Detection of C-Nitroso Dimer Formation by Field Desorption Mass Spectrometry

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Field desorption mass spectrometry is shown to be a useful technique for observing dimer formation in C-nitroso compounds. Mixed dimer formation (RN_2O_2R') is shown to be readily observed by field desorption mass spectrometry.

INTRODUCTION

Early investigators^{1,2} of C-nitroso compounds were intrigued by the color or lack of color exhibited by these compounds in their various physical states. They were able to show by melting point depression experiments that the colored state of a C-nitroso compound was due to a monomeric form of the compound, while the colorless state was due to a dimeric form. The dimer can exist as either a cis or a trans isomer. The color of the monomers is associated with an $n \rightarrow \pi^*$ transition which has a weak absorption in the 630-830 nm range.³⁻⁶ The formation of a dimer removes the possibility of this type of transition occurring. Other methods of dimer identification and characterization have been by their ultraviolet and infrared (IR) absorption patterns. Nakamoto and Rundle⁷ characterized the IR absorption bands due to both monomers and dimers. Electron impact (EI) mass spectrometry has been successful in identifying dimers.⁸⁻¹⁰ However, these dimers had relatively low molecular weights. Experience in this laboratory has shown that the EI spectra of larger nonaromatic C-nitroso dimers in almost all cases produce spectra whose largest ion is less than the molecular weight of the corresponding monomer, and that these fragment ions are not sufficient to characterize the monomer or dimer molecules. For this reason the use of field desorption (FD) mass spectrometry was investigated as a tool in characterizing C-nitroso dimers.

FD mass spectrometry was also used to investigate the formation of mixed C-nitroso dimers (dimers formed from two different C-nitroso compounds). Hammick *et al.*,¹¹ reported the formation of mixed dimers of aromatic C-nitroso compounds. Their method of melting point depression characterization was not fully conclusive, however. Kabasakalian *et al.*,¹² reported a mixed dimer of 2-nitrosoheptane and 4-nitroso-1-octanol which was not completely characterized. To date, the only mixed dimer fully characterized has been that of nitrosomethane and nitrosoethane reported by Fornstedt and Lindquist.⁸ The use

[†] Address: The Wellcome Research Laboratories, Burroughs Wellcome Co., 3030 Cornwallis Road, Research Triangle Park, North Carolina 27709, USA. of IR spectroscopy to study the formation of mixed dimers is impractical. A study of the data obtained by Nakamoto and Rundle show that those bands which characterize the dimer formation do not give large shifts from compound to compound. It would be difficult to tell the difference between the formation of two pure dimers and a mixed dimer when all three are in solution. In this paper we will demonstrate that FD mass spectrometry is suitable for characterizing monomers and dimers of C-nitroso compounds as well as mixed dimers.

EXPERIMENTAL

General methods

Melting points were run on a Buchi melting point apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra were determined with a Varian T-60 spectrometer with tetramethylsilane as internal standard. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, Georgia, and osmometric molecular weight determinations were carried out by Galbraith Laboratories, Inc., Knoxville, Tennessee.

Instrumental methods

The EI mass spectra were obtained on a Varian MAT CH-5-DF double focusing mass spectrometer. Samples were introduced for EI studies via a direct insertion probe. The trap current for both the 20 eV and 70 eV mass spectra was regulated at 300 μ A while the accelerating voltage was maintained at 3 kV. The FD mass spectra were obtained on a Varian MAT 731 double focusing instrument equipped with an EI/FI/FD source. The field anode voltage was +8 kV while the cathode voltage was maintained at -3 kV. The emitters for the FD work were $10 \,\mu m$ diameter tungsten wire which were activated in the presence of benzonitrile. Samples were placed on emitters using the dipping technique with methanol as solvent. All mass spectra (FD and EI) were obtained at 1000 resolution (10% valley definition). All spectra were

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recorded using a Varian SS-100 data system. FD mass spectra were taken at single milliampere step intervals. The FD mass spectra, Figs. 3-9, are summed spectra taken at 5-15 mA.

Materials

Nitroso pyrimidines 6 and 7 were kindly provided by Dr L. N. Bell of Burroughs Wellcome Co., and aromatic nitroso compound 5 was purchased from Aldrich Chemical Co. Nitroso chlorides 1-4 were prepared by the addition of nitrosyl chloride (generated *in situ*) to alkyl 3-methyl-2-butenyl ethers 8-11, which were available by reaction of the corresponding sodium alkoxide with dimethylallyl bromide. Reaction of nitrosyl chloride with trisubstituted olefins produces compounds consistent with the structural assignments of 1-4.¹³

Cyclopentyl 3-methyl-2-butenyl ether (8). A mixture of cyclopentanol (75 g), sodium metal (9.3 g) and hexamethylphosphoric acid (25 cm³) was heated under nitrogen at 120 °C until all sodium had dissolved, then cooled to c. 85 °C, whereupon dimethylallyl bromide (61.1 g) was added dropwise as the temperature was maintained at c. 70 °C. After 20 h at 20 °C, the reaction mixture was poured into water and the product was isolated by ether extraction. Distillation provided **8** (45.6 g, 74%) as a colorless liquid, b.p. 78–80 °C (9 mm). ¹H NMR δ (CDCl₃): 1.3–1.9 (m, 14H), 3.95 (bd, J = 7 Hz, 2H superimposed over c. 3.9 (m, 1H), 5.33 (complex t, primary J = 7 Hz, 1H).

Cyclohexyl 3-methyl-2-butenyl ether (9). The desired compound 9 (b.p. 94-95 °C, 9 mm) was obtained (38% yield) from cyclohexanol sodium salt and dimethylallyl bromide by a procedure similar to that described for 8. ¹H NMR δ (CDCl₃): 1.0-2.1 (m, 16H; includes two 3H broadened s at 1.67 and 1.73), 3.27 (br, 1H), 3.98 (bd, J = 7 Hz, 2H), 5.37 (complex t, primary J = 7 Hz, 1H).

Benzyl 3-methyl-2-butenyl ether (10). A mixture of sodium (9.2 g) and benzyl alcohol (120 g) was refluxed under nitrogen until homogeneous, then cooled to 45 °C, whereupon a solution of dimethylallyl bromide (64 g) in tetrahydrofuran (20 cm³) was added over a 90 min period. After 16 h at 20 °C, the product was isolated by dilution with water followed by ether extraction. Distillation gave **10** (41.2 g, 58%) as a colorless liquid (b.p. 116–118 °C, 10 mm; lit.¹⁴ b.p. 239–240 °C, 680 mm). ¹H NMR δ (CDCl₃): 1.65 (bs, 3H), 1.77 (bs, 3H), 4.00 (bd, J = 7 Hz, 2H), 4.47 (s, 2H), 5.43 (complex t, primary J = 7 Hz, 1H), 7.37 (s, 5H).

Methyl 3-methyl-2-butenyl ether (11). Dimethylallyl bromide (149 g) was added during 3 h to a stirred solution of sodium methoxide in methanol (from 23 g sodium and 300 cm³ methanol) at such a rate to keep the temperature <40 °C. After 45 h the mixture was diluted with water and extracted with ether. Removal of solvent through a Vigreux column followed by

two distillations of the residue gave ether **11** (36 g, 34%) as a colorless liquid (b.p. 104.5–107 °C; Lit.¹⁴ b.p. 100–101 °C) which contained (by NMR) <1% of the isomeric 3-methoxy-3-methyl-1-butene. ¹H NMR δ (CDCl₃); 1.68 (bs, 3H), 1.75 (bs, 3H), 3.31 (s, 3H), 3.89 (bd, J = 7 Hz, 2H), 5.34 (bt, J = 7 Hz, 1H).

3-Chloro-1-cyclohexyloxy-3-methyl-2-nitrosobutane dimer (1). A mixture of allylic ether **9** (1.77 g) and isopentyl nitrite (1.45 cm³) was stirred at 0 °C while conc. HCl (1.75 cm³) was added during 10 min. Methanol (6 cm³) was added to facilitate stirring and after 10 min the mixture was cooled to -70 °C and filtered. The precipitate was washed with cold methanol to provide a white powder (1.37 g). Recrystallization from acetone (10 cm³) gave **1** (1.01 g, 41%) as colorless plates, m.p. 124–124.5 °C. ¹H NMR δ (CDCl₃): 0.9–2.1 (m, 32H), 3.0–3.5 (br, 2H), 3.80–4.40 (m, 4H), 6.10 (dd, J = 9, 4 Hz, 2H). (Found: C, 56.51, H, 8.63; N, 5.97; Cl, 15.16. C₂₂H₄₀N₂O₄Cl₂ requires C, 56.52; H, 8.63; N, 5.99; Cl, 15.17%).

1-Benzyloxy-3-chloro-3-methyl-2-nitrosobutane dimer (2). A cold $(0 \,^{\circ}\text{C})$ mixture of allylic ether 10 (1.88 g) and isopentyl nitrite (1.25 g) was stirred as conc. HCl (2 cm^3) was added dropwise during 1 min. Glacial acetic acid (1 cm³) was added and after 10 min the thick mixture was diluted with cold methanol and filtered to give a white solid (1.55 g) which was washed with cold methanol. Recrystallization from acetone (10 cm^3) gave 2 (1.07 g, 41%) as colorless needles, m.p. 123–124 °C, of 97% purity (NMR). ¹H NMR δ (CDCl₃): 1.53 (s, 12H), 3.84-4.50 (m, 4H), 4.52 (s, 4H), 6.22 (dd, J = 10, 4 Hz, 2H), 7.30 (s, 10H). (Found: C, 59.62; H, 6.69; N, 5.77; Cl, 14.65. C₂₄H₃₂N₂O₄Cl₂ requires C, 59.62; H, 6.67; N, 5.80; Cl, 14.67%).

3-Chloro-1-methyl-3-methyl-2-nitrosobutane dimer (3). Conc. HCl (84 cm³) was added over 75 min to a cold (-5 °C) stirred mixture of allylic ether **11** (51 g) and isopentyl nitrite (56.4 g). Methanol (50 cm³) was added and the mixture was cooled to -70 °C, filtered and the white solid was washed with cold methanol. The crude product (51.3 g; m.p. 126–128 °C, dec.) was recrystallized from acetone (0.38 l) to provide **3** (38.1 g, 41%) as colorless needles, m.p. 126–128 °C (dec.). ¹H NMR δ (CDCl₃): 1.63 (s, 12H), 3.32 (s, 6H), 3.77–4.33 (m, 4H), 6.17 (dd, J = 4, 10 Hz, 2H). (Found: C, 43.52; H, 7.34; N, 8.39; Cl, 21.38. $C_{12}H_{24}N_2O_4Cl_2$ requires C, 43.51; H, 7.30; N, 8.45; Cl, 21.41%).

3-Chloro-1-cyclopentyloxy-3-methyl-2-nitrosobutane dimer (4). To a cold $(0 \,^{\circ}\text{C})$ mixture of allylic ether **8** (1.15 g) and isopentyl nitrite (0.89 g) was added during 1 min conc. HCl $(1.3 \,\text{cm}^3)$, and glacial acetic acid $(1 \,\text{cm}^3)$ was added to facilitate stirring. After 10 min the mixture was diluted with cold methanol $(10 \,\text{cm}^3)$ and the precipitate was collected and washed with cold methanol to give a white solid $(0.90 \,\text{g})$. Recrystallization from acetone $(5 \,\text{cm}^3)$ gave **4** $(0.35 \,\text{g}, 21\%)$ as colorless needles, m.p. 116–118 °C. ¹H NMR δ (CDCl₃): 1.3–1.8 (m, 28H), 3.67–4.33 (m, 6H), 6.08 (dd, J = 9, 4 Hz, 2H). (Found: C, 54.68; H, 8.29; N, 6.35; Cl, 16.13. C₂₀H₃₆N₂O₄Cl₂ requires C, 54.66; H, 8.26; N, 6.38; Cl, 16.14%).

RESULTS

Seven C-nitroso compounds were studied by EI and FD mass spectrometry. Nitroso chlorides 1-4 were colorless and thus were suspected to be dimers. In contrast, compounds 5-7 were highly colored substances and were suspected of being monomers. In addition, osmometric data were obtained for compounds 1, 2, 4 and 7. This data showed 1, 2 and 4 to have molecular weights of 448, 480 and 450 in solution, respectively, which are in good agreement with the molecular weights of the dimeric forms (466, 482 and 438). Compound 7 was shown to be monomeric by this method (mol. wt = 269; osmometric mol. wt = 273). EI mass spectrometery at both 20 eV and 70 eV was carried out on the compounds in question. None of the compounds suspected as being dimeric could be determined to be dimers from this data, and compounds 6 and 7 gave no EI spectra other m/z 44 and 45. Thus, EI mass spectrometry gave no information concerning the monomeric-dimeric nature of any of the compounds, and it gave no information at all on pyrimidines 6 and 7. Figures 1 and 2 show the EI mass spectra at 20 eV and 70 eV respectively of compound 1, a suspected dimer. The FD mass spectrum of 1 is given in Fig. 3. This spectrum clearly shows the presence of a $[M_D]^+$ (where M_D is the molecular weight of the dimer) ion at m/z 466. The possibility was considered that this ion is a cluster ion, $[2M_M]^+$ (where M_M is the molecular weight of the monomer), and not a



		monomer	unner	osmometric
I	R = cyclohexyl	233	466	448 (CHCI ₃)
2	R = benzyl	241	482	480 (CHCI ₃)
3	R = methyl	165	330	_
4	R = cyclopentyl	219	438	450 (CHCIa)





Figure 1. 20 eV EI mass spectrum of compound 1.



Figure 2. 70 eV EI mass spectrum of compound 1.

molecular species. However, this is ruled out by the behavior of the mass spectra as the current applied to the emitter is increased. As the current is increased from zero to a point past the appearance of $[M_D]^{+}$ no ion representing the monomer appears. It has been the laboratory¹⁵ experience in this and other laboratories¹⁶ that the ratio of $[2M]^{+}/[M]^{+}$ and [2M+ $H^{+}/[M+H]^{+}$ decreases as the emitter temperature (current) increases. The fact that an ion is observed at an m/z value equivalent to $[M_D]^{+}$ and no ion is observed for $[M_M]^+$ over a wide range of emitter heating currents is evidence for the field desorption of



Figure 3. FD mass spectrum of compound 1.

Table 1. Behavior of the $[M_M]^{+}$ and $[2M_M]^{+}$ ions of compound 5 as a function of emitter current

Emitter current (mA)	[M _M] ^{+.} (% base)	[2M _M] ^{+.} (% base)
0	100	6
2	100	5
4	100	0
6	100	0
7	100	0
8	100	0
10	100	0
11	100	0
12	100	0
13	100	0
15	100	0

a molecular species, the dimer, and not the formation in field desorption of a cluster ion. The behavior of the $[M_M]^+$ and $[M_D]^+$ ions in the field desorption of compound 5, a highly colored compound thought to exist as a monomer because of its highly colored nature, is given in Table 1. As can be seen this



Figure 4. FD mass spectra of (a) compound 2, (b) compound 3, and (c) compound 4.



Figure 5. FD mass spectra of (a) compound 5, (b) compound 6, and (c) compound 7.

behaves as one would expect the monomer to behave. The ratio $[2M]^{+}/[M]^{+}$ decreases as the emitter current is raised.

Figures 4 and 5 present the FD spectra of the remaining compounds studied. The data show that for those compounds which we expect to be monomers as shown by their highly colored nature and/or osmometric study we observe mainly the $[M_M]^+$ or $[M_M+H]^+$ ions in their FD mass spectra. Those we suspect as being dimers by their lack of color and/or osmometric study exhibit mainly $[M_D]^+$ or $[M_D+H]^+$ ions. The respective ions are prominent over a wide range of emitter heating currents.

To show the presence of mixed dimers, two experiments were conducted. In the first experiment, separate solutions of compounds 1-4 were prepared in methanol. Pairs of the solutions were mixed together. A FD mass spectrum of the mixture was taken immediately using the dipping technique. Mixtures of compounds 1 and 2, 2 and 3, 2 and 4, and 1 and 4 were made. Table 2 shows the molecular weight expected for the mixed dimer of each mixture. In the



Figure 6. FD mass spectra of a mixture of compounds 2 and 4 (a) just after mixing and (b) 24 hours later.



Figure 7. FD mass spectra of a mixture of compounds 1 and 4 (a) just after mixing and (b) 24 hours later.

second experiment, the mixtures of the four compounds as prepared above were allowed to stand for 24 hours. The FD mass spectrum of each mixture was taken using the dipping technique. Figures 6–9 show the spectra obtained from the two procedures. These spectra clearly show the molecular ions for mixed dimers to be small or not present just after mixture preparation, while they have come to dominate the FD spectra of the mixtures after 24 hours. The mixed



Figure 8. FD mass spectra of a mixture of compounds 2 and 3 (a) just after mixing and (b) 24 hours later.



Figure 9. FD mass spectra of a mixture of compounds 1 and 2 (a) just after mixing and (b) 24 hours later.

dimer formation suggests that an equilibrium between monomer and dimer is established in methanol. Although the equilibrium undoubtedly strongly favors the dimeric species, the monomers diffuse apart to a sufficient degree to allow a random recombination of individual monomer units.

CONCLUSION

FD mass spectrometry has been shown to be a useful technique in the detection of C-nitroso dimers. Furthermore, FD mass spectrometry has been used to show conclusively the presence of mixed C-nitroso dimers for the compounds studied. Although it was not attempted in this study, it appears that the kinetics of the equilibrium between mixed and pure C-nitroso dimers can be studied by FD mass spectrometry. The amount of pure and mixed dimers present in a solution could be measured versus time and the kinetics of the dimer formation resolved.

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