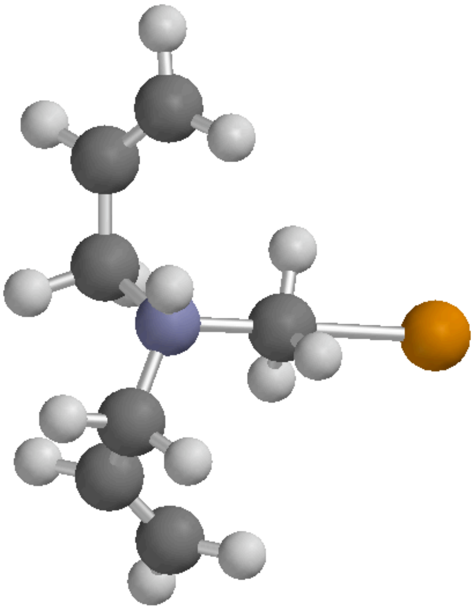


Figure 3.3 Fully optimized (AM1) geometry corresponding to the transition state for the nucleophilic displacement with diallylamine (**A4**).

Table 3.3 Ground State Energy, Transition State Energy, Activation Energy (Hartrees) for the AM1 *in vacuo* optimized molecular systems corresponding to the nuclophilic displacement of the amines (**An**) with CH_3Cl. **A1**: octylamine. **A2**: adamantylamine. **A3**: (R)-1-cyclohexylethylamine. **A4**: diallylamine. **A5**: bis(2-methoxyethyl)amine. **A6**: (*R*)-1-phenylethylamine. **A7**: aniline.

Amine	Ground State Energy	Transition State Energy	Activation Energy
A1	-0.11903055	-0.036061498	0.082969052
A2	-0.08961646	-0.004809547	0.08480692
A3	-0.10042388	-0.016256693	0.08416719
A4	0.02173608	0.111233215	0.089497126
A5	-0.19380133	-0.104469942	0.08933139
A6	-0.00959415	0.077413795	0.08700795
A7	0.002150816	0.094710592	0.092559776

Figure 3.4 shows a plot of the reactivity index versus the basicity of the amines (pKa) for the reactions performed under MW irradiation and in oil-bath.

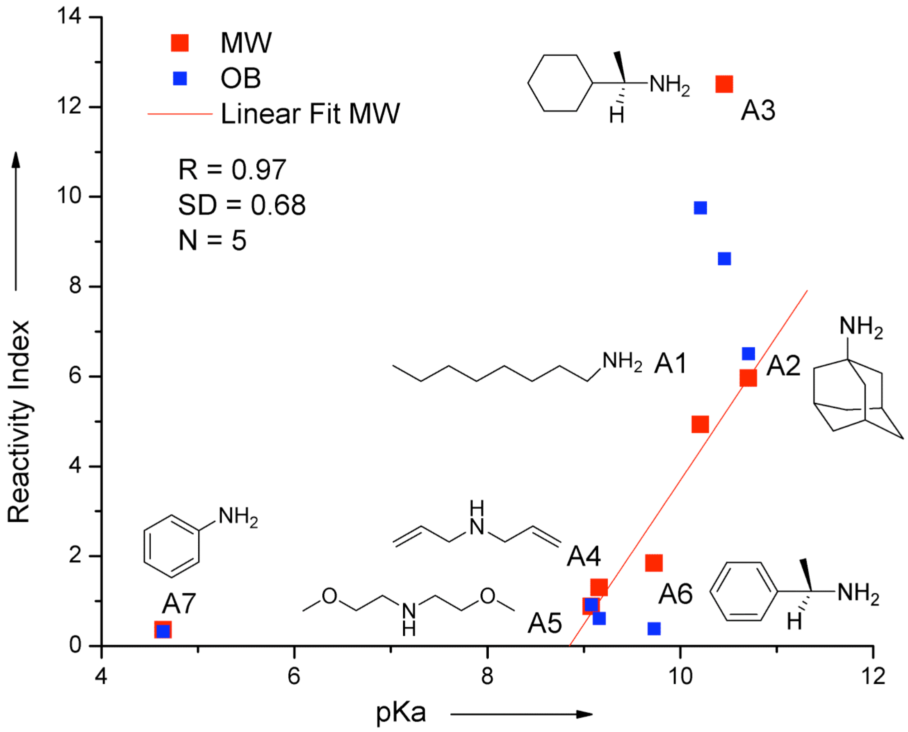


Figure 3.4 Comparison between the reactivity index and the basicity of the amines expressed as pKa values

For the MW runs, a direct comparison of basicity and reactivity results in a poor correlation mainly because aniline (**A7**) and (R)-1-cyclohexylethylamine (**A3**) strongly deviate from a linear relationship. Anyway, when the comparison was made for 5 out of the 7 amines (**A1**, **A2**, **A4**, **A5** and **A6**), an excellent correlation (R=0.97, SD=0.68) was obtained (Figure 3.4). Aniline itself can be considered on the same trend (lowest basicity, lowest reactivity), however, its relatively poor basicity does not fit into the linearity range. Accordingly, a linear relationship comparing an aromatic amine with aliphatic amines could not be expected. Furthermore, the relatively high reactivity of (R)-*N*-1-cyclohexylethylamine (**A3**) under the applied conditions is not yet understood. The data corresponding to the thermally heated reactions are in contrast roughly distributed without any simple correlation with the reactivity index.

The predicted nucleophilicity, obtained from E_a calculations, was compared with the reactivity index for both kinds of reactions (Figure 3.5).

Considering the oil-bath reactions, only (R)-*N*-1-phenylethylamine (**A6**) seems not to correlate with the proposed activation energy model. The other amines show instead a very good correlation (R=0.97, SD=1.13). On the other hand, the data corresponding to the MW assisted reactions are largely scattered.

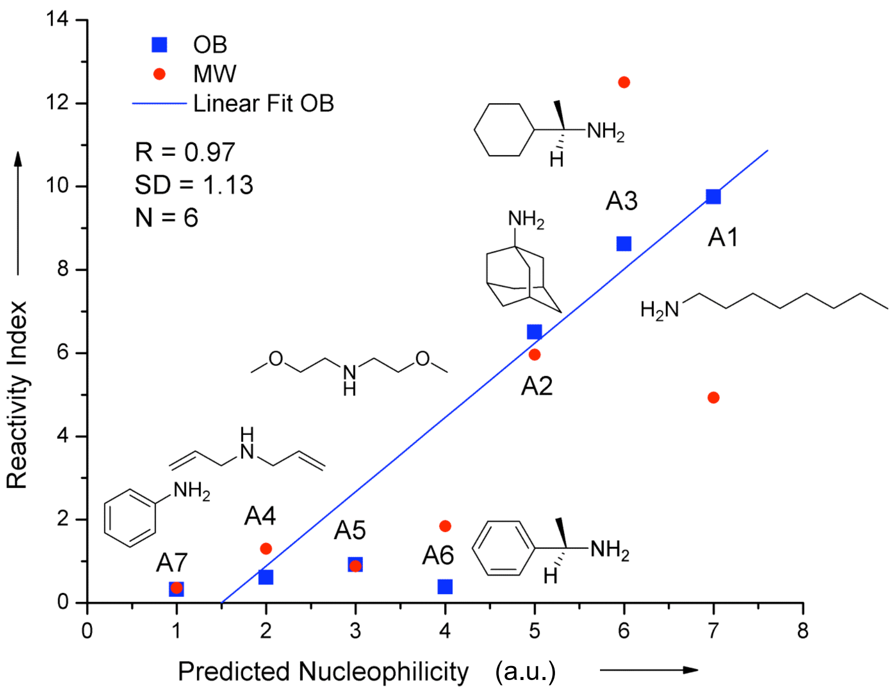


Figure 3.5 Comparison between the reactivity index and the predicted nucleophilicity obtained from E_a calculated using the semiempirical model AM1.

Even without considering **A6**, as in the oil-bath case, only a weak correlation with a large standard deviation can be obtained (R=0.75, SD=3.39).

The correlation of reactivity-basicity observed in microwave (Figure 3.4) has to be attributed to the strong microwave-absorbing capacity of ionic species (carboxylic salts obtained by neutralization of the acrylic acid moiety on the polymer) that can interact with the electric field vector associated to the microwaves behaving as molecular antennas for the electromagnetic field. Thus, the most basic amine (**A2**), providing the highest concentration of ionic species, is the most reactive in MW (excluding **A3**) even though not being the most reactive nucleophile. Under conventional thermal heating, the amidation reaction is mainly ruled by the nucleophilicity as it was possible to expect considering the reaction mechanism. As further experimental evidence of the relationship between basicity and concentration of ionic species, the electric conductivity of DMF solutions of the ammonium salts obtained by neutralization of the used amines with dodecanoic acid was measured (Table 3.1). This latter was used as a low molecular weight compound to mime the behavior and acidity of **P0**. From the conductivity values reported in Table 3.1 it appears clear that the less basic amine (aniline) shows the lowest concentration of ionic species in solution while the second most basic (octylamine) shows the highest. In the case of adamantylamine (**A2**), that is the most basic amine within the series, it was not possible to measure the conductivity because it was not soluble in DMF at the needed concentration. The other amines (excluding **A3**) correlate with the proposed model as well, the electric conductivity of the solution increasing with the basicity.

Differential scanning calorimetry was used for the thermal analysis of the prepared polymers. In order to ensure a similar thermal history to all samples to be compared, a heating scan was first run at 10ºC / min from -50 to 200 ºC for each sample. A second and third scan were then performed, the average value of the transition temperatures, listed in Table 3.4, was used for comparison.

Table 3.4 Thermal data for the prepared polymers.

Polymer	T_g (ºC) [a)]	T_m (ºC) [a)]
P0	8.1	82.2
P1MW	4.4	72.4
P1OB	3.4	76.5
P2MW	33.2	81.5
P2OB	20.5	78.3
P3MW	16.4	75.8
P3OB	10.8	76.4
P4MW	7.1	76.8
P4OB	3.6	77.6
P5MW	2.4	79.2
P5OB	3.1	78.6
P6MW	15.0	79.1
P6OB	12.3	79.8
P7MW	9.1	78.3
P7OB	8.9	78.6

a) Average value of the second and third scan at a heating rate of 10 º/min.

The parent copolymer (**P0**) showed a glass transition temperature (T_g) and a melting point of 8.1 and 82.2 ºC, respectively. In all the cases it was observed a slight depression of the melting point that ranged from 72.4 (**P1MW**) to 81.5 ºC (**P2MW**) and minor differences between the corresponding values for the reactions in microwave and in oil-bath.

The glass transition temperature values reflected the modifications in terms of molecular rigidity brought into the starting copolymer (**P0**).

The polymers **P1**, **P4**, and **P5** (where **P0** was modified with relatively long aliphatic chain containing amines) showed lower T_g values than **P0** whereas **P2**, **P3**, **P6** and **P7**, obtained by reaction with adamantylamine, (R)-*N*-1-cyclohexylethylamine, (R)-*N*-1-phenylethylamine and aniline, respectively, showed higher T_g values. The differences observed between the corresponding values in MW and in oil-bath could account for the different degree of substitution of the carboxylic moiety. Anyway, the presence of a single glass transition temperature can be an indication that even if the substitution was not quantitative, under the applied experimental conditions, there was no or only neglectable amount of unreacted starting material.

The findings concerning the reactivity are taken as a proof for the existence of “specific” microwave effects. Conversion increases or reduced reaction times, so often observed in microwave reactions, could be sometimes explained in term of thermal acceleration due to the fast and homogeneous heating that is a peculiarity of the microwave dielectric heating. However, a reactivity behavior based on dissimilar parameters, for the same reaction performed under MW irradiation and under conventional thermal heating, cannot be rationalized only by invoking purely thermal effects. The strong dependence conductivity-basicity and basicity-reactivity observed for the MW-assisted reactions suggests the use of the basicity, or the conductivity for more general cases, as a predictive tool for a qualitative evaluation of the conversion for new microwave reactions. Additional investigations are still needed for a more quantitative description and rationalization of these effects.

3.3 Experimental

All the reagents, 1-octylamine (Aldrich), adamantylamine (Aldrich), (*R*)-1-cyclohexylethylamine (Fluka), diallylamine (Aldrich), bis(2-methoxyethyl)amine (Acros), (*R*)-1-phenylethylamine (Fluka), aniline (Aldrich), dodecanoic acid (Aldrich), were commercially available and used as received. Poly (ethylene-*co*-acrylic acid) (Aldrich) was reported to have 20 wt % of acrylic acid units. Pellets of the polymer were used without any further purification or treatment. All the syntheses carried out under MW irradiation were performed under power control. The obtained polymers were characterized by FT-IR spectroscopy. Electric conductivity measurements were performed using a WTW inoLab Level 3 multifunction box equipped with a standard conductivity cell TetraCon 325 with a cell constant of 0.475 cm^{-1}.

The detailed amounts of reagents and the characterizations are reported for **P1** as a typical example.

3.3.1 Synthesis of P1

Poly(ethylene-*co*-acrylic acid) (538 mg, 1.5 mmol of acrylic acid units) was mixed together with n-octylamine (1.95 g, 15 mmol) in a pressure resistant vial equipped with a Teflon coated stirring bar and sealed with a septum. The sample was then irradiated with a power of 300 W for 20 minutes, keeping a maximum average temperature of 180 °C (IR-pyrometer). After completion, the reaction mixture was diluted with toluene and precipitated in a large excess of n-hexane to remove the unreacted amine.

The reaction was also performed in an oil-bath preheated at a temperature that provided 190 °C inside the reaction vessel. This temperature was evaluated within a range of ±10°C to the real temperature inside the reaction vessel in the MW.

P1: FT-IR (diamond): 3287 (ν_{N-H}), 2917, 2849 (ν_{C-H} aliphatic), 1704 ($\nu_{C=O}$ carboxylic acid residue), 1640 ($\nu_{C=O}$ amide I band), 1549 (δ_{N-H} amide II band), 1464 (-CH_2- scissoring polyethylene back-bone) cm^{-1}.

3.3.2 Electric conductivity measurements

Dodecanoic acid (0.2 g, 1 mmol) was mixed together with 10 mmol of the corresponding amine and stirred until complete dissolution. 15 ml of DMF were added and the solution was stirred for 48 h at room temperature before measuring the conductivity. In the case of adamantylamine, the solid mixture was not soluble in DMF.

3.4 References

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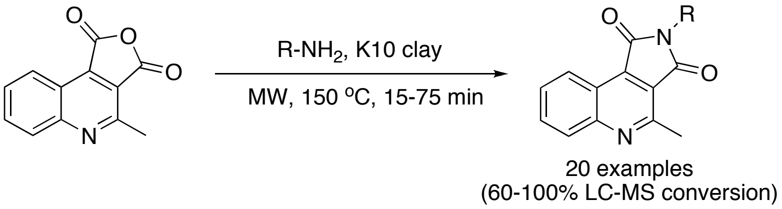
4 Imidization Reactions

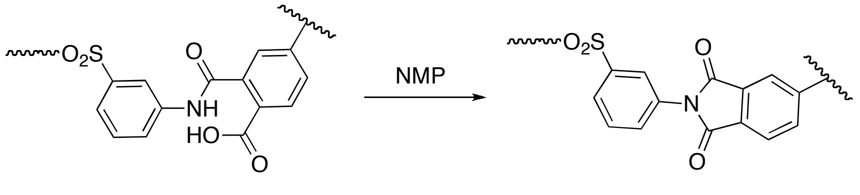
4.1 Introduction and Literature Survey

Mortoni and coworkers described the conversion of 2-methylquinoline-3,4-dicarboxylic acid anhydride to a quinoline-3,4-dicarboxyimide library by treatment of the anhydride with a diverse set of primary amines under " dry media " microwave conditions (Scheme 4.1).[1]



Scheme 4.1 Formation of imides from anhydrides.

Lewis et al.[2] reported the microwave-assisted imidization reaction of a polyamic acid, obtained through the condensation of 3,3,4,4-benzophenonetetracarboxylic acid dianhydride (BTDA) with diaminodiphenylsulfone (DDS) (Scheme 4.2). Analysis of the kinetic parameters showed that the apparent activation energy for the reaction was reduced from 105 (thermal heating) to 57 kJ mol^{-1}.



Scheme 4.2 Imidization of polyamic acid.

4.2 Synthesis of N-benzensulfonamide maleimide

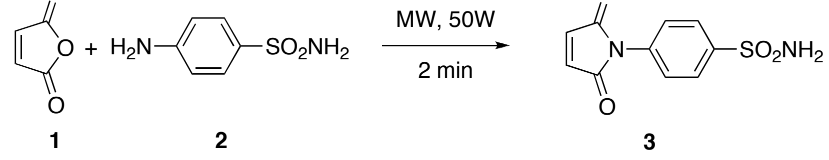
Unsaturated imide derivatives are of a certain interest due to their biological properties, synthetic and industrial applications.[3-5] The classical approach to the synthesis of N-substituted maleimides starts from maleic anhydride and the corresponding amine through a double step process that generally requires long reaction times. The easily obtained intermediate, maleamic acid, is converted in maleimide by a ring-closure reaction using many different dehydrating agents as acetic anhydride, phosphorus pentoxide, acetyl chloride, thionyl chloride.[6,7]

It is well known that sulfonamides were the first substances used to prevent bacterial infections in human being and also to inhibit the growth of bacteria mainly by interfering with their enzymatic systems. The parent sulfonamide can be considered a prominent predecessor of the sulfonamide drugs that are still widely used today in medicine despite the discovery of modern antibiotics.[8,9]

Ritter *et al.* reported the synthesis of a number of (meth)acryl derivatives based on different sulfonamides by using activating agents.[10] Tawney et al. first polymerized maleimides by free-radical polymerization.[11]

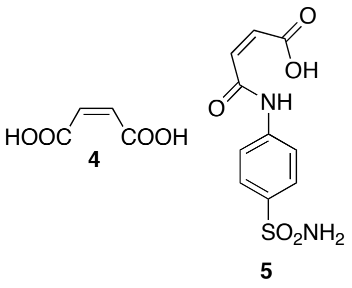
In a recent work,[12] Ritter et al. showed that the application of MW energy enhances the formation of N-phenylmaleimide.

In this connection, a one-pot bulk synthesis of the imide **3** starting from maleic anhydride (**1**) and sulfanilamide (**2**) was realized. The reaction took place without any chemical activation of the reagents and bypassing the ring-closure step normally needed by the classical synthetic approach. Under the applied MW conditions, it was possible to synthesize the desired monomer with a yield (after purification) up to 50 % after only 2 minutes of irradiation (Scheme 4.1). Longer reaction times did not afford any yield improvement and resulted in partial decomposition of the samples.



Scheme 4.3 Microwave-assisted synthesis of **3**.

^{1}H-NMR spectroscopy was used to confirm the structure of the products. Analyzing the side products it was possible to recognize, among others unidentified, the maleic acid ((*Z*)-but-2-enedioic acid) (**4**) due to the hydrolysis of the starting maleic anhydride and the intermediate maleamic acid (3-(4-sulfamoyl-phenylcarbamoyl)-acrylic acid) (**5**).



Scheme 4.4 Main side products obtained in the MW-assisted synthesis of **3**.

The maximum reached temperature was 100 °C according to the IR-pyrometer equipped with the MW reactor. It is well known that this temperature does not correspond to the real temperature inside the reaction vessel. Anyway, considering that the reaction takes place between two solids in conditions far below the melting temperature and in a heterogeneous system, using a fiber-optic contact thermometer to evaluate the temperature seemed to be of lesser significance. To qualify the benefit of the MW dielectric heating, the same synthesis was also performed by conventional thermal heating in oil-bath. Without having accurate temperature measurements in the MW and knowing that the real temperature is still higher than the one observed outside of the reaction vessel, we carried out the comparison in oil-bath working with temperatures ranging from 100 °C to 170 °C for 15 min. Performing the reaction for 2 min (like in the MW case), it only afforded unreacted educts. The relative conversions (evaluated by ^{1}H-NMR), referred to the identified products considering them as the only ones present in the raw mixture, are plotted against the reaction temperature (Figure 4.1).

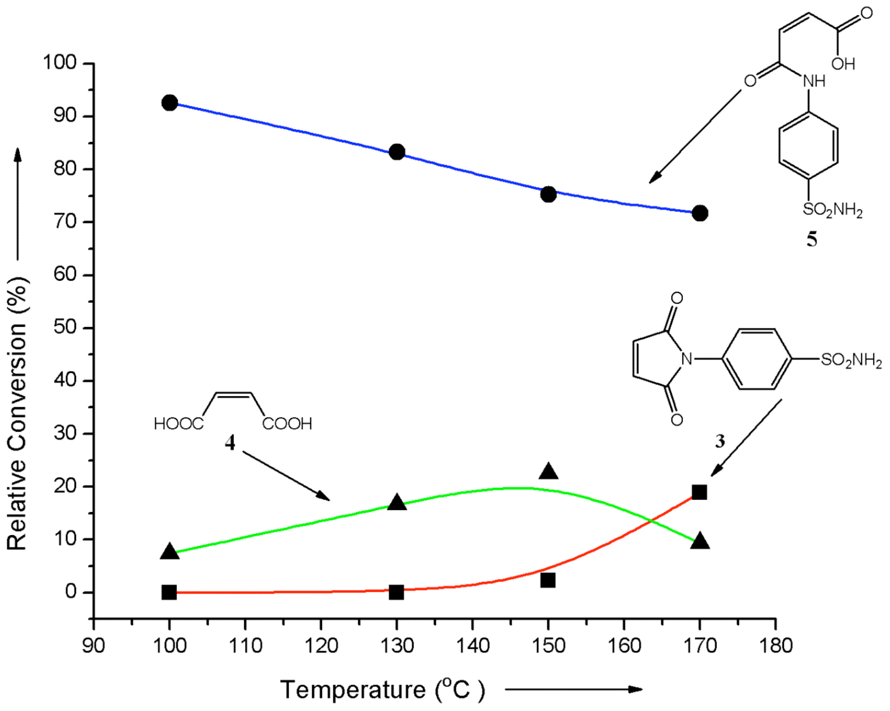


Figure 4.1 Relative products distribution for the reaction between **1** and **2** in oil-bath in function of the temperature.

According to Figure 4.1, it is possible to conclude that for temperatures below 150 °C there was no imide formation and the main product was the maleamic acid (**5**) accompanied by minor percentages of maleic acid (**4**). Increasing the temperature the percentage of maleimide **3** increased progressively up to 19% (170 °C) with the corresponding decrease of both acids **4** and **5**. These results are in good accordance with the accepted two steps mechanism that leads to the maleimide through dehydration of maleamic acid certainly enabled by the high reaction temperature. Starting from 150 °C it also occurred the partial decomposition of the samples with formation of unidentified side products.

4.3 Polymerization of N-benzensulfonamide maleimide

The monomer **3** was polymerized in DMF solution using benzopinacol as a free radical initiator. MW irradiation under temperature control was used. The maximum temperature, checked internally using a fiber optic thermometer, was 100 ^oC. Even the preset power was 80 W, the irradiation power was ranging between 5 and 25 W due to the reaching of the maximum temperature. The most commonly used radical initiators, such as peroxides or aliphatic azo compounds, do not seem to be very efficient for MW-assisted polymerization due to their relatively low decomposition temperature. Using a good MW absorber solvent like DMF , even irradiating with a quite low power, it can be difficult to maintain suitable temperatures for these initiators. High reaction temperatures result in a fast consumption of the radicals and finally in low yield even after long reaction times. Moreover, in this particular case, the polymerization at 60 °C using AIBN as a free radical initiator yielded only a few percentages of the polymer. The use of C-C-bond splitting initiators offers the possibility to polymerize at relatively high temperature due to their improved thermal stability. Benzopinacol is the most used among this class of initiators and can be handled up to 160 °C without danger as it does not decompose under explosion in this temperature range. The diarylhydroxy radicals formed from its decomposition do not react directly with the monomer under addition, but in a secondary reaction by hydrogen transfer forming monomer radicals that initiate the polymerization. Using this kind of initiators it is possible to get polymers with hydrogen atoms at the end of the chain, i.e. “end-group free polymers”.[19] The structure of the obtained polymer was confirmed by ^{1}H-NMR and FT-IR spectroscopy (Figure 4.2).

In the ^{1}H-NMR, the signal at 7.95 and 7.47 ppm were identified as the $-NH_2$ and the aromatic group respectively. The signal at 3.36 ppm was attributed to the main polymeric chain. The FT-IR spectra exhibited the characteristic absorptions for the imide ring at 1706 and 1784 cm^{-1} ascribed to the symmetrical and asymmetrical carbonyl stretching vibration. MALDI-TOF analyses indicated that the mass signals of polymeric ions are distributed approximately between 1000 and 4200 *m/z* corresponding to chain lengths of about 4 up to 17 repeating units. The maximum of intensity at about *m/z* 1283 corresponds to 5 repeating units. The low molecular weight obtained and the relative low isolated yield (62 %) could be related to the low homopolymerization tendency typical of N-phenyl maleimide derivatives. GPC analyses showed an average molecular weight (Mw) of 5 017 Da, corresponding to about 20 repeating units with a polydispersity index of 1,3. However, a calibration with polystyrene leads to higher values compared to MALDI-TOF analyses because of coil extension due to the more rigid main chain of the polyimide.

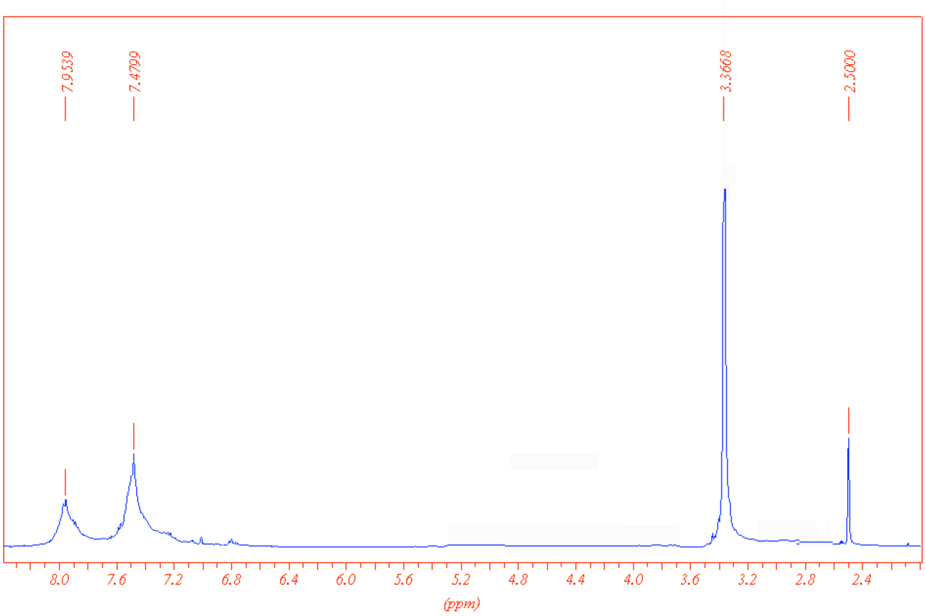
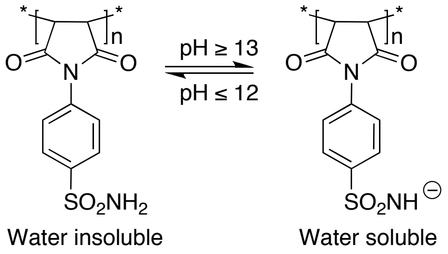


Figure 4.2 ^{1}H-NMR spectrum (500.13 MHz) of poly (N-benzensulfonamide maleimide) (DMSO-d_6)

The presence of the -SO_2NH_2 group provides the polymer with a pH dependent solubility behavior. A qualitative analysis showed that the polymer is insoluble for pH values below 12 and becomes highly soluble at pH above 13 (Scheme 4.5).



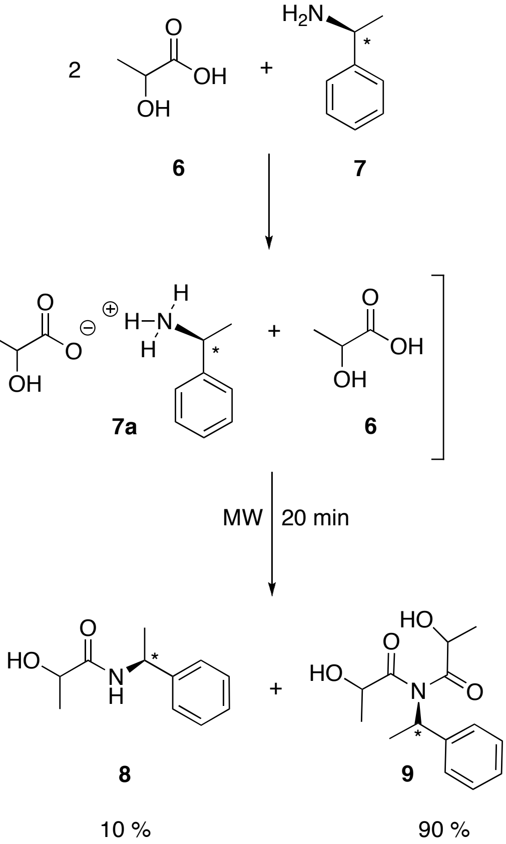
Scheme 4.5 pH-dependent solubility behavior of poly (N-benzensulfonamide maleimide).

Ritter et al. previously reported a similar behavior in a work concerning polymeric sulfonamides as potential carriers for antitumor agents.[13]

In conclusion, 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-benzensulfonamide (**3**) was synthesized by MW irradiation of a solid mixture of maleic anhydride and sulfanilamide. The one step reaction proceeded with good yield in only 2 min of reaction time. The oil-bath reaction, investigated as comparison, resulted in lower yield even after 15 min. The polymerization of **3**, performed in MW under temperature control using benzopinacol as a free radical initiator, afforded in good yield pH-responsive polymers that could find applications in pharmaceutical areas, such as site-specific targeting, and sensors.

4.4 Synthesis of 2-hydroxy-*N*-(2-hydroxypropanoyl)-*N*-(1-phenylethyl)propanamide

(2-hydroxy-*N*-(2-hydroxypropanoyl)-*N*-(1-phenylethyl)propanamide (**9**) was synthesized by MW irradiation of a stoichiometric mixture of lactic acid (**6**) and of the optically active (*R*)-*N*-(1-phenylethyl)amine (**7**) (Scheme 4.6).



Scheme 4.6 Microwave-assisted synthesis of **9**.

After 20 minutes of reaction time, the microwave-assisted reaction afforded the desired imide-containing diol (**9**) in 90 % yield. The reaction was performed in closed system under power control at an average maximum temperature of 150 °C (IR-pyrometer).

As comparison, the synthesis was also realized in a preheated oil-bath at a temperature of 170 °C. This temperature was evaluated as the closest (± 10 °C) to the real temperature inside the MW using the experimental setup already described (see § 2.2).

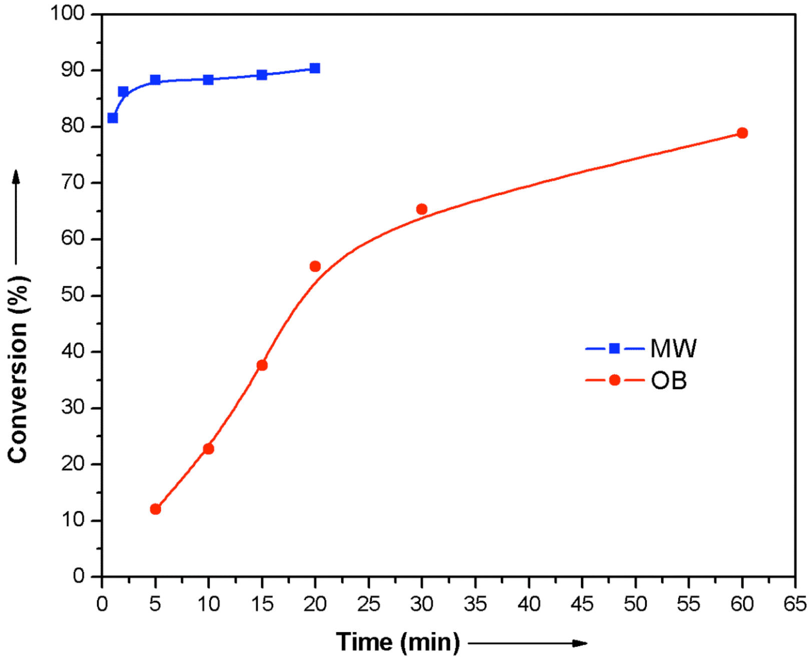


Figure 4.3 Comparative kinetic plots for the formation of **3** under MW irradiation (■) and in a preheated oil-bath (●). The plotted curves are only visual aids and not to be meant as fitting curves.

Kinetic analyses, obtained by GC/MS measurements, show the superiority of the MW-approach (Figure 4.3). The maximum conversion obtained in oil-bath was 75 % after a reaction time of 60 minutes.

As in the case of acrylamide and methacrylamide (§ 2), the acceleration obtained by MW irradiation could be rationalized considering that the acid-base reaction brings to the formation of the ammonium salt (**7a**) that strongly absorbs microwave energy. Missing in this case the possibility of a Michael-addition side reaction, the only possible products are the amide (**8**) and the imide (**9**). The amide is converted in imide through the condensation with the free lactic acid (**6**). The reaction is certainly enabled also by the high temperature reached.

The structure of the obtained product was confirmed by FT-IR (Figure 4.4) and ^{1}H-NMR (Figure 4.5).

The FT-IR spectrum showed a broad band centered at about 3400 cm^{-1} attributed to the stretching vibration of the hydroxy groups and the typical absorption peaks of imide at about 1727 and 1650 cm^{-1} assigned, respectively, to the symmetric and the asymmetric stretching vibration of the imidic carboxylic group.

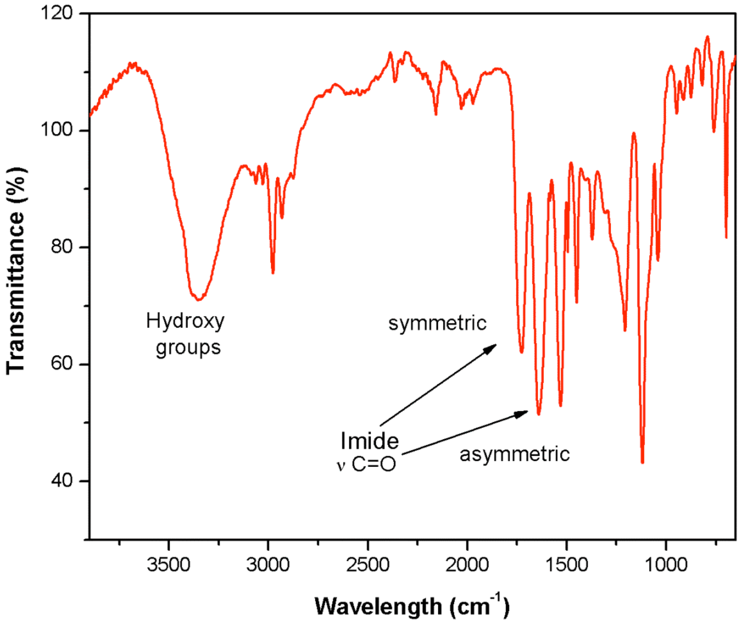


Figure 4.4 FT-IR spectrum of the imide-containing diol (**4**).

In the ^{1}H-NMR spectrum, the group of signals centered at 1.50 ppm was assigned to the methyl groups (a, a' and e, see Figure 4.5). The quartet at 4.36 ppm was attributed to the methylene groups (b and b') and the overlapped signal centered at about 5.14 ppm accounted for the hydroxy groups (c and c') and for the methyne group (d). The aromatic protons (f) could be detected at 7.35 ppm.

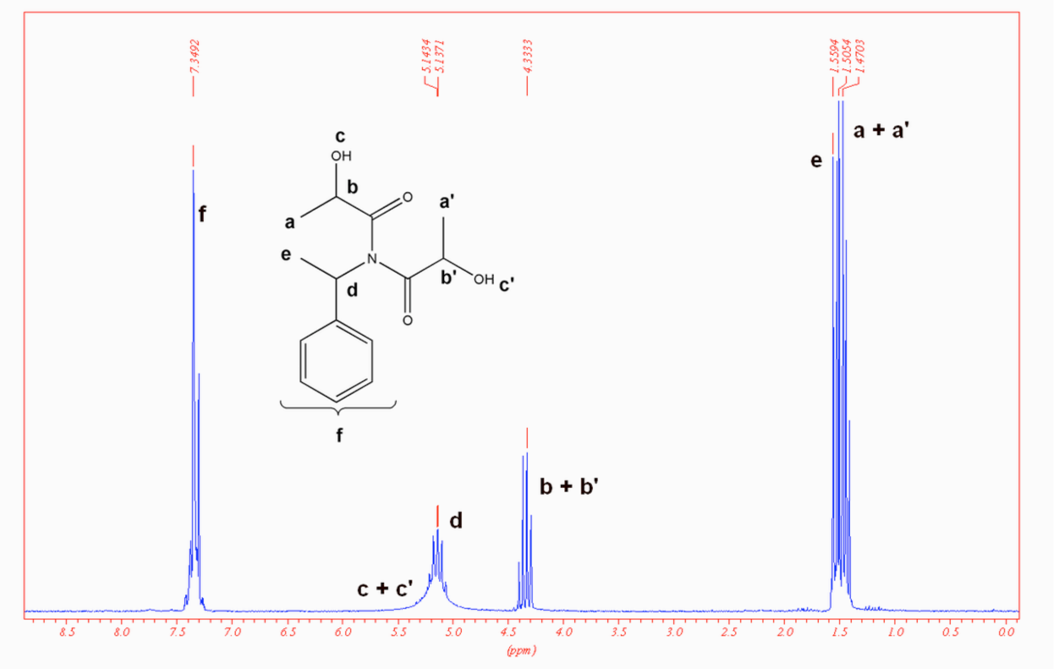


Figure 4.5 ^{1}H-NMR spectrum of the imide-containing diol (**4**) in $CDCl_3$

4.5 Experimental

All the reagents were commercially available. Maleic anhydride (Aldrich) was recrystallized from chloroform. Sulfanilamide (Fluka), lactic acid (Aldrich), (R)-*N*-1-phenylethylamine (Fluka) were used as received.

4.5.1 Synthesis of 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-benzensulfonamide (3).

0.45 g (4.6 mmol) of maleic anhydride (**1**) and 0.80 g (4.6 mmol) of sulfanilamide (**2**) were mixed in a pressure-resistant test tube and sealed with a septum. The sample was subjected to MW irradiation under power control for a total time of 120 sec. The preset MW power was 50 W with a maximum preset temperature of 200 ^{o}C. The maximum temperature reached was 100 ^{o}C (IR pyrometer). The obtained product was purified by Soxhlet extraction with ethanol and dried under vacuum. The yield, after purification, was 50 %.

For the reactions performed in oil-bath, an equimolar mixture of the reagents (**1** and **2**) was heated up for 15 minutes in a preheated oil-bath at a temperature that allowed to have 100, 130, 150 and 170 °C inside the reaction vessel. The products were purified as reported above and characterized as follow.

FT-IR (diamond): 3362 ($\nu_{N\text{-}H}$ *asymm.*), 3265 ($\nu_{N\text{-}H}$ *symm.*), 1782 ($\nu_{C=O}$ *asymm.*), 1720 ($\nu_{C=O}$ *symm.*), 1303 ($\nu_{O=S=O}$ *asymm.*), 1156 ($\nu_{O=S=O}$ *symm.*) cm^{-1}; ^{1}H-NMR (500.13 MHz, $(CD_3)_2SO$): δ = 7.94, 7.91, 7.57, 7.54 (*Arom*), 7.24 (s, -CH=CH-), 7.46 (s, $-NH_2$) ppm; ^{13}C-NMR (125.77 MHz, $(CD_3)_2SO$): δ = 126.74, 127.12, 134.81, 135.27 (*Arom*), 143.24 (*Vinyl*), 169.90 (Carbonyl) ppm.

Elemental analysis: $C_{10}H_8N_2O_4S$	Calc.	C 47.61	H 3.17	N 11.11
	Found	C 46.52	H 3.40	N 11.25

4.5.2 Polymerization of 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-benzensulfonamide (3).

2.05 g (8.13 mmol) of **3** and 0,15 g of benzopinacol (5.0 mol% in respect to the monomer) in 10 ml DMF were charged in a polymerization vial and purged with argon for 20 minutes. The solution was then subjected for 120 min to MW irradiation under temperature control with a preset power of 80 W and a maximum temperature of 100 ^{o}C (fiber optic). The crude product was purified by precipitation in boiling isopropanol from DMF solution and dried under vacuum. The yield was 62 %. FT-IR (diamond): 3358 ($\nu_{N\text{-}H}$ *symm.*), 3269 ($\nu_{N\text{-}H}$ *symm.*), 1784 ($\nu_{C=O}$ *symm.*), 1706 ($\nu_{C=O}$ *asymm.*), 1332 ($\nu_{O=S=O}$ *symm.*), 1158 ($\nu_{O=S=O}$ *asymm.*) cm^{-1}; ^{1}H-NMR (500.13 MHz, $(CD_3)_2SO$): δ = 7.98 ($-SO_2NH_2$), 7.51 (-N-*Arom*), 3.40 (*Aliphatic*) ppm.

4.5.3 Synthesis of 2-hydroxy-*N*-(2-hydroxypropanoyl)-*N*-(1-phenylethyl)propanamide (9).

1.48 g (16 mmol) of lactic acid (**7**) and 1 g (8 mmol) of (R)-*N*-1-phenylethylamine (**8**) were mixed in a pressure-resistant test tube and sealed with a septum. The sample was subjected to MW irradiation (100 W) under power control for a total time of 20 min reaching a maximum temperature (IR-pyrometer) of 150 ^{o}C. The raw mixture was purified by flash chromatography (SiO_2 gel, acetone/hexane 1:1) yielding 2.23 g (90 %) of the desired diol (**9**).

For the reaction performed in oil-bath, a stoichiometric mixture of the reagents (**7** and **8**) was heated up in a sealed test tube for a time up to 60 minutes in a preheated oil-bath at a temperature that allowed to have 170 °C inside the reaction vessel.

FT-IR (diamond): 3410 ($\nu_{O\text{-}H}$), 1727 ($\nu_{C=O}$ *symm.*), 1650 ($\nu_{C=O}$ *asymm.*), 1531, 1119 cm^{-1};

^{1}H-NMR (200 MHz, ($CDCl_3$)): δ = 7.35 (5H, Arom), 5.14 (3H, -OH, -NCH-Arom), 4.36 (2H, CH_3-C*H*-OH), 1.50 (6H, CH_3-CH-OH, CH_3-CH-NC=O) ppm.

4.6 References

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5 Free Radical Polymerization

5.1 Introduction and Literature Survey

Free radical polymerization is a widely used technique in industry for the production of numerous bulk materials, for example, polystyrene and poly(methyl methacrylate). The main drawback of this technique is the poor control of the molecular weights and polydispersity indices. Therefore, controlled free radical techniques have been introduced during the last decades, the most successful being nitroxide-mediated polymerization (NMP),[1] atom transfer radical polymerization (ATRP),[2,3] and reversible addition-fragmentation chain-transfer polymerization (RAFT).[4,5]

Gourdenne et al. initially investigated the microwave-assisted free radical polymerization of an unsaturated polyester with styrene.[6] A later contribution reported the bulk homo polymerization of hydroxyethylmethacrylate (HEMA).[7] Since HEMA bears ester as well as alcohol functions, it is a polar species capable of interacting and absorbing microwaves. Therefore, the reactions were carried out without any radical initiator, and the liquid monomer polymerized to form a solid material demonstrating that the radical polymerization could be achieved by microwave irradiation of neat reagents. In a similar example, Palacios et al. showed that in the case of bulk copolymerization of HEMA with methyl methacrylate (MMA), microwave-assisted polymerizations gave copolymers with molecular weight twice as high and of narrower molecular weight distribution in comparison with copolymers obtained under conventional thermal conditions.[8] Boey *et al.* [9,10] observed a strong auto acceleration of radical styrene and MMA polymerization under microwave conditions. These results are somehow not in agreement with recent findings of Greiner and co-workers on the same topic. The latter group investigated homo and copolymerization of styrene and MMA in toluene and N,N'-dimethylformamide (DMF) with different initiators, coming to the conclusions that only styrene in DMF showed a certain increased conversion in microwave.[11] It seems that no reports have already appeared on the free radical polymerization of pairs of reactive monomers (acid-base) that, due to salt formation, could be expected to show improved conversion in microwave compared to classical thermal heating.

5.2 Polymerization of Acrylic Monomers

Methylmethacrylate (MMA), methacrylic acid (MA), dimethylaminoethylmethacrylate (DMAEM) and zinc methacrylate (ZMA) (Figure 5.1) were polymerized in a 3,5 M tetrahydrofuran (THF) solution using AIBN (0,5 mol %) as a free radical initiator for 15 minutes.

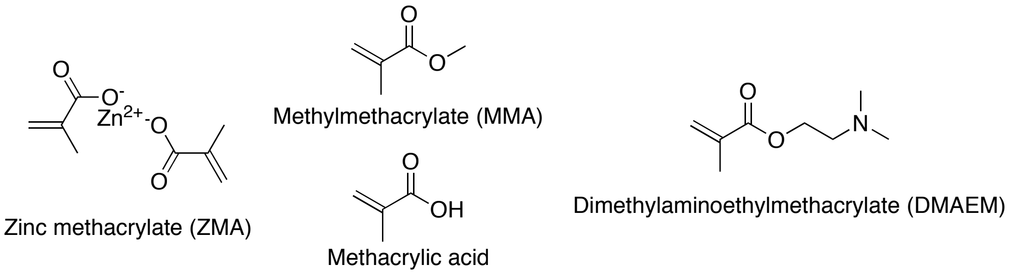

Figure 5.1 Monomers used in the polymerization experiments.

The polymerizations were realized in closed vials under an inert argon atmosphere. Being aware of the problems concerning temperature measurements in MW, especially in closed systems, and knowing that the temperature showed by the infrared pyrometer equipped with the microwave reactor lacks in accuracy, the reactions in oil-bath were performed at an opportune temperature that allowed to reproduce the same pressure (± 0.2 bar) observed for the microwave runs. It is in fact reasonable to think that, at least on a first approximation, two molecular systems that show the same pressure also have the same temperature.

A series of preliminary experiments (homopolymerization and copolymerization) were performed, under MW irradiation, and as comparison in oil-bath, with the aim to evaluate the microwave influence, if any, on the monomer conversion (Table 1).

In the case of the homopolymerization of MMA (**P1MW** and **P1OB**) no real differences could be observed (Table 5.1). Being MMA a monomer with a relative low polarity and lacking of molecular group that could efficiently couple with the microwaves, this result was not unexpected and confirms the need of molecular antennas (susceptors) to observe any kind of MW effects (thermal or athermal). That becomes even more important in a free radical polymerization reaction where no polar intermediates are expected to be involved in the propagation mechanism.

The conversion for the copolymerization of MA and DMAEM showed a remarkable MW applied power dependence increasing from 40 % (**P2MW,** 200 W) to 50 % (**P3MW**, 100 W) up to 80 % (**P4MW**, 50W) with decreasing power (Table 5.1).

Table 5.1 Conditions of polymerization and conversion of the prepared polymers.

Polymer	**Monomeric system** [a)]	**Power (W)**	**Temperature** [b)] **(°C)**	**Pressure** [c)] **(bar)**	**Conversion** [d)] **(%)**
P1MW	MMA	200	117	3.1	31
P1OB	MMA	-	130	3.1	32
P2MW	MA/DMAEM	200	140	4.6	40
P2OB	MA/DMAEM	-	156	4.6	60
P3MW	MA/DMAEM	100	140	4.6	50
P4MW	MA/DMAEM	50	130	4.2	80
P4OB	MA/DMAEM	-	148	4.2	55
P5MW	ZMA	200	135	2.8	62
P5OB	ZMA	-	140	2.8	63

a) For all the copolymerizations the monomeric feed ratio was 1:1.
b) In the case of the MW runs is the temperature showed by the IR-pyrometer. In the case of the oil-bath runs is the oil temperature.
c) Average pressure ± 0.2 bar.
d) Average gravimetric conversion on three experiments after 15 min of reaction time.

The oil-bath comparisons showed a conversion of 60 % for the run at 4.6 bar (**P2OB**) corresponding to the MW reactions at 200 and 100 W, and 55 % for that at 4.2 bar (**P4OB**) corresponding to the reaction at 50 W. In this case 4.2 bar was the maximum reachable pressure. The relative high conversion in oil-bath (compared to the case of MMA) could be explained assuming that the salt formation, producing molecular aggregates (ion pairs), has a positive influence on the propagation rate of the polymeric radicals. Being the polymerizable groups much closer one to each other, there should be a higher probability of effective collisions among the growing polymeric chains and the molecules of the monomers.

In the case of the MW runs, considering that the reaction between MA and DMAEM should result in a strong MW-absorbing medium (ammonium salt) that should enhance the reactivity by a more effective coupling with the microwaves, the lower conversion compared to the oil-bath, comes quite unexpected. A possible interpretation is that the microwaves could have an influence on the acid-base equilibrium. It should be assumed that, in the presence of an electromagnetic field, the proton exchange equilibrium and the relative strength of acid (MA) and base (DMAEM) is unlike that observed in standard conditions (absence of field).

In a microwave field there should be a lower amount of salified species resulting in a reaction medium with reduced MW-absorbing capacity and diminished concentration of ion pairs (Figure 5.2). Reducing the MW-power, the acid-base equilibrium should be shifted toward the salt (aggregates) formation resulting in a higher probability of effective collisions during the polymerization, these latter accountable for the improved conversion. As already mentioned, the reaction performed at 50 W (**P4MW**) yielded higher conversion in MW than in oil-bath (**P4OB**).

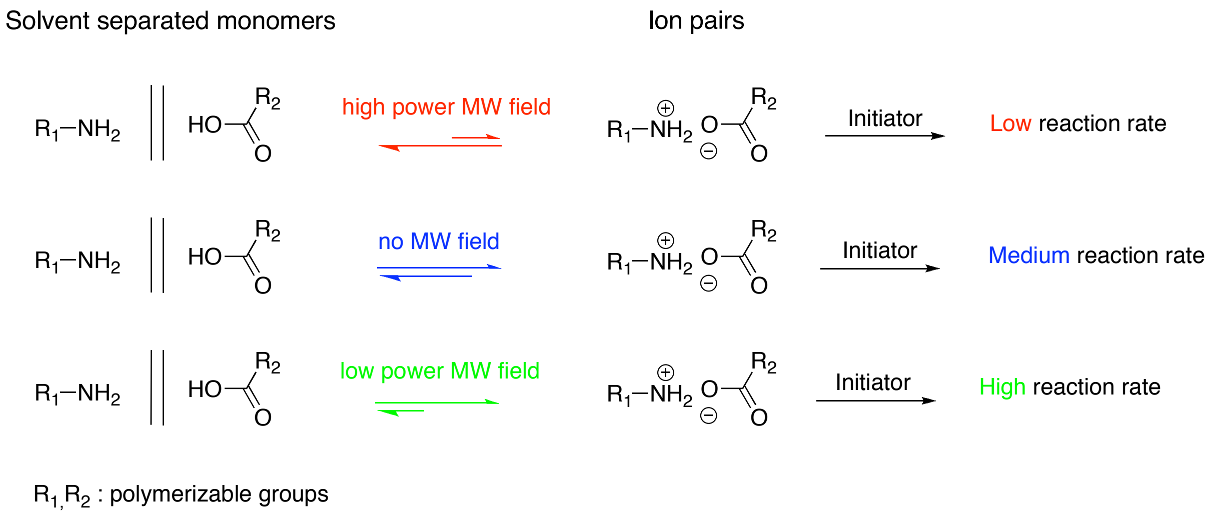

Figure 5.2 Hypothesized influence of a microwave field on the relative equilibrium position of a generic acid-base reaction.

The homopolymerization of ZMA did not show any significant difference between MW and conventional conditions. This result could be attributed to the fact that the salt is preformed and no proton exchange (acid-base equilibrium), which could be influenced by the electromagnetic field, occurs in the reaction medium. Instead, when proton exchange equilibrium (acid-base) occurs, as in the case of the copolymerization MA/DMAEM, the concentration of molecular aggregates (salt) should be function of the MW applied power. At high power (200 W, **P2MW**) there should be a lower concentration of aggregates (lower probability of effective collisions) than in standard conditions. That could explain the lower conversion in microwave than in oil-bath. At low power (50 W, **P4MW**) the behavior should be inverted having higher concentration of aggregates than in standard conditions resulting so in higher conversion in MW than in oil-bath (Figure 5.3).

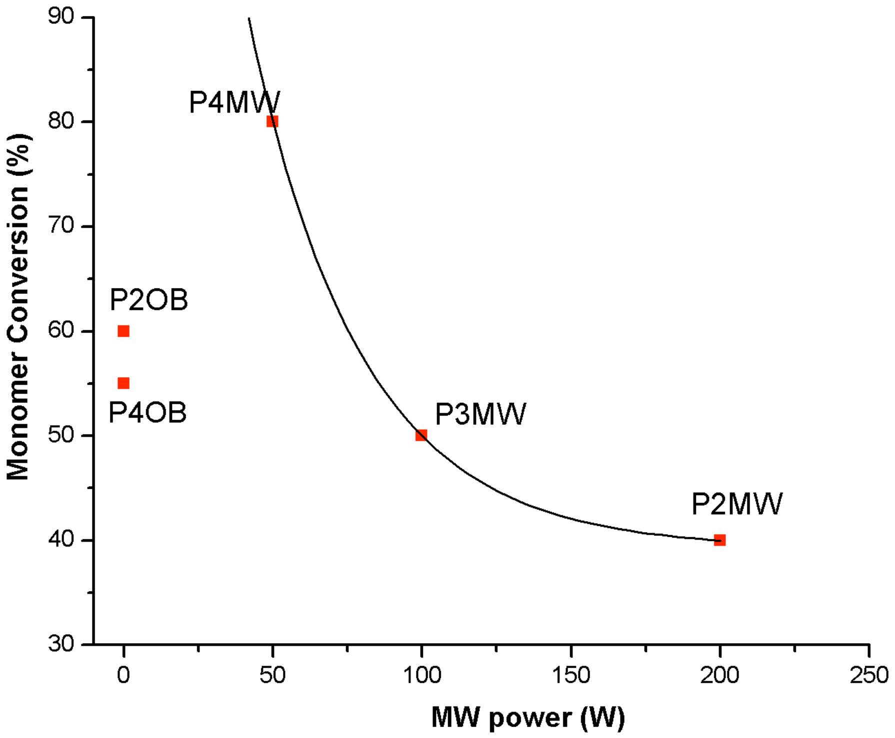

Figure 5.3 Monomer conversion versus MW power for the copolymers MA/DMAEM. Fitting curve: first order exponential decay.

From Figure 5.3 it is possible to argue that there should be an optimum (minimum) power that should maximize the ion pairs formation and hence strongly enhance the monomer conversion. The molecular structure of the prepared polymers was preliminarily confirmed by FT-IR analyses; anyway a complete characterization is still in due. More detailed investigations that also take in account other parameters, like for example solvent effects, monomer and initiator concentration, reaction temperature, have still to be performed for better clarify the proposed rationalization of the experimental results.

5.3 Experimental

All the monomers, methacrylic acid (Acros), dimethylaminoethylmethacrylate (Aldrich), methylmethacrylate (Degussa), zinc methacrylate (Aldrich) were commercially available and used as received. All the polymerizations were conducted under inert atmosphere obtained flushing the sample for 20 minutes with a stream of argon. The MW-experiments were performed under power control. In all the case 25 ml of a 3.5 M stock solution were prepared mixing together the opportune amount of monomer, initiator and solvent.
The detailed experimental procedure is reported for **P1MW** and **P1OB** as typical examples.

P1MW: 3 ml of the stock solution were transferred into a pressure resistant test tube provided of a stirring bar, sealed with a septum, flushed with argon for 20 minutes and irradiated for 15 minutes with a MW power of 200 W keeping an average pressure of 3.1 bar through opportune cooling within the cavity with compressed air. The raw reaction mixture was purified by precipitation in a large excess of cold diethyl ether from DMF solution. The polymer was recovered by vacuum filtration and dried under vacuum until constant weight. The yield, expressed as an average on three experiments, was 31 %.

P1OB: 3 ml of the stock solution were transferred into a pressure resistant test tube provided of a stirring bar, sealed with a septum, flushed with argon for 20 minutes and immersed in a preheated oil-bath at a temperature that allowed having an average pressure of 3.1 bar. The polymer was purified and isolated as reported for P1MW. The yield, expressed as an average on three experiments, was 32 %.

5.4 References

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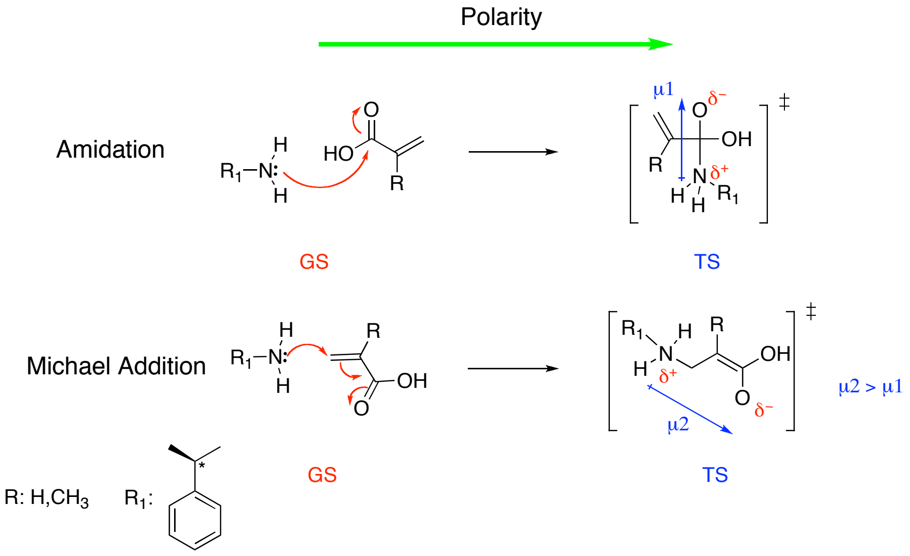
6 Conclusive Mechanistic Considerations

The experimental results presented in the previous chapters can be analyzed in terms of general mechanistic considerations.

The high selectivity in (meth)acrylamide formation (§ 2) can be related to the increasing polarity passing from the ground state (GS) (mixture of educts) to the transition state (TS) through the intermediate salt formation. A determining role is played by the reversibility of the Michael addition side-reaction. The Michael addition adduct has a more polar transition state than the amide one (larger charge separation), due to that, its formation results the most favorite pathway in microwave (Scheme 6.1).



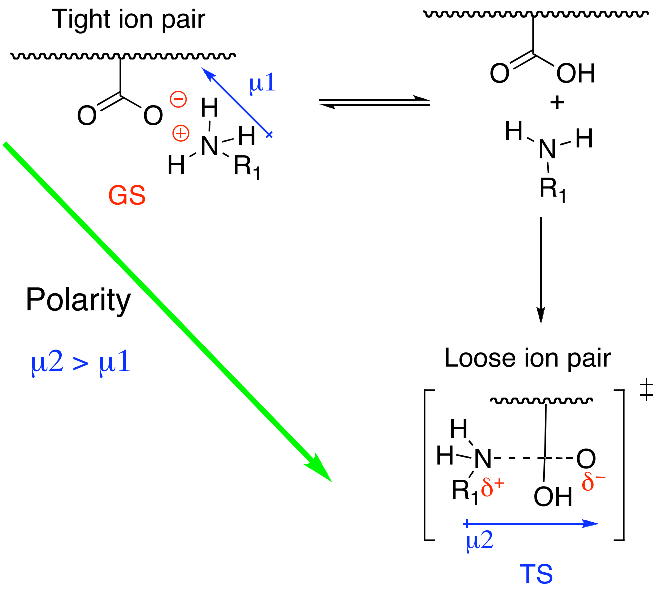
Scheme 6.1 Reaction mechanism and schematic comparison between the TS for amide formation and Michael addition reaction

Anyway its reversibility and the microwave absorbing capacity of its betaine structure selectively drive the reaction towards the amide formation.

The amidation of poly(ethylene-*co*-acrylic acid) (§ 3) can be ruled in the same way. Missing the possibility of the Michael addition side-reaction the amidation is favorite by the increase in polarity GS-TS.

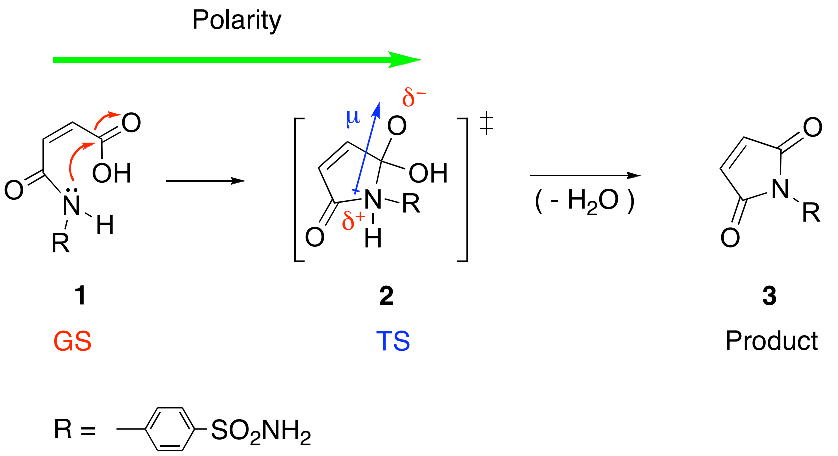
The specific reactivity enhancement observed in the case of the stronger bases has to be accounted considering that passing from GS to TS there is a transformation from tight ion pairs to more polar loose ion pairs.

Taking into consideration that the ion pairs obtained from the most basic amine are tighter than those obtained from the less basic one, the former shows higher reactivity than the latter.

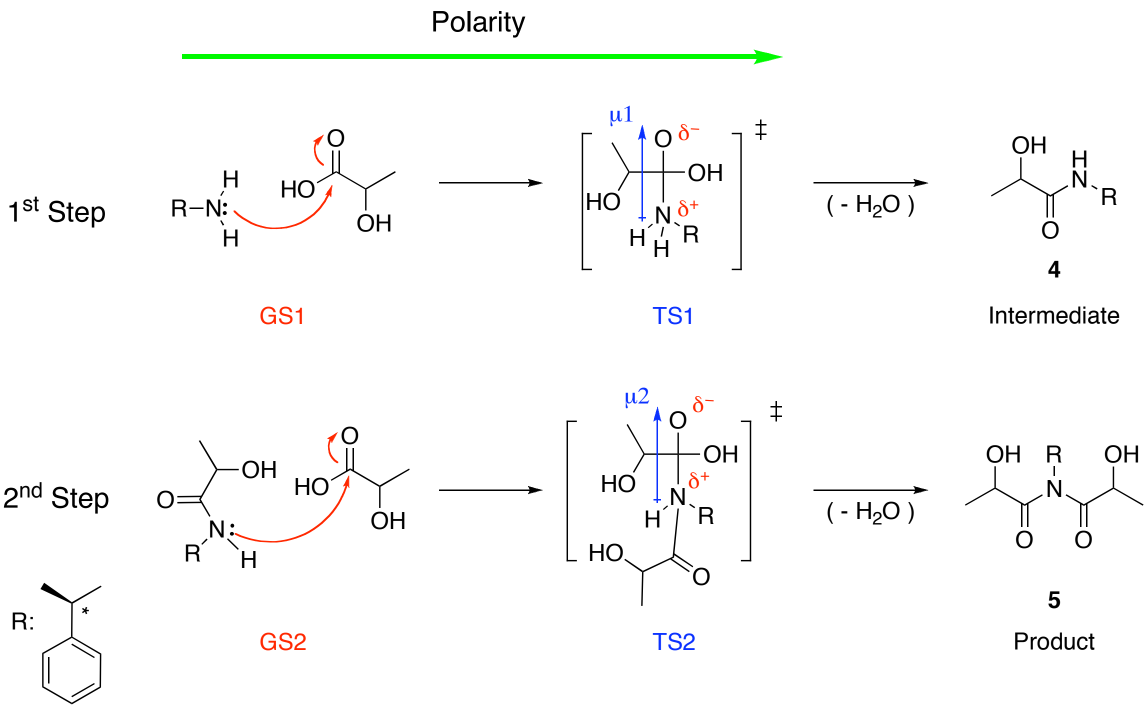


Scheme 6.2 Loosening of ion pair passing from GS to TS for the amidation of poly(ethylene-*co*-acrylic acid).

In the case of imide synthesis (§ 4), is still the increased polarity GS-TS accountable for the microwave acceleration. The unimolecular cyclization that brings the maleamic acid (**1**) to the N-substituted maleimide (**3**) passes, in fact, through a dipolar transition state (**2**) (Scheme 6.3).



Scheme 6.3 Reaction mechanism for the synthesis of **3** from maleamic acid.



Scheme 6.4 Two steps reaction mechanism for the synthesis of the imide-containing diol **5**.

The formation of the imide containing diol has to be rationalized as a one-pot two steps addition-elimination reaction. The first one leads to the amide (**4**) and the second to the imide (**5**) (Scheme 6.4). Both steps involve reactions between neutral reactants that lead to dipolar transition state.

The preliminary results obtained for the free radical polymerization of reactive (acid-base) monomers (§ 5) seem to show the possibility of strong athermal effects even in the case no polar transition states are involved. Microwaves are thought to interact on a molecular level with the forming ion pairs influencing the equilibrium constant of the proton exchange. The real nature of these interactions and the interaction mechanisms are still unknown. Theoretical studies should be performed to support the experimental evidences and to provide more accurate theories with stronger predictive capacity.

7 Experimental Notes

If not otherwise stated, all reagents were commercially available and used as received.

The solvents were distilled and, when the case, opportunely dried before use.

^{1}H-NMR and ^{13}C-NMR spectra were performed using a Brucker Advance DRX 500 spectrometer at 500.13 MHz for proton and 125.77 MHz for carbon, using $(CD_3)_2SO$ or $CDCl_3$ as solvents. The δ-scale relative to TMS was calibrated to the deuterium signal of the solvent as an internal standard. Infrared spectra were recorded on a Nicolet 5SXB FT-IR spectrometer.

Optical rotations were recorded on a Perkin-Elmer 241MC polarimeter using a sodium lamp as a light source.

Gel permeation chromatography (GPC) was performed on a GPC-system consisting of a Waters 486 tunable absorbance detector at 275 nm and a Waters 410 differential refractometer, using THF as eluent. The system was calibrated with polystyrene standards with a molecular weight range from 580 to 1 186 000 D. The flow rate was 1 mL·min^{-1}. 100 µL of a 0.125% (wt./wt.) polymer solution was given to a HEMA-column-combination consisting of a pre-column of 40 Å and main columns of 40, 100, and 300 Å porosities.

GPC was also performed on a GPC-system consisting of a Viscotek VE 3580 differential refractometer and a Viscotek viscometer model 250, using DMF as eluent. The system was calibrated with polystyrene standards with a molecular weight ranging from 580 to 1 186 000 D. The flow rate was 1 mL·min^{-1}. 100 µL of a 0.125% (wt./wt.) polymer solution was given to a SDVB based ViscoGEL column-combination consisting of a pre-column HHR-H and two main columns GMHHR-M.

Glass transition temperatures (T_g) were determined using a Mettler Toledo TC15 TA Controller apparatus at a heating rate of 10 ºC per minute. The T_g values are reported as the average of three measurements using the midpoint method. The same instrument was also used to perform the syntheses in normal thermal heating conditions (§ 2).

A monomode microwave reactor (CEM-Discover) operating at a maximum power of 300 W equipped with an infrared pyrometer and a fiber optic contact thermometer was used.

The calibration curve of the infrared pyrometer was built using a digital thermometer Heidolph EKT 3001.

The kinetic measurements were performed using a Thermo Electron Trace DSQ instrument of a GC-MS system.

Acknowledgements

I thank the Lord, God-Almighty, for being always with me all over my life.

I wish to thank my supervisor Prof. Dr. H. Ritter for giving me the opportunity to work on a fascinating topic and for sharing with me successes and failures. I am gratefull to him for his positivity and enthusiasm that always prompted our joint quest for "specific microwave effects". It has been a real pleasure to meet him, to be part of his research group, and to come to know him as a chief, as a coworker and, last but not least, as a friend.

Many thanks to Frau Tabatabai for her continuous support and her constant availability and for always inciting me in learning german. On this point I should have listened to her more often.

Special thanks to Ella for many things that is not possible to express simply by words.

Special thanks to my friends and labmates Alenka, Heike, Jenz and Valentina for all the times they helped me in trying to understand chemistry, life and Germany!

I cannot forget Matthias that first inspired in my mind the idea to come to Germany for Ph.D. and to have fun with chemistry. Marion and him first, Noelle and Patrick afterwards, have been my very first guide in this country with their support and their friendship. Many thanks.

Thanks a lot to Mahesh, one of the best persons I have ever met in my life. He has been a real friend in every circumstance. I wish to get very soon the pleasure to call him " Herr Doktor ".

Thanks to Sandeep for being a special friend and a special housemate. I will never forget the efforts we made and the fun we got in renovating our actual apartament.

Last but not least, I am very grateful to the all AK Ritter, AK Schmidt and to all my friends. Spending three years in Germany has been a valid experience for my growth as a chemist and as a person. Each of them have contributed to this development with the little and big things of the everyday life.
Vielen Danke!!

Die hier vorgelegte Dissertation habe ich eigenständig und ohne unerlaubte Hilfe angefertigt. Die Dissertation wurde in der vorgelegten oder in ähnlicher Form noch bei keiner anderen Institution eingereicht. Ich habe bisher keine erfolglosen Promotionsversuche unternommen.

Düsseldorf, den 06.12.2006