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Synthesis and characterization of a new chiral functional polymer

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Abstract

Recently, we have reported the synthesis and ring-opening metathesis polymerization of enantiomerically pure and racemic methyl-*N*-(1-phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate. In this paper, we present a new optically active 2-azanorbornene derivative that undergoes ring-opening metathesis polymerization in the presence of molybdenum alkylidene initiators of the type Mo(CH-*t*-Bu) (NAr)(OR_2). Enantiomerically pure (1-phenylethyl)-*N*-(1-phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxamide **1** can be obtained through an asymmetric Lewis-acid-catalyzed Diels–Alder reaction of cyclopentadiene with the corresponding imine of the glyoxylic amide. Ring-opening metathesis polymerization of **1** leads to the polymers, **2a** and **2b**, which are investigated by traditional methods such as GPC, DSC (differential scanning calorimetry) and polarimetry, as well as by ESI (electrospray ionisation)-MS (mass spectroscopy), a method that has been shown to reveal valuable information about polymer structure and end groups.

Keywords: Ring-opening metathesis polymerization (ROMP); Chiral polymer; Electrospray ionisation (ESI); Mass spectrometry; Asymmetric Diels–Alder; Heterocyclic norbornene

1. Introduction

Recent trends in technology have raised the interest in new polymeric materials. There is a rapidly increasing demand for highly functionalized polymers that can offer unique properties for special applications in various fields such as electronics or analytical chemistry [1,2]. However, the use of catalytic polymerization methods in the synthesis of such polymers is limited by the tolerance of the catalytic system towards the desired functionality.

In addition to chemical functionalities, special stereochemical features have gained increasing importance. Amongst polymers with well-defined stereoregularity (tacticity), chiral polymers have high theoretical and technological interest. Such molecules can offer insight to the mechanism of polymerization, especially in cases where prochiral compounds or pure enantiomers are used as monomers [3]. Additionally, polymers with chiral pendant groups are used in different applications, e.g., for chiral separations [2].

Living ring-opening metathesis polymerization (ROMP) employing well-defined metal alkylidene catalysts has been shown to be a suitable method for the preparation of various polymers [4]. Especially Schrock's molybdenum alkylidene catalysts Mo(CH-*t*-Bu) (NAr) (OR_2)

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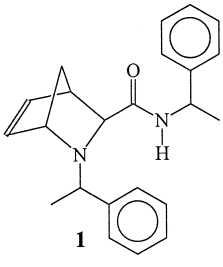
[5,6] and Grubbs' ruthenium carbenes Cl_2-Ru(CH=CPh$_2$) (PCy$_3$)$_2$ and Cl_2Ru(CH-Ph) (PCy$_3$)$_2$ [7,8] have successfully been employed in the polymerization of highly functionalized cyclic olefins, as well as in the condensation of diolefins via acyclic diene metathesis (ADMET) [9,10] and ring-closing reactions [11]. Since the development of these well-defined transition metal complexes [12], even monomers containing nitrogen in the cyclic system are accessible for ROMP [13,14]. However, the nitrogen has to be sterically hindered to prohibit complexation with the catalyst, causing deactivation [13].

Previous studies on the polymerization of racemic and enantiomerically pure methyl-*N*-(1-phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate have again shown the versatility of the molybdenum alkylidene catalysts in ROMP, e.g., in terms of stereoselectivity [14].

In this, work we present a new functionalized and chiral monomer containing an amine and an amide functionality. (1-Phenylethyl)-*N*-(1-phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxamide **1** was polymerized with molybdenum alkylidene catalysts to give polymer **2**.

Both monomer **1** and polymer **2** were characterized by standard methods including ESI-MS.



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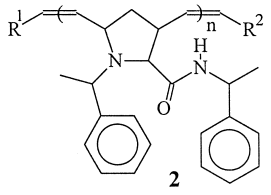

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2. Experimental

All chemicals were used as purchased. All solvents were purified using standard methods [15]. All polymerizations were carried out in a dry box under nitrogen at room temperature. As a general procedure, monomer **1** and catalyst were dissolved separately in dry chlorobenzene or benzene-d_6 (for NMR control), then the solutions were united in a vial or NMR tube. NMR spectra were recorded on a Varian Gemini 200 MHz spectrometer. Gel permeation chromatography was carried out in THF using an HPLC system equipped with a Merck-Hitachi L6200 pump, a Viscotek Model 200 differential refractive viscometer, 100 μl injection loop, and three columns (5 μm SDV gels from PSS with 10^6, 10^4 and 10^3 Å pore width). Molecular weight and polydispersities were reported vs. polystyrene standards. Differential scanning calorimetry data were recorded on a STA 625 from Polymer Laboratories.

Optical rotations were determined with a Perkin Elmer Polarimeter Model 341 with chloroform as solvent.

A detailed description of the ESI-MS equipment can be found in previous paper [9].

2.1. Monomer synthesis

2.1.1. (2R, 3R)-Dimethyl-di-O-isopropylidene tartrate (4)

Twenty grams (112.2 mmol) of (2*R*, 3*R*) dimethyltartrate **3** and 14 g (134 mmol) of 2,2-dimethoxypropane were dissolved in 200 ml of toluene. Fifteen milligrams of *p*-toluenesulfonic acid were added and the mixture was refluxed for 4 h using a Soxhlet extractor filled with 10 g Å^3 and 30 g Å^4 molecular sieves to remove water and evolving methanol from the reaction. After cooling to room temperature, the *p*-toluenesulfonic acid was neutralized by addition of K_2CO_3. The liquid phase was decanted, toluene evaporated and the remaining oil was dissolved in 200 ml diethyl ether. The organic phase was extracted with 100 ml saturated $NaHCO_3$ solution, 100 ml water and 100 ml saturated NaCl solution. The ether was evaporated and the product was purified by a vacuum distillation, yielding 14.80 g of compound **4** (60.4%).

^{1}H-NMR ($CDCl_3$) δ: 4.73 ppm (2H, s, H-2, H-3), 3.82 ppm (6H, s, CH_3–O), 2.73 ppm (6H, s, CH_3–C–O).

*2.1.2. (2R, 3R)-Bis-[(R)-N-(1-phenylethyl)]-2,3-di-O-isopropylidene tartaric amide (**5**)*

Six grams (27.5 mmol) of compound **4** and 9.12 g (75.3 mmol) *R*-(+)-1-phenylethylamine are stirred together with 6 g Å^4 molecular sieves and 20 mg of *p*-toluenesulfonic acid at 40°C. After 48 h, the mixture was diluted with 300 ml dichloromethane and filtered through silica gel. The solvent was evaporated and the residue was recrystallized from diethyl ether. Yield: 4.89 g (45%).

^{1}H-NMR ($CDCl_3$) δ: 7.34 ppm (10H, s, aromatic), 5.17 ppm (2H, m, H–C–NH), 4.55 ppm (2H, s, H-2, H-3), 1.53 ppm (6H, d, CH_3–C–NH), 1.49 ppm (6H, s, CH_3–C–O).

*2.1.3. (2R, 3R)-Bis-[(R)-N-(1-phenylethyl)] tartaric amide (**6**)*

An amount of 4.20 g (10.6 mmol) of compound **5** were stirred with 12 g of strongly acidic ion exchanger (Amberlite 1R-120, Merck) in a mixture of 50 ml water, 50 ml methanol and 6 ml conc. HCl at 40°C–50°C for 72 h. Afterwards, the mixture was neutralized with $NaHCO_3$ and the solution volume was reduced to approximately 20 ml. The residue was diluted with 100 ml water and extracted with 100 ml dichloromethane. After washing the organic phase with 50 ml H_2O, the dichloromethane was evaporated. The product was a white, amorphous material. Yield: 3.63 g (96%).

^{1}H-NMR ($CDCl_3$) δ: 7.32 ppm (10H, s, aromatic), 5.07 ppm (2H, m, H–C–NH), 4.23 ppm (2H, s, H-2, H-3), 1.53 ppm (6H, d, CH_3–C–NH).

*2.1.4. Bis-[(R)-N-(1-phenylethyl)]glyoxylic amide (**7**)*

An amount of 3.00 g (8.4 mmol) of amide **6** were suspended in 90 ml toluene. Then 3.87 g (8.73 mmol) $Pb(OAc)_4$ were added in small portions. After 1 h, a precipitate of $Pb(OAc)_2$ had formed, which was removed by filtration. The organic phase was extracted with 100 ml of 10% acetic acid in water, water and saturated $NaHCO_3$ solution. The aqueous phase was saturated with NaCl and extracted two times with each 100 ml ethylacetate. The solvent was evaporated, giving 1.2 g (40.0%) of amorphous product **7** which still contained traces of acetic acid.

^{1}H-NMR ($CDCl_3$) δ: 9.23 ppm (s, H–C=O), 8.88 ppm (m, ev. $(HO)_2C$), 7.33 ppm (5H, m, aromatic), 5.16 ppm (1H, m, H–C(CH_3)(Ph)(NH)), 4.12 ppm + 1.26 ppm (impurity: acetic acid), 1.56 ppm (3H, d, CH_3–C–NH).

*2.1.5. (1′R, 1S, 3S, 4R, 8R)-(1′-phenylethyl) -N-(1-phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxamide (**1**)*

An amount of 1.00 g (5.6 mmol) of amide **7** and 0.68 g (5.6 mmol) of (*R*)-1-phenylethylamine were dissolved in 25 ml dichloromethane and stirred for 12 h after addition of 2.5 g Å^3 molecular sieves. The mixture was cooled to −50°C. An amount of 0.64 g (5.6 mmol) trifluoroacetic acid in 5 ml dichloromethane and 0.80 g (5.6 mmol) borontrifluoride etherate also dissolved in 5 ml dichloromethane were added during 15 min. After another 30 min 0.58 g (8.4 mmol) freshly cracked cyclopentadiene in 5 ml dichloromethane were added. The mixture was stirred at −50°C for 6 h, then poured into a saturated solution of $NaHCO_3$ and extracted with dichloromethane. The organic phase was dried over Na_2SO_4, the solvent was evaporated and the residue was purified by flash chromatography. The crystallization from petroleum ether yielded 0.62 g (32%) white, crystalline monomer **1**.

^{1}H-NMR ($CDCl_3$) δ: 7.40 ppm (10H, m, aromatics), 6.55 ppm (1H, m, H-5), 6.25 ppm (1H, m, H-6), 4.80 ppm (1H, m, CH_3–CH–NHCO), 4.20 ppm (1H, s, H-1), 3.18 ppm (1H, s, H-4), 3.05 ppm (1H, qua, CH_3–CH–NR_2), 2.42 ppm (1H, s, H-3), 1.60–1.30 ppm (2H, m,

H-$7_{syn+anti}$), 1.45 ppm (3H, d, CH_3–CH–NR_2), 1.12 ppm (3H, d, CH_3–CH–NHCO).

^{13}C-NMR ($CDCl_3$) δ: 172.9 ppm (CONH); 144.5 ppm, 143.3 ppm (C_{ipso},); 137.1 ppm (C-6), 133.3 ppm (C-5); 129–126 ppm (aromatics); 65.4 ppm (C-3); 63.8 ppm (CH_3–C–NR_2); 63.0 ppm (C-1); 49.5 ppm (C-4); 48.5 ppm (CH_3–C–NHCO); 45.2 ppm (C-7); 23.6 ppm, 22.0 ppm (CH_3).

2.2. Polymerizations

All polymerizations were performed in a dry box under nitrogen atmosphere in dry solvents.

In polymer **2a**, 100 mg (0.289 mmol) of monomer **1** were dissolved in 1.5 ml dry chlorobenzene. An amount of 254 μl of a solution of catalyst **I** in dry chlorobenzene (1 mg **I** in 100 μl chlorobenzene) were added. After 24 h, the reaction was stopped by addition of 20 mg benzaldehyde (the samples for ESI-MS were quenched with acetone), the polymer was precipitated twice from petroleum ether and dried in vacuo.

Polymer **2b** was prepared according to the procedure described above. Catalyst **II** was used instead of catalyst **I**.

2.2.1. Preparation of the sample for the ESI-MS investigation

A solution of 20 mg (0.058 mmol) of monomer **1** in 400 μl benzene-d6 was added to a solution of 8.1 mg (0.012 mmol) **I** in 200 μl benzene-d_6 in an NMR tube. The conversion of the monomer was controlled through ^{1}H-NMR observing the intensities of the olefinic signals of the monomer and the newly formed oligomers. After 5 min, **1** was fully consumed; after 7 min, the reaction was quenched with 100 μl acetone and the polymer was precipitated from *n*-hexane.

MS: M^+ 346 Da, M^+—cyclopentadiene 280 Da, M + —amide group 198 Da, phenylethyl$^+$ 105 Da, cyclopentadiene$^+$ 66 Da.

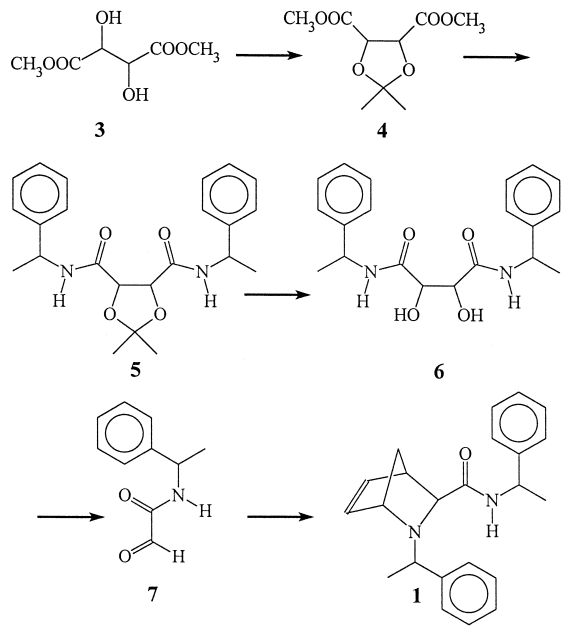
3. Results and discussion

3.1. Monomer synthesis and polymerization

Monomer 1 was synthesized according to Scheme 1.

This path allows the synthesis of monomer **1** with acceptable yields. Experiments to achieve **1** by the modification of methyl-*N*-(1-phenylethyl)-2-azabicyclo[2.2.1]-hept-5-ene-3-carboxylate were not successful so far.

The hydroxy groups of dimethyl tartrate **3** were protected with dimethoxy propane, giving acetal **4**. The following amidation to obtain compound **5** could be performed without solvent and at higher temperature (50°C). Cleavage of the acetal group in **5** gave diol **6**, which was treated with lead(IV) acetate to give the free glyoxylic amide **7**. The conversion of compound **6** to **7** is the most challenging step during the preparation of monomer **1**. The high solubility of **1** in water complicates the isolation. Saturation of the aqueous phase with NaCl was necessary to transfer **7** into the organic phase during the work-up. Compound **7** was treated in



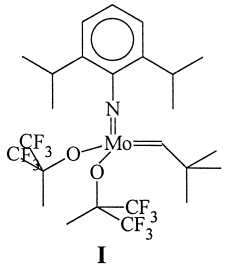
Scheme 1. Synthesis of monomer **1**.

a single-step reaction with (*R*)-phenylethylamine, trifluoroacetic acid, boron trifluoride etherate and cyclopentadiene to give monomer **1** according to a Lewis-acid-catalyzed asymmetric Diels–Alder reaction [16].

Both catalysts **I** and **II** were used for the polymerization of monomer **1**. The reaction times of the polymerizations were usually 24 h, the reaction time for the samples prepared for the ESI-MS experiment was 7 min. This time was considered to be sufficient for the relatively low number of turnovers required for full consumption of the monomer and to ensure the formation of low-molecular-weight polymers, which are preferable over polymers with high molecular weight for the investigation by ESI-MS.

However, we expected it to be still short enough to prevent the formation of side products, which could appear in the ESI-MS spectra.

To isolate polymer **2** by precipitation, we chose petroleum ether rather than methanol, because **2** was found to form suspensions in methanol, especially when the degree of polymerization was low.



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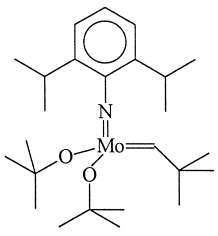


II

The conversion of monomer **1** with the catalysts **I** or **II** (24 h) gave the polymers **2a** and **2b**, respectively. After the precipitation, the molecular masses, M_n (obtained by GPC, calibration vs. polystyrene), were determined to be 18 000 and 13 700, respectively.

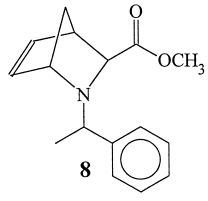
3.2. Polymer characterization

The DSC of both polymers **2a** and **2b** showed a T_g at approximately 107°C, with no further transitions observed except for decompositions beginning at 260°C.

Measurement of the optical rotation $[\alpha]_{20}^{D}$ gave a value of $-148°$ ($c = 0.785$, toluene) for 1 and $+87.4°$ ($c = 0.453$, $CHCl_3$) and $+92.7°$ ($c = 0.605$, $CHCl_3$) for **2a** and **2b**, respectively.

The chemical structure of the end groups, R^1 and R^2, of polymer **2a** was determined by electrospray ionisation mass spectrometry (ESI-MS).

Previously, we reported our results on the investigation of polymer **9**, resulting from the polymerization of enantiomerically pure methyl-*N*-(1-phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate **8** [12] employing various molybdenum alkylidene catalysts. We expected the chemical environment of the active species during the polymerization of our new monomer **1** to be comparable to the polymerization of monomer **8** due to the similar structure of these norbornene derivatives. Therefore, it should also be possible to compare the resulting polymers with respect to their structures.



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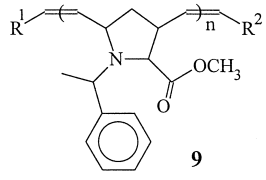


9

Living ring-opening metathesis polymerization leads to polymers of the general structure $R^1M_nR^2$, with M being the repeating unit and *n* the degree of polymerization. The end groups, R^1 and R^2, result from the initiation step, which is the insertion of the first monomer in the molybdenum alkylidene complex, on the one hand and from quenching reactions on the other hand. The regioselectivity of the insertion of the monomer into the alkylidene species has not been determined yet. As a result, R^1 and R^2 have not been unequivocally assigned to date.

Group **A** is the neopentylidene group from the catalyst, which is connected to the first

inserted monomer in the initiation step. The groups **B** and **C** are products of the reaction of the active species with acetone and water, respectively (a solvent mixture acetone/water = 99/1 was used in that case for the termination of the polymerization reaction). Furthermore, we found group **D** (Scheme 2), which is typical for intramolecular reactions of the active species with ester groups.

To obtain an oligomer sample of polymer **2a** for the ESI-MS investigation, the monomer **1** was converted by catalyst **I** at a ratio of 1/**I** = 5/1 in benzene-d_6. After full conversion of the monomer, the reaction was quenched with acetone to achieve oligomers with defined end groups (concentration calculated on monomer **1** approximately 1 mmol/l). After the complete decomposition of the active species, the polymer was precipitated in *n*-hexane and dissolved in a mixture of acetone and water (ratio acetone/water = 99/1), to create a media that would allow a sufficient ionisation in the subsequent ESI-MS. The results of the ESI-MS investigations are shown in Fig. 1.

All important peaks of the ESI mass spectrum correspond to protonated oligomers with one end group **A** and one group **B**, respectively. No side reactions, such as reactions of the active species with amide groups, were detected.

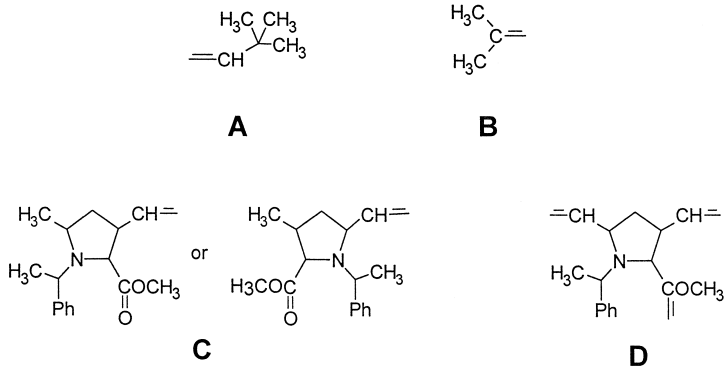
During the investigation of **9**, we found that the initiation step was much slower than the propagation. The ratio of the velocity constants for these reactions was found to be $k_p/k_i \approx 50$ in the case of initiator **I** and ≈ 2 with initiator **II**. These results explain the comparatively high degrees of polymerization that were achieved in oligomerization reactions at low ratios of monomer to initiator.

Since the active species formed in the course of the polymerization of **8** was much more active than the initial catalyst, it was not surprising that in the ESI-MS spectrum of a similar oligomer sample of **2a**, we also found structures of high molecular weight. Multiply-charged pseudomolecular ions corresponding to oligomers with degrees of polymerization *n* up to 20 were clearly identified.

The ^{1}H-NMR spectra showed the signals of two alkylidene species at 12.05 and 12.71 ppm, respectively, which also indicate that only a fraction of the initiator took part in the polymerization because of the slow initiation reaction.

The results of the GPC analysis showed an average molecular weight of $M_n = 4500$ (vs. PS) which is significantly higher than the theoretical $M_n = 1800$ corresponding to a polymerization degree of $n = 5$.

It should be noted that the mass spectrum shown in Fig. 1 was obtained for a sample where low-molecular-weight oligomers (polymerization degree $n = 2,3,4$) were removed from



Scheme 2. End groups R^1 and R^2 of polymer **9** observed by ESI-MS.

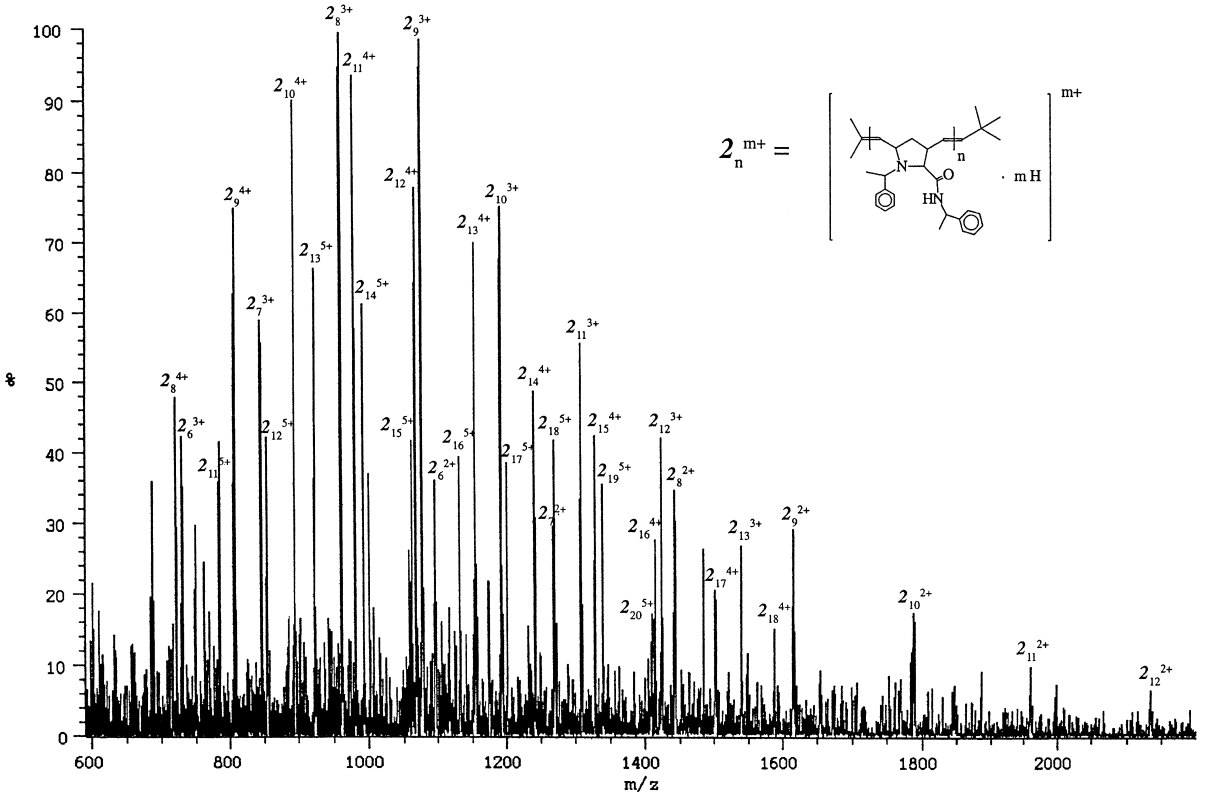


Fig. 1. ESI mass spectra of polymer **2a**. Peaks are assigned as 2_n^{m+} (n polymerization degree, m charge due to the addition of m protons).

the polymer by reprecipitation. These oligomers caused problems during ESI-MS due to mass discrimination [17], only the low-molecular-weight oligomers were observed.

4. Conclusions

Enantiomerically pure (1′*R*, 1*S*, 3*S*, 4*R*, 8*R*)-(1-phenylethyl)-*N*-(1-phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxamide **1** has been synthesized through an asymmetric Lewis-acid-catalyzed Diels–Alder reaction analogous to the previously described methyl (1-phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene-3-carboxylate **8**. Both monomers undergo ring-opening metathesis polymerization in the presence of well-defined molybdenum alkylidene initiators. In both cases, the initiation step is slower than the propagation steps. When the polymerizations were carried out at low ratios of monomer to initiator, the average molecular weight of the oligomers was usually higher than expected because the monomers were fully converted by only a fraction of the initiator present. The ESI mass spectrometry gave proof about the expected end groups of the oligomer chains which are formed by the initiation and by quenching reactions. In the case of monomer **8**, we also found structures that were formed by the conversion of the ester groups to give vinyl ethers. No evidence for a similar conversion of amide groups was found in this investigation.

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