JOURNAL OF LABELLED COMPOUNDS AND RADIOPHARMACEUTICALS
J Label Compd Radiopharm 2005; **48**: 1031–1039.
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/jlcr.1015

Research Article

Synthesis of labeled acrylamide and *N*-methylolacrylamide (NMA): ^{15}N-acrylamide, ^{13}C-NMA, ^{15}N-NMA, and ^{13}C,^{15}N-NMA

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Summary

Labeled derivatives of *N*-methylolacrylamide (NMA) including ^{15}N-NMA, ^{13}C-NMA, and ^{13}C,^{15}N-NMA were synthesized and purified. A required chemical precursor, ^{15}N-acrylamide, was also prepared. Reported methods for synthesizing unlabeled analogs are noted, and modifications to these methods for achieving the labeled materials are specified. Monomers were examined via ^{1}H, ^{13}C, and ^{15}N nuclear magnetic resonance (NMR) spectroscopy. Peak assignments and coupling constants are reported for each compound. To our knowledge, this is the first reported publication on the preparation and characterization of ^{13}C-NMA, ^{15}N-NMA, ^{13}C,^{15}N-NMA, and ^{15}N-acrylamide.

Key Words: *N*-methylolacrylamide (NMA); ^{13}C-NMA,^{15}N-NMA,^{13}C,^{15}N-NMA; ^{15}N-acrylamide; nuclear magnetic resonance (NMR) spectroscopy

Introduction

N-methylolacrylamide (NMA) is an important co-monomer for increasing water and/or wrinkle resistance in textile,[1–14] coating, and adhesive[15,16] applications. In the 1960s it was discovered that the addition of limited quantities of NMA imparted durability to interior grade wood adhesives.[17–19] The ultimate objective of this work was to investigate the molecular

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Contract/grant sponsor: United States Department of Agriculture; contract/grant number: 9702186

Received 7 September 2005
Revised 21 September 2005
Accepted 22 September 2005

mechanisms for enhanced durability in latex wood adhesives by probing NMA distribution. The method, initially developed by Bonardi *et al.*[20] and modified by our group, was based upon variable temperature solution nuclear magnetic resonance (NMR) spectroscopy of latex samples. Since the latex adhesive of interest contained limited quantities of NMA (less than 5% of the overall formulation), the production and inclusion of labeled NMA was required to facilitate detection. This article details synthetic strategies for producing and purifying ^{13}C-NMA, ^{15}N-NMA, ^{13}C,^{15}N-NMA, and^{15}N-acrylamide. Monomers were examined via ^{1}H, ^{13}C and ^{15}N NMR spectroscopy, and peak assignments as well as coupling constants are reported. Purity of the compounds was estimated from proton NMR spectra. The level of isotopic enrichment in the molecules was found to range from 93 to 97%. Apart from unlabeled analogs, only slight impurities (less than 2%) were noted. These included minor quantities of hydrolysis products and oligomers of ^{13}C-formaldehyde.

Synthesis of unlabeled analogs

Methods for producing unlabeled NMA and a chemical precursor, acrylamide, have been previously reported. Modifications were made to these methods to achieve the labeled monomers and to improve reaction yields. Synthetic methods for producing unlabeled NMA were discussed by Warson.[21] Heating acrylamide and either formaldehyde solution or paraformaldehyde to 50°C under alkaline conditions are both common paths.[21,22] Variations of this method, largely dealing with the choice of solvent, reaction temperature, time, or catalyst, exist in the patent literature. Kinetic studies using sodium hydroxide as a catalyst indicated that the reaction rate increases with temperature and pH, and that the activation energy for the reaction is 24.3 kcal/mol.[21] Temperatures above 50°C and exposure to ultraviolet light are both avoided to prevent polymerization.[22]

The production of acrylamide was also necessary, as ^{15}N-acrylamide was utilized in the synthesis of ^{15}N-NMA. Carpenter and Davis reported synthetic methods for producing unlabeled acrylamide.[23] The first synthesis of acrylamide was published by Moreu[24] who slowly bubbled dry ammonia into a saturated solution of acryloyl chloride in benzene at 10°C. Ammonium chloride, the by-product, was removed via filtration after the benzene solution was boiled, allowing acrylamide flakes to precipitate upon cooling. Several other authors[25,26] have produced the monomer in a similar fashion. Most industrial synthetic routes proceed from acrylonitrile.[27] One such process reacts acrylonitrile with hydrogen chloride to form β-chloropropionamide; hydrogen chloride is then eliminated upon treatment with base. Other methods are based upon the hydrolysis of acrylonitrile with sulfuric acid monohydrate.

The primary difference among these approaches is the means of separating the acrylamide from the sulfuric acid mixture.

Results and discussion

^{13}C-NMA

A ^{13}C label was positioned on the NMA methylol carbon by reacting acrylamide with commercially available ^{13}C-paraformaldehyde in the presence of base and inhibitor (Figure 1).[28] Since the reaction of acrylamide and paraformaldehyde is reversible, poor solvents for the product were utilized to drive the reaction to completion.[22,29] Reported solvents for the reaction include tetrachloroethylene,[21] ethylene chloride,[22] and water,[30,31] but in our experience product recovery was simplified with carbon tetrachloride. Reaction progress was monitored visually as the opaque reagents gradually clarified and separated to a translucent layer on top of the organic phase. Trials using unlabeled reagents indicated that satisfactory yields of NMA were achieved after 1 h of reaction at 50°C. However, initial attempts to produce ^{13}C-NMA revealed that the ^{13}C-paraformaldehyde was noticeably less reactive than its unlabeled counterpart, as reactions required considerably more time (more than 2 h) and catalyst. Poor reactivity was thought to be due to the ^{13}C-paraformaldehyde having a higher molecular weight than the unlabeled paraformaldehyde (compounds were received from different sources). The possibility of an isotope effect was also considered, but the mass change from ^{12}C to ^{13}C is only 8%, which does not account for the observed rate decrease. Due to the cost of the ^{13}C-paraformaldehyde, no attempt was made to measure molecular weight. Instead, the ^{13}C-paraformaldehyde was re-hydrated at high temperature to decrease its molecular weight. This step resulted in only slightly improved reactivity, and resulted in a 10% loss of labeled material. Purification of the resulting ^{13}C-NMA was accomplished by filtration, washing, and recrystallization of the monomer from warm ethyl acetate.

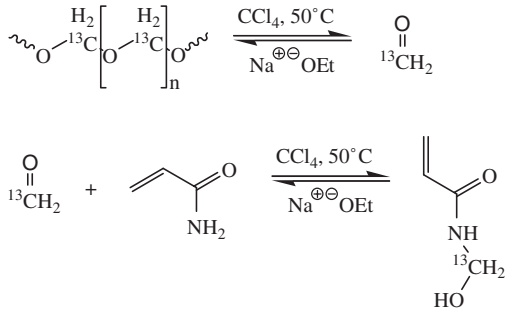

Figure 1. Synthesis of ^{13}C-*N*-methylolacrylamide (NMA)

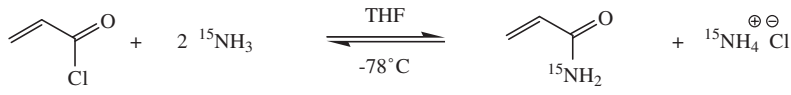

Figure 2. Synthesis of ^{15}N-acrylamide

^{15}*N-acrylamide*

The method of Moreu[24] was modified to produce ^{15}N-acrylamide in very high yields. Anhydrous tetrahydrofuran (THF) was used as a solvent (as opposed to benzene), allowing the reaction to be conducted at much lower temperatures (-78°C). Due to the low boiling point (-33°C) of ammonia, the reaction was conducted in a pressure vessel. Two equivalents of ^{15}N-ammonia gas were added to produce one equivalent of ^{15}N-acrylamide. Figure 2 illustrates the reaction scheme. It should be noted here that the synthesis was attempted with a stoichiometric equivalent of many bases in order to limit the consumption of ^{15}N-ammonia to one equivalent. These included sodium carbonate, polyvinyl pyridine, dimethylaminopyridine, trioctylamine, tributylamine, and triethylamine.[32] Of all the bases utilized in trials, triethylamine was the most promising. However, separation and purification of the products from the by-product hydrochloride salts was difficult and resulted in decreased yields. For this reason, the simpler method of using two equivalents of ^{15}N-ammonia was employed here. Purification was accomplished by filtration, rotary evaporation of the THF, and recrystallization of the product from warm benzene.[25]

^{15}*N-NMA*

^{15}N-acrylamide was reacted with paraformaldehyde in the presence of sodium ethoxide (catalyst) to produce ^{15}N-NMA. Reaction conditions here were identical to those described for ^{13}C-NMA production, with the obvious exception of the labels on the respective starting compounds.

^{13}C,^{15} *N-NMA synthesis*

The reaction to produce ^{13}C,^{15}N-NMA closely followed that described for ^{15}N-NMA, with the exception that re-hydrated ^{13}C-parformaldehyde was reacted with ^{15}N-acrylamide in the second step. Despite our attempts to improve the reactivity of the ^{13}C-paraformaldehyde via re-hydration, the production of ^{13}C,^{15}N-NMA still required several hours. This suggests that the re-hydration conditions were not successful in decreasing molecular weight. Reactivity issues were not probed in greater detail as they were secondary to our objective of producing the labeled materials in sufficient quantities for adhesive synthesizing (Figure 3).

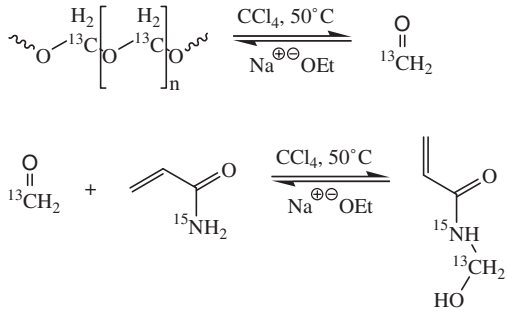

Figure 3. Synthesis of ^{13}C,^{15}N-NMA

Experimental

Materials

The following chemicals were purchased and used as received: ethanol (95%, Mallincrodt), dry-ice pellets, tetrahydrofuran (Aldrich, anhydrous, 99.9%), ^{15}N-ammonia (Cambridge Isotope Labs, 98 + %), calcium chloride (Fisher, 4 mesh), benzene (Aldrich, anhydrous, 99.8%), 4-methoxyphenol (Aldrich, 99%), carbon tetrachloride (Aldrich, anhydrous, 99.5 + %), paraformaldehyde (Aldrich, powder, 95%), sodium ethoxide (Aldrich, 96%), 4-methoxyphenol (Aldrich, 99%), ethyl acetate (Aldrich, anhydrous, 99.8%), deuterated dimethylsulfoxide (DMSO-d6) (Cambridge Isotope Labs, 99.96%), acrylamide (Aldrich, 99 + %), ^{15}N-aniline (Cambridge Isotope Labs, 98%).

Acryloyl chloride (Aldrich, 96%) was distilled over calcium chloride and stored over molecular sieves. ^{13}C-Paraformaldehyde (Cambridge Isotope Labs, ^{13}C 99%) was re-hydrated (method described later) prior to use.

Methods

NMR spectra: NMR spectra were obtained in deuterated dimethyl sulfoxide (DMSO-d6), using either a Varian Unity 400, a Bruker AMX-2-500, or a Bruker AMX-360 spectrometer. ^{1}H and ^{13}C spectra were referenced to DMSO (2.50 and 39.50 ppm, respectively), while ^{15}N spectra were referenced to ^{15}N-aniline (0 ppm).

^{13}C-NMA synthesis: ^{13}C-paraformaldehyde re-hydration was accomplished via mixing (4.2 g) with distilled water (4.5 g) under constant stirring in a sealed glass tube at 90°C for 24 h. Product was vacuum dried for 24 h, then ground with a mortar and pestle. Ninety percent of the product was recovered; the losses were incurred during vacuum drying.

Acrylamide (2.46 g, 0.0341 mol) and re-hydrated ^{13}C-paraformaldehyde (1.05–1.1 equivalents, ~1.115 g) were reacted in carbon tetrachloride (20 ml) for 1 h at 50°C. Inhibitor (4-methoxyphenol, ~0.020 g, 0.16 mmol) and sodium ethoxide (0.025 g, 0.37 mmol) were added at the beginning of the

reaction. During the first 5–15 min, a viscous white layer began to separate from the solution, appearing on top of the organic phase. The layer gradually clarified. Immediately after the reaction, the flask was placed in a freezer (−20°C), allowing the top layer to completely solidify over the organic phase. Carbon tetrachloride was removed first via pipette, the remainder via vacuum. Product was ground to a fine powder then warmed in ethyl acetate (20 ml) in the presence of inhibitor (4-methoxyphenol, ~0.050 g, 0.40 mmol). Exposure to light and temperatures above 50°C were avoided. The mixture was filtered through a warm sintered glass frit. NMA crystals formed upon cooling. Yield: 73%.

^{1}H NMR: (360.13 MHz, DMSO-d_6, δ): 8.68 (1H, complex, J = 132.8 Hz, 6.0 Hz, 5.5 Hz, –N**H**–); 6.21 (1H, dd, J = 17.2 Hz, 9.8 Hz, CH_aH_b = C**H**–); 6.12 (1H, dd, J = 2.6 Hz, 17.2 Hz, C**H$_a$**H$_b$ = CH–); 5.62 (1H, dd, J = 2.6 Hz, 9.8 Hz, CH$_a$**H$_b$** = CH–); 5.63 (1H, t overlapping, J = 5.0 Hz, –O**H**); 4.57 (2H, dt, J = 154.6 Hz, 6.1 Hz, $-^{13}C\mathbf{H_2}$–). ^{13}C NMR: (90.56 MHz, DMSO-d_6, δ): 164.9 (**C**=O); 131.9 (d, J = 1.9 Hz, CH_2 = **C**H–); 126.2 (**C**H$_2$ = CH–); 62.5 (–**C**H$_2$OH).

^{15}*N-acrylamide synthesis:* A cold bath was prepared from dry-ice pellets and ethanol to achieve a temperature of approximately −78°C. The reaction vessel (1000 ml Ace Glass medium pressure glass reactor) was set up, purged with nitrogen gas, and flamed under heavy nitrogen flow. Approximately 250 ml of tetrahydrofuran (THF) was introduced into the flamed reactor via canula transfer. The reactor was transferred to the cold bath and allowed to cool under nitrogen pressure. Two equivalents of ^{15}N-ammonia (6.20 l, 0.256 mol) were introduced via bubbling through an 18-gauge stainless-steel needle. The flow rate of the gas was monitored with a Gilmont® direct-reading flow meter; indicated values for air were multiplied by a correction factor of 1.3 to obtain the flow rate of ammonia. The reactor was then sealed to prevent the escape of ammonia gas. One equivalent (10.2 ml, 0.128 mol) of acryloyl chloride (previously distilled over calcium chloride) was syringed into the reactor dropwise under stirring. Upon addition of the acryloyl chloride, the headspace in the reactor became clouded. The colorless ammonia/THF solution gradually became an opaque white mixture and stirring was difficult to maintain as ammonium chloride precipitated. The reaction vessel gradually warmed to room temperature. Acrylamide was separated from the ammonium chloride precipitate via filtration through a sintered glass funnel. Ammonium chloride was washed (2 × 100 ml THF) to recover additional product. Impure acrylamide (9.15 g, 0.127 mol) was recovered when the combined filtrates were removed (via rotary evaporator) and vacuum dried. Yield: 99%.

Impure product was purified by filtration through a warm ground glass filter after boiling in benzene in the presence of a small amount of inhibitor (4-methoxyphenol, 0.01 g, 0.08 mmol). Large flakes of acrylamide crystallized

upon cooling. Recovered crystals were dried under vacuum to obtain 8.27 g (0.115 mol, 90% yield) of ^{15}N-acrylamide.

^{1}H NMR: (500.13 MHz, DMSO-d_6, δ): 7.54 (1H, dd, J = 88.0 Hz; 2.2 Hz, –^{15}N**H$_a$**H$_b$); 7.11 (1H, dd, J = 88.0 Hz; 2.2 Hz, –^{15}NH$_a$**H$_b$**); 6.19 (1H, dd, J = 17.0 Hz; 10.2 Hz, CH$_a$H$_b$ = C**H**–); 6.07 (1H, dd, J = 2.2 Hz; 17.0 Hz, C**H$_a$**H$_b$ = CH–); 5.58 (1H, dd, J = 2.2 Hz; 10.2 Hz, CH$_a$**H$_b$** = CH–). ^{13}C NMR: (125.77 MHz, DMSO-d_6, δ): 166.6 (d, J = 15.5 Hz, **C** = O); 132.0 (d, J = 9.3 Hz, CH$_2$ = **C**H–); 125.7 (d, J = 1.1 Hz, CH$_2$ = CH–). ^{15}N NMR: (50.68 MHz, DMSO-d_6, ^{15}N-aniline standard, referenced to 0 ppm, δ): 50.3 (s).

^{15}N-NMA synthesis: One equivalent (2.46 g, 0.0341 mol) of ^{15}N-acrylamide was reacted with a slight excess (1.05–1.1 equivalents, ~1.115 g) of paraformaldehyde in carbon tetrachloride (20 ml). Reaction conditions and purification methods then followed that detailed for ^{13}C-NMA. Yield: 3.48 g, 77%.

^{1}H NMR: (500.13 MHz, DMSO-d_6, δ): 8.75 (1H, dt, J = 91.1 Hz; 6.4 Hz, –^{15}N**H**–); 6.21 (1H, dd, J = 17.0 Hz, 10.0 Hz, CH$_a$H$_b$ = C**H**–); 6.12 (1H, dd, J = 2.3 Hz, 17.0 Hz, C**H$_a$**H$_b$ = CH–); 5.62 (1H, dd, J = 2.3 Hz, 10.0 Hz, CH$_a$**H$_b$** = CH–); 5.60 (2H, t overlapping, J = 6.8 Hz, –CH$_2$–); 4.57 (1H, dd overlapping, J = 6.8 Hz, 6.4 Hz, –O**H**). ^{13}C NMR: (125.77 MHz, DMSO-d_6, δ): 164.5 (d, J = 14.5 Hz, **C** = O); 131.9 (d, J = 9.2 Hz, CH$_2$ = **C**H–); 125.8 (**C**H$_2$ = CH–); 62.4 (d, J = 10.5 Hz, –**C**H$_2$OH). ^{15}N NMR: (50.68 MHz, DMSO-d_6, ^{15}N-aniline standard, referenced to 0 ppm, δ): 75.5.

^{13}C,^{15}N-NMA synthesis: ^{15}N-acrylamide was reacted with ^{13}C-paraformaldehyde (re-hydrated, as described previously). This reaction, even with re-hydrated ^{13}C-paraformaldehyde, proceeded slowly. It took approximately 3 h for the product layer to become translucent, whereas the reaction time for unlabeled compounds was 1 h. Purification steps followed those given previously. Product yield was lower, 67%.

^{1}H NMR: (500.13 MHz, DMSO-d_6, δ): 8.67 (1H, complex, J = 91.1 Hz, 6.4 Hz, 1.1 Hz, –^{15}NH–); 6.21 (1H, dd, J = 17.2 Hz, 10.1 Hz, CH$_a$H$_b$ = C**H**–); 6.13 (1H, dd, J = 2.2 Hz, 17.2 Hz, C**H$_a$**H$_b$ = CH–); 5.62 (1H, dd, J = 2.2 Hz, 10.1 Hz, CH$_a$**H$_b$** = CH–); 5.60 (H$_G$, complex, overlapping, –^{13}C**H**$_2$–); 4.57 (1H, dt, J = 6.4 Hz, 154.7 Hz, –O**H**). ^{13}C NMR: (125.77 MHz, DMSO-d_6, δ): 164.7 (d, J = 14.7 Hz, **C** = O); 131.9 (dd, J = 2.0 Hz, 9.2 Hz, CH$_2$ = **C**H–); 125.9 (d, J = 1.3 Hz, **C**H$_2$ = CH–); 86.2 (d, J = 1.4 Hz, methylene glycol (impurity resulting from sample hydrolysis)); 62.5 (d, J = 10.5 Hz, –**C**H$_2$OH). ^{15}N NMR: (50.68 MHz, DMSO-d_6, ^{15}N-aniline standard, referenced to 0 ppm, δ): 75.4 (NMA, d, J = 10.5 Hz); 50.2 (acrylamide (impurity resulting from hydrolysis), s).

Conclusions

^{13}C-NMA, ^{15}N-NMA, ^{13}C,^{15}N-NMA and ^{15}N-acrylamide monomers were produced as described. ^{1}H, ^{13}C and ^{15}N-NMR spectroscopy provided chemical shifts and coupling constants for the purified compounds. The

production and inclusion of labeled NMA in adhesives, coatings, and textile treatments provides a means of monitoring both NMA distribution and NMA cross-linking.

Acknowledgements

The authors would like to acknowledge the efforts of Dr Xiaobing 'Joe' Zhou for his efforts towards developing the synthetic approach. Also noted is the assistance of Mr Tom Glass, Mr Bernie O'Hare, and Dr Alan Benesi in collecting the NMR spectra.

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