ropyridinium ion, 54560-55-3; 1-methyl-3-iodopyridinium ion, 54560-56-4; 1-benzyl-3-iodopyridinium ion, 58219-40-2; 1-methoxy-3-carbamoylpyridinium ion, 54212-29-2; 1-methylpyridinium ion, 694-56-4; 1-benzylpyridinium ion, 15519-25-2; 1-methoxypyridinium ion, 30718-14-0; 1,2,5-trimethylpyrazinium ion, 58091-57-9; 1-methyl-3-chloropyrazinium ion, 58219-41-3; 1-methyl-3-methoxypyrazinium ion, 58219-42-4; 1-methyl-3-carbamoylpyrazinium ion, 58091-58-0; 1-methylpyrazinium ion, 17066-96-5.

Supplementary Material Available. Additional information on side reactions and NMR interpretation (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) W. L. F. Armarego, *Adv. Heterocycl. Chem.*, **1**, 253 (1963); A. Albert and W. L. F. Armarego, *ibid.*, **4**, 1 (1965); D. D. Perrin, *ibid.*, **4**, 43 (1965); A. Albert, *Angew. Chem., Int. Ed. Engl.*, **6**, 919 (1967).
(2) D. Beke, *Adv. Heterocycl. Chem.*, **1**, 167 (1963).
(3) J. W. Bunting and W. G. Meathrel, *Can. J. Chem.*, **52**, 981 (1974), and earlier references cited therein; C. J. Cooksey and M. D. Johnson, *J. Chem. Soc. B*, 1191 (1968), and references cited therein.
(4) R. Valters, *Russ. Chem. Rev.*, **43**, 665 (1974).
(5) J. A. Zoltewicz, L. S. Helmick, T. M. Oestreich, R. W. King, and P. E. Kandetzki, *J. Org. Chem.*, **38**, 1947 (1973).
(6) J. A. Zoltewicz and L. S. Helmick, *J. Am. Chem. Soc.*, **94**, 682 (1972).
(7) A. P. Kroon, H. C. van der Plas, and G. van Garderen, *Recl. Trav. Chim. Pays-Bas*, **93**, 325 (1974); J. P. Geerts, C. A. H. Rasmussen, H. C. van der Plas, and A. van Veldhuizen, *ibid.*, **93**, 231 (1974); P. J. Lont, H. C. van der Plas, and A. van Veldhuizen, *ibid.*, **92**, 708 (1973); J. P. Geerts, H. C. van der Plas, and A. van Veldhuizen, *ibid.*, **92**, 1232 (1973).
(8) H. C. van der Plas, "Ring Transformations of Heterocycles", Vol. 2, Academic Press, New York, N.Y., 1973.
(9) J. A. Zoltewicz, "Topics in Current Chemistry", Springer-Verlag New York, New York, N.Y., **59**, 35 (1975).
(10) A. P. Kroon and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas*, **93**, 227 (1974), and references cited therein.
(11) J. A. Zoltewicz, T. M. Oestreich, J. K. O'Halloran, and L. S. Helmick, *J. Org. Chem.*, **38**, 1949 (1973).
(12) J. A. Zoltewicz, L. S. Helmick, and J. K. O'Halloran, *J. Org. Chem.*, following paper in this issue.
(13) J. A. Zoltewicz and J. K. O'Halloran, *J. Am. Chem. Soc.*, **97**, 5531 (1975).
(14) R. A. Ogg, Jr., *Discuss. Faraday Soc.*, 215 (1954).
(15) D. Kost, E. H. Carlson, and M. Raban, *Chem. Commun.*, 656 (1971).
(16) U. Eisner and J. Kuthan, *Chem. Rev.*, **72**, 1 (1972).
(17) T. Severin, H. Lerche, and D. Batz, *Chem. Ber.*, **102**, 2163 (1969).
(18) D. R. Clutter and T. J. Swift, *J. Am. Chem. Soc.*, **90**, 601 (1968).
(19) J. A. Zoltewicz and L. W. Deady, *J. Org. Chem.*, **37**, 501 (1972).
(20) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry", 2nd ed, Pergamon Press, Elmsford, N.Y., 1969.
(21) R. Huisgen, K. Herbig, A. Siegl, and H. Huber, *Chem. Ber.*, **99**, 2526 (1966); W. Bottomley, J. N. Phillips, and J. G. Wilson, *Tetrahedron Lett.*, 2957 (1967).
(22) T. J. van Bergen and R. M. Kellog, *J. Org. Chem.*, **36**, 1705 (1971).
(23) R. Eisenthal, A. R. Katritzky, and E. Lunt, *Tetrahedron*, **23**, 2775 (1967); R. Kuhn and E. Teller, *Justus Liebigs Ann. Chem.*, **715**, 106 (1968); A. F. Kluge and C. P. Lillya, *J. Org. Chem.*, **36**, 1977 (1971).
(24) U. Fritzsche and S. Hünig, *Justus Liebigs Ann. Chem.*, 1407 (1974).
(25) J. Schnekenburger and D. Heber, *Chem. Ber.*, **107**, 3408 (1974).
(26) K. Schofield, "Hetero-Aromatic Nitrogen Compounds", Plenum Press, New York, N.Y., 1967, pp 264–269.
(27) R. Eisenthal and A. R. Katritzky, *Tetrahedron*, **21**, 2205 (1965); A. R. Katritzky and E. Lunt, *ibid.*, **25**, 4291 (1969).
(28) E. A. Oostveen, H. C. van der Plas, and H. Jonegejan, *Recl. Trav. Chem. Pays-Bas*, **93**, 114 (1974).
(29) Y. T. Pratt in "Heterocyclic Compounds", Vol. 6, R. C. Elderfield, Ed., Wiley, New York, N.Y., 1957, Chapters 9 and 10.
(30) J. W. Bunting and W. G. Meathreal, *Can. J. Chem.*, **50**, 917 (1972); A. Albert and K. Ohta, *J. Chem. Soc. C*, 2357 (1971).
(31) A. Nagel, H. C. van der Plas, and A. van Veldhuizen, *Recl. Trav. Chim. Pays-Bas*, **94**, 45 (1975).
(32) M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970).
(33) J. A. Zoltewicz and R. E. Cross, *J. Chem. Soc., Perkin Trans. 2*, 1363 (1974); J. A. Zoltewicz and L. S. Helmick, *J. Am. Chem. Soc.*, **92**, 7547 (1970); L. W. Deady and J. A. Zoltewicz, *ibid.*, **93**, 5475 (1971).

Competitive Addition of Carbon, Sulfur, and Nitrogen Nucleophiles to Quaternized Heteroaromatic Compounds in Liquid Ammonia

John A. Zoltewicz,* Larry S. Helmick, and John K. O'Halloran

Department of Chemistry, University of Florida, Gainesville, Florida 32611

Received September 9, 1975

Nitromethide and ethanethiolate ions when present as ammonium salts in liquid ammonia add to the 4 position of 1-methylpyridinium ion. Each anion adds to the 4 positions of 3-iodo- and 3-cyano-1-methylpyridinium ions, to the 6 position of 1,2,5-trimethylpyrazinium ion, and to the 1 positions of 2-benzylisoquinolinium and 2-benzylphthalazinium ions. Carbanion addition to the 4 position of 3-substituted 1-methylpyridinium ions having CH_3, $CONH_2$, $COCH_3$, CO_2CH_3, and CF_3 substituents and to the 2 position of 3-methoxy-1-methylpyridinium ion also was observed. Carbanion addition is complete except with the 1-methyl-, 1,3-dimethyl-, and 1-methyl-3-methoxypyridinium and 2-benzylphthalazinium ions; aromatic starting material is present in the case of the pyridinium ions while 1-amino adduct is present in the phthalazinium ion case. Amino and not carbon adducts are detected for 3-chloro- and 3-carbamoyl-1-methylpyrazinium ions. Thiolate ion adds to the 4 and 6 positions of 3-acetyl- and 3-carbomethoxy-1-methylpyridinium ions to give mixtures. 3-Carbamoyl-1-methylpyridinium ion adds thiolate ion at the 4 and 6 positions; interconversion is fast enough to make the mixture appear by NMR as a single adduct. Thiolate ion addition is complete except in the cases of 1-methyl- and 1-methyl-3-methoxypyridinium ions.

Many quaternized heteroaromatic molecules on addition to liquid ammonia rapidly and quantitatively add solvent at an annular carbon atom to yield amino dihydro derivatives.[1-4] We now report that nitromethide and ethanethiolate ions dissolved in ammonia successfully compete with solvent to give carbon and sulfur addition products. In these competition reactions aromatic substrates often are completely transformed to a carbon or sulfur addition product. However, the site of addition of the carbon and sulfur nucleophiles may be different from that of ammonia. Nitromethide ion was selected for study because it is readily formed from nitromethane in ammonia[5] and it seemed likely that successful competition with ammonia might result. Many quaternized heteroaromatic molecules are known to add nitromethide ion in hydroxylic solvent.[6-8] The high carbon affinity of sulfur nucleophiles[9] prompted the selection of ethanethiolate ion, which is known to add to aromatic compounds to form anionic σ complexes.[10]

Results and Discussion

Addition of Nitromethide Ion. Deprotonation of nitroalkanes by liquid ammonia is unusual. The extent of proton transfer from the carbon acid to ammonia increases with decreasing temperatures,[5] in contrast to deprotona-

Table I. Chemical Shifts (τ) and Coupling Constants (Hz) for Compounds Produced by the Addition of Nitromethide Ion[a]

Compd	H-α	H-2	H-4	H-5	H-6	Other	$J_{4,5}$	$J_{5,6}$	$J_{4,\alpha}$	Other
Ia	4.29	4.01	5.8[b]	5.6[b]	4.01	NCH_3, 7.15		7		
b	4.27	3.45	5.63	5.54	3.95	NCH_3, 7.10	4	7	7.5	
c	4.34	4.24	5.90	5.67	4.06	NCH_3, 7.19 CCH_3, 8.47	3.5	7.5	7.5	
d	4.24	2.95	5.56	5.25	3.79	NCH_3, 6.91	5	7.5	8	
e	4.51	2.51	5.69	4.86	3.85	NCH_3, 6.90 $COCH_3$, 7.87	4.5	7.5	6.5	
f	4.39	2.73	5.68	4.92	3.95	NCH_3, 6.92 OCH_3, 6.36	4.5	8	6.5	
g	4.26	3.19	5.63	5.19	3.91	NCH_3, 6.96	4.5	7.5	7	
h	4.17	2.90	5.62	5.18	3.95	NCH_3, 6.95	4	8	7.5	
II	3.99	5.08	4.86	5.34	4.21	NCH_3, 7.26 OCH_3, 6.43	6	7		$J_{2,\alpha} = 8.5$
III	3.97	5.16		4.36		NCH_3, 7.18 CCH_3, 8.03; 8.18				$J_{2,\alpha} = 8.5$
IV	3.74[b]	4.42[b,c]	4.80	3.69[d]		H-5–8, 2.8–3.3 C_6H_5, 2.67 CH_2, 5.55; 5.73				$J_{3,4} = 7.5$ $J_{1,\alpha} = 8$ $J_{CH_3} = 15.7$
V	3.79[b]	4.44[b,c]				H-4–H-8 and C_6H_5 2.5–2.9				$J_{1,\alpha} = 8.5$

[a] $J_{2,6}$ for pyridine derivatives ≤ 1.5 Hz. [b] Assignments may be interchanged. [c] H-1. [d] H-3.

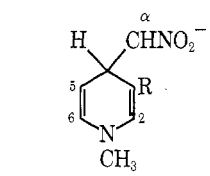
tion by hydroxide ion or water in aqueous solution.[11] Ionization of nitromethane in ammonia becomes detectable by NMR at about −10°C.[5]

Addition of nitromethide ion to the annular position of an aromatic electrophile is easily recognized by NMR. Spectra of the carbon adducts, shielded with respect to aromatic starting material, show a sharp doublet with coupling constant about 7–8 Hz. A doublet results because the nitromethyl side chain formed in the addition step undergoes deprotonation by the solvent. The remaining single proton of the side chain is spin coupled to the annular proton at the site of addition.

The presence of this doublet confirms that the nucleophilic atom of the ambident nitromethide ion is carbon and not oxygen and indicates that turnover of the side chain must be slow. A likely mechanism of turnover first involves protonation of the side chain prior to elimination. An upper limit of $J\,\pi/\sqrt{2}$ or about 17 s^{-1} can be set for protonation and ligand loss by a pseudo-first-order reaction. Supporting this conclusion is the observation that separate signals always were observed for bound ligand and methide ion in solution.

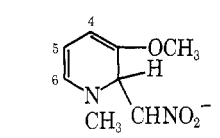
The greater affinity of the carbon nucleophile over ammonia is readily seen in the results for 1-methylpyidinium ion. Reaction of this electrophile with ammonia is not apparent by NMR analysis over a wide temperature range. By contrast, addition of the carbon nucleophile is extensive but incomplete. Substrate and a slight excess of nitromethide ion were allowed to warm to 10 °C in order to achieve solution and then cooled. Spectra recorded over the interval −50 to −20 °C clearly showed the presence of both adduct and starting material; at −50 °C about 90% of the material was present as adduct. The simplicity of the adduct spectrum and the integrated areas clearly indicate that the major adduct is Ia, which results from addition to the 4 position of the ion, Table I. No attempt was made to extract coupling constants from the second-order spectrum involving the five annular protons.[12] Previous attempts to achieve addition between nitromethane and 1-alkylpyridinium ions have failed.[6]

A series of 3-substituted 1-methylpyridinium ions was examined. Included are the 3-methyl ion, which does not give detectable addition with ammonia, and the 3-methoxy compound, which shows only a trace of reaction with solvent. Also considered are ions which quantitatively add

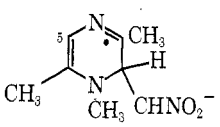


R

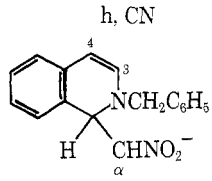
Ia, H
b, I
c, CH_3
d, $CONH_2$
e, $COCH_3$
f, CO_2CH_3
g, CF_3
h, CN



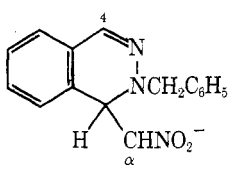
II



III



IV



V

ammonia, the 6 position of the ion being favored except in the case of the 3-iodo compound where the 2 position is the site of addition of ammonia. All these ions underwent addition with nitromethide ion. Addition of the carbon nucleophile to position 4 was observed for all except the 3-methoxy compound, which reacts at position 2.

Coupling constants of 4-position adducts are similar to those of known structure.[7,13] The known adducts do not, however, have an ionized nitromethyl side chain.[7] A deuterium-labeling experiment was utilized to show that the carbon nucleophile added to position 4 of the 3-iodo compound to give the 4-deuterio derivative of Ib. Details are given in the supplementary material.

At −5 °C a little protonated 3-iodo adduct was produced; essentially complete conversion to the adduct having a nitromethyl chain was observed on raising the temperature to 20 °C. Relative to the anion, H-2 and H-6 of the carbon protonated adduct are deshielded by about 14 Hz while H-4 and H-5 are shielded by about 21 and 7 Hz, respectively.

Interestingly, the presence of an electron-donating meth-

Table II. Chemical Shifts (τ) and Coupling Constants for Compounds Produced by the Addition of Ethanethiolate Ion[a]

Compd	H-2	H-4	H-5	H-6	Other	J, Hz
VIb[b]	3.30	5.30	5.45	3.62	NCH_3, 6.98	$J_{4,5} = 4.5$; $J_{5,6} = 7$
c	2.69	5.49	5.07	3.63	NCH_3, 6.86	$J_{4,5} = 5$; $J_{5,6} = 7.5$
d	2.19	5.33	4.90	3.51	NCH_3, 6.74; CH_3, 7.85	$J_{4,5} = 5.5$; $J_{5,6} = 7.5$
e	2.52	5.40	4.96	3.50	NCH_3, 6.79; CH_3, 6.32	$J_{4,5} = 5.5$; $J_{5,6} = 7$
VIf and VIIc[f]	2.59	4.40	4.96	3.80	NCH_3, 6.83	$J_{4,5} = 7$; $J_{5,6} = 6.5$
VIIa[c]	4.24	3.21	4.71[d]	2.04	NCH_3, 6.67 CH_3, 7.72	$J_{2,3} = 4.5$; $J_{3,4} = 10$
b	4.18	3.35	4.78[d]	2.39	NCH_3, 6.71 CH_3, 6.28	$J_{2,3} = 4.5$; $J_{3,4} = 9.5$
VIII	4.46		4.18		NCH_3, 7.01 CH_3, 7.92, 8.12	
IX	4.33		3.00[d]	2.75	NCH_3, 6.79	$J_{2,3} = 3.5$; $J_{3,6} = 1$; $J_{2,6} < 1$
X	4.10[e]	4.57	3.52[d]		CH_2, 5.41 band, 2.6–3.1	$J_{1,3} = 1.5$; $J_{3,4} = 7.5$
XI	4.18[e]				CH_2, 5.22 band, 2.4–2.9	

[a] Free and bonded ethanethiolate ions undergo rapid averaging in all cases except VIc, IX, and XI, where separate but overlapping signals are found; $CH_2 \sim \tau$ 7.6 and $CH_3 \sim \tau$ 8.8. [b] $J_{2,6}$ and $J_{2,4} \leq 1.5$ Hz. [c] $J_{2,6} < 1$ Hz; $J_{4,6} = 1.5$ Hz. [d] H-3. [e] H-1. [f] Positions are numbered according to VIf.

yl group at the 3 position of 1-methylpyridinium ion does not prevent adduct Ic from being formed. However, conversion to adduct was only about one-half complete in the presence of a slight excess of nucleophile over the range −65 to −25 °C. The 3-carbamoylpyridinium ion formed adduct Id; good spectra were recorded at −45 and at −25 °C, although solubility was a problem. Similarly, the 3-acetyl ion gave adduct Ie at −31 °C; a minor component (~20%) was not identified.

Amino adduct formed by the addition of ammonia to the 6 position of a pyridinium ion was present along with carbanion adducts If–h when the substituent at position 3 was CO_2CH_3, CF_3, or CN. Some 2-amino adduct also was present in the case of cyano substrate. Initial spectra recorded at about −60 °C showed the presence of multiple adducts. Raising the temperature at about −25 °C caused the formation of more carbon adduct to take place at the expense of amino compound.

Reaction of 1-methyl-3-methoxypyridinium ion with nitromethide ion constitutes an exception to the pattern of addition to position 4. The nucleophile adds to position 2 to give II. All the annular proton signals of adduct show major couplings; the largest involves the side chain, being 8.5 Hz. The splitting pattern is different from those observed for the other 3-substituted pyridinium ion adducts and indicates another site of addition which can only be position 2. The presence of starting material signifies that conversion to adduct is incomplete over the range −65 to 25 °C but the adduct is the major component. Adduct formation again demonstrates the greater affinity of the carbon nucleophile over that of ammonia. Essentially no adduct is detected in the presence of the latter nucleophile alone.

Failure to undergo the carbon addition reaction was found with some pyrazinium ions. Neither the 3-chloro- nor the 3-carbamoyl-1-methylpyrazinium ion gave carbon adduct. Only the known amino adducts[4] were detected over the range −60 to 0 °C. Observation time was about 0.5 h; no attempt was made to determine whether carbon adduct slowly forms over longer periods. By contrast, addition of nitromethide ion to 1,2,5-trimethylpyrazinium ion to give III was complete at −60 °C. The spectrum did not change on raising the temperature to 0 °C; no other component was detected.

Comparison of the results for 2-benzylisoquinolinium ion and its 3-aza derivative, 2-benzylphthalazinium ion, provides a striking contrast. Only carbon adduct IV formed by the addition of nitromethide ion to position 1 of the isoquinolinium ion was observed over the temperature range −51 to 0 °C. However, the phthalazinium ion only formed amino adduct at low temperatures; a very small amount of carbon adduct V was finally observed at 0 °C, as evidenced by the presence of a pair of doublets resulting from coupling of H-1 with the ionized nitromethyl side chain. Signal overlap with the main component prevents full characterization of the carbon adduct, however.

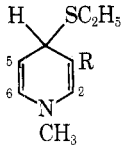
Addition of Ethanethiolate Ion. Results for a mixture of 1-methylpyridinium iodide and ethanethiolate ion are understandable if it is assumed that starting material and thiolate ion adduct both are present and that the resultant spectrum is an average of the two forms. Thiol ligand turnover is rapid enough to give rise to signal averaging, leading to a single spectrum. Lack of separate signals for free and bonded thiolate ions supports this assumption.

As a mixture of 1-methylpyridinium ion and the thiolate ion was warmed from −60 °C signals for the annular protons and those of the methyl group shifted upfield as more of the ammonium thiolate salt dissolved and reacted. Above about −10 °C the spectrum began to shift in the opposite direction, probably owing to dissociation of the adduct. The spectrum consists of an apparent doublet at low field due to H-2 and -6 and overlapped multiplets for the remaining annular protons. The extent of overlap increases as more adduct is formed. The spectrum is qualitatively similar to that for Ia, resulting from the addition of nitromethide ion to the 4 position of the same heterocycle. The simplicity of the spectrum indicates that the thiolate ion adds largely to position 4 to give VIa. Chemical shifts taken from the most shielded spectrum employing a large excess of thiolate ion in order to shift the equilibrium position to favor adduct are τ 2.41 (H-2, -6), 3.48 (H-4), 3.75 (H-3, -5), and 6.34 (NCH_3). Comparison of these values with those reported in Table II for other 4 adducts shows that conversion to adduct is incomplete.

Similar results were observed for 3-methoxy-1-methylpyridinium ion and ethanethiolate ion. Again, on raising the temperature from −50 to −10 °C the spectrum shifted upfield as more of the thiolate salt dissolved and added. At 10 °C the spectrum shifted downfield, apparently as a result of dissociation of an adduct or adducts. Cooling the mixture to −10 °C caused the signals to shift back upfield, indicating reversibility. The most shielded spectrum has

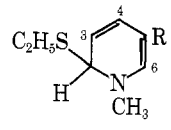
the following characteristics: τ 2.36 (J = 6 Hz, H-4, or H-6), 2.41 (J = 1 Hz, H-2), 2.97 (J = 1 and 7.5 Hz, H-6 or H-4), and 3.32 (J = 6 and 7.5 Hz, H-5), 6.08 and 6.14 (CH_3 groups). Insufficient adduct is present to assign a structure. Interestingly, both 1-methyl- and 3-methoxy-1-methylpyridinium ion undergo less addition with ethanethiolate ion than with nitromethide ion. However, addition of the thiolate ion proceeds to a greater degree than ammonia.

1-Methyl-3-iodopyridinium ion in the presence of ethanethiolate ion does not give the known amino adduct.[4] Adduct VIb results from addition of thiolate ion to position 4 of the ion. Supporting this conclusion is the observation that a signal at high field (τ 5.30) disappeared on deuteration of position 4. At 20 °C signals due to another ethylthio group appeared slightly downfield from those due to adduct and thiolate ion. The new signals probably result from displacement of the iodo group to form a 3-ethylthio substitution product.



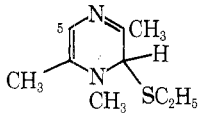
R

VIa, H
b, I
c, CN
d, $COCH_3$
e, CO_2CH_3
f, $CONH_2$

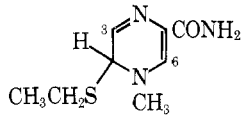


R

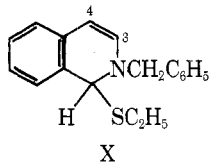
VIIa, $COCH_3$
b, CO_2CH_3
c, $CONH_2$



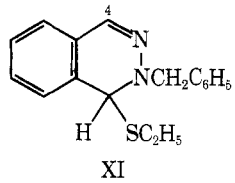
VIII



IX



X



XI

3-Cyano-1-methylpyridinium ion in the presence of ethanethiolate ion first forms the known adduct resulting from the addition of solvent to the 6 position of the ion.[4] This amino adduct was the major product at −65 °C but at −25 °C appreciable amounts of thiol adduct were present. At −10 °C only the new product was observable; cooling the sample to −35 °C did not regenerate the spectrum of amino adduct. At −10 °C separate but overlapping signals were found for the methylene protons of free and bonded thiolate ion, indicating that ligand turnover is slow. However, signal overlap prevents determination of coupling constants of bonded thiolate ion. The shielded position of H-4 in the spectrum requires the adduct to have structure VIc resulting from the addition of the nucleophile to position 4 of the ion.

Broadening was clearly evident in the spectrum of a sample of 1-methyl-3-acetylpyridinium ion and ethanethiolate ion in ammonia. At 35 °C the spectrum consisted of a sharp peak at τ 2.5 (H-2), a very broad signal at τ 4.1, and a sharp apparent triplet at τ 4.8 (H-5) along with sharp singlets at τ 6.8 (NCH_3) and 7.8 ($COCH_3$). Raising the temperature to 70 °C produced no significant change. Cooling to −40 °C, however, resulted in a dramatic increase in resolution. An approximately equimolar mixture of two adducts clearly was present. Cycles of broadening and resolving of spectra were observed on repeated warming and cooling, indicating reversibility. Both adducts are due to the addition of thiolate ion to the pyridinium ion, one to position 4 to give VId and the other to position 6 of the ion to yield VIIa,[14] Table II. Assignments are supported, for example, by the fact that each adduct shows a signal for H-2 at the lowest field portion of the spectrum, eliminating a 2 adduct from consideration. The known amino adduct[4] can be eliminated as a possibility; see supplementary material.

The pattern of signal averaging at high temperatures is understandable when the spectra of the two adducts are considered. The two annular protons which show sharp signals at higher temperatures have chemical shifts which are very similar in both adducts. However, the two broadened signals are associated with adducts in which there is a large separation between signals for equivalent protons. Consider, for example, H-4, which shows a signal at τ 3.21 in one adduct and at τ 5.33 in the other, a separation of 127 Hz. Interconversion of these widely separated signals requires a much faster rate (higher temperature) than that, say, for H-2 where the separation of the signals in the two adducts is only 10 Hz. The protons with similar shifts coalesce at a much lower temperature than the more widely spaced ones as the adducts interconvert.

Spectra for a mixture of 1-methyl-3-carbomethoxypyridinium ion and ethanethiolate ion are similar to those for the 3-acetyl ion. At −10 °C broad peaks were observed but cooling to −40 °C resulted in an increase in resolution. Again, two adducts present to approximately the same degree clearly were observed. As in the 3-acetyl case, products VIe and VIIb[14] are likely to be the result of addition of thiolate ion to positions 4 and 6 of the pyridinium ion, respectively, Table II.

At 35 °C the spectrum of 1-methyl-3-carbamoylpyridinium ion and ethanethiolate ion was much like those for the 3-acetyl and 3-carbomethoxy ions under similar conditions. A sharp peak at τ 2.5, broad bands at τ 3.8 and 4.1, and an apparent triplet at τ 4.7 were observed for the annular protons. Cooling, however, led to a completely different result. The two broad bands resolved into two multiplets. Superficial examination suggests that one, rather than two, adducts appears to be present.

In an effort to obtain more information about the reaction of the 3-carbamoyl ion, the 1-benzyl derivative was examined. Although the benzyl methylene protons of an adduct are diastereotopic and therefore can give rise to separate signals, they appeared as a singlet even at −25 °C. Moreover, separate signals for the diastereotopic ethylthio protons were not observed. Hence, ligand turnover seems to be rapid, causing diastereotopic protons to appear enantiotopic.

Careful consideration of the spectrum for the carbamoyl substrate leads to a most interesting conclusion. A rapidly equilibrating mixture of adducts resulting from thiolate ion addition to the 4 (VIf) and 6 (VIIc) positions of the ion is being observed. Equilibration is so fast that the spectrum appears to be that of a single substance. There is strong support for this conclusion. If the spectra of the two adducts of the 3-acetyl or 3-carbomethoxy compound are assumed to be models of those for similar adducts of the 3-carbamoyl compound and if it also is assumed that an equimolar mixture of the two adducts is present, then the observed spectrum, chemical shifts and coupling constants, is essentially that calculated using parameters for these known adducts. In making this calculation, appropriate shifts and coupling constants were averaged. Those proton

signals which undergo the largest changes in shift and therefore constitute the most sensitive test of the hypothesis concerning averaging may be used to illustrate the method of calculation. The average of τ 5.40 for H-4 of VIe and τ 3.35 for H-4 of VIIb is 4.38. This is to be compared with the observed value τ 4.40 for the carbamoyl substrate. Although the difference between observed and calculated values is slightly larger (0.13 ppm) using the acetyl adducts as models, the difference again is insignificant. Moreover, the rate constant for the interconversion of the two adducts may be estimated. Thus, at coalescence, $k = \Delta\pi/\sqrt{2} = 265^{-1}$, where Δ is the difference in hertz between the signals being averaged. Since the spectra showing sharp signals are recorded above the coalescence temperature, the lifetime of an adduct under these conditions is less than $1/k$ or 3.8 ms. Turnover of adducts indeed is rapid.

Interconversion of the two adducts formed from carbamoyl substrate is so facile that we have not been able to "freeze out" the individual adducts by lowering the temperature. By contrast, with acetyl and carbomethoxy substrates it is possible to see the spectra of two adducts at low temperatures. However, we have not been able to interconvert them rapidly enough on raising the temperature to get a single, averaged spectrum, as in the case of the carbamoyl compound. The reason for broad signals at probe temperature in the carbamoyl case is unknown; raising the temperature of the sample led to uninformative results. It should be noted that although adduct structures are written with a neutral carbamoyl group, ionization of this group may take place. We have no independent evidence concerning the extent of such deprotonation for these or any other adducts containing a "carbamoyl" group.

Both 1,2,5-trimethylpyrazinium and 1-methyl-3-carbamoylpyrazinium ions react at probe temperature with ethanethiolate ion to give adducts VIII and IX,[14] respectively. In the first case the product structure can be assigned easily because the two CH_3 groups bonded to carbon have similar chemical shifts, indicating nucleophilic addition to a site unoccupied by a methyl group. In the second example the 3.5-Hz coupling constant suggests that the thiolate ion adds to the 6 position of the pyrazinium ion; addition to position 2, the other possibility, would result in an adduct with a larger coupling constant.[4] The methylene protons of IX clearly are diastereotopic, indicating slow ligand turnover. However, partial overlap with those of the free ion prevents us from determining coupling constants.

Both 2-benzylisoquinolinium and 2-benzylphthalazinium ions in the presence of a slight excess of thiolate ion are completely converted at 30 °C to sulfur adducts. Addition to position 1 led to the formation of X and XI, respectively. The *N*-methylene protons of both adducts show a singlet rather than a multiplet signal. Separate signals were not observed at 30 °C for free and bonded thiolate ion in the case of X, suggesting that ligand turnover may be rapid enough to make the diastereotopic protons of X appear enantiotopic. However, with XI separate but largely overlapping signals were observed at 30 °C for free and bonded thiolate ions, suggesting that the presence of the second annular nitrogen atom in XI causes a reduced rate of turnover. The reason for the singlet signal for the benzyl methylene protons of XI is unclear. The singlet may be due to accidental degeneracy of the diastereotopic protons[15] or to ligand exchange.

Successful formation of adducts IX and XI involving thiolate ion and 3-carbamoyl-1-methylpyrazinium and 2-benzylphthalazinium ions, respectively, is especially interesting. By contrast, the first heterocyclic ion did not give rise to an adduct with nitromethide ion while the second yielded only a minor amount of product. In the presence of the carbon nucleophile, amino adduct is the major product in both cases. Reaction temperatures were very different in experiments involving the carbon and sulfur nucleophiles, however. The thiolate ion reactions were examined at about 30 °C, while those with nitromethide ion were conducted below about 0 °C. Higher temperatures were avoided with the carbanion because it is largely converted to nonnucleophilic nitromethane under such conditions. It would be worthwhile to examine the thiolate ion and the two quaternized compounds at low temperatures; perhaps thiolate ion adduct formation would be slow because starting material is converted largely to amino adduct.

General. Reversibility of the addition of the carbon and sulfur nucleophiles was demonstrated by recovering aromatic starting material from addition reactions. Details are found in the Experimental Section. Attempts were not made to isolate adducts or to broaden the scope of the investigation by studying other nucleophiles. Certainly, other carbon nucleophiles are likely to undergo addition reactions similar to those of nitromethide ion.[13,16]

A solid foundation has been laid for the addition of various nucleophiles to quaternized heteroaromatic electrophiles in ammonia. Possibilities for extensive studies dealing with kinetic and thermodynamic control of addition reactions and their relationships to structural effects are obvious. Methods utilizing the nitrogen, carbon, and sulfur adducts as intermediates in synthetic sequences await exploitation.

Experimental Section

All compounds with the exception of 1-methyl-3-iodopyridinium-*4-d* iodide were available from previous studies.[17] 3-Iodopyridine-*4-d*[18] (55–60% D) was quaternized with methyl iodide.[19] Reaction mixtures were prepared in NMR tubes as previously indicated.[1] Ethanethiol or nitromethane (1–2 equiv) was added by syringe to cooled mixtures. Spectra were recorded on a Varian A-60A spectrometer equipped with a V-6040 variable temperature controller.

Recovery of Heteroaromatic Starting Material Following Adduct Formation. After NMR spectra of a mixture of 1-methylpyridinium iodide and nitromethane were recorded, the sample was cooled in an acetone–dry ice bath, and then poured into 5 ml of ether cooled in the same bath. The yellow resultant precipitate was removed by filtration and dissolved in D_2O containing sodium acetate internal standard. The NMR spectrum was identical with that of starting material; integration with reference to the standard indicated that recovery was 91%. The same procedure was employed for a mixture of ethanethiol and 1-methyl-3-carbamoylpyrazinium iodide which had stood at room temperature for 1 week; recovery of starting material was 40%.

A mixture of 100 mg (0.426 mmol) of 1-methyl-3-acetylpyridinium perchlorate and 100 μl (1.35 mmol) of ethanethiol in 5 ml of ammonia was held at −33 °C for 5 min. After 5 ml of cold ether was added, the mixture was allowed to warm slowly to evaporate the ammonia. The ether was decanted and the crystalline material was washed once with ether; 59 mg (59%) of compound having an NMR spectrum identical with that of starting material was recovered. The same procedure was employed with the same substrate and nitromethane (100 μl, 1.87 mmol) and afforded 75 mg (75%) of starting material.

Registry No.—Ia, 58091-32-0; Ib, 58091-33-1; Ic, 58091-34-2; Id, 58091-35-3; Ie, 58091-36-4; If, 58091-37-5; Ig, 58091-38-6; Ih, 58091-39-7; II, 58091-40-0; III, 58091-41-1; IV, 58091-42-2; V, 58091-43-3; VIb, 58091-44-4; VIc, 58091-45-5; VId, 58091-46-6; VIe, 58091-47-7; VIf, 58091-48-8; VIIa, 58091-49-9; VIIb, 58091-50-2; VIIc, 58091-51-3; VIII, 58091-52-4; IX, 58091-53-5; X, 58091-54-6; XI, 58091-55-7; 1-methylpyridinium ion, 694-56-4; 3-iodo-1-methylpyridinium ion, 54560-56-4; 1,3-dimethylpyridinium ion, 18241-34-4; 3-carbamoyl-1-methylpyridinium ion, 3106-60-3; 3-acetyl-1-methylpyridinium ion, 51061-43-9; 3-carbomethoxy-1-methylpyridinium ion, 18899-18-8; 3-trifluoromethyl-1-methylpyridinium ion, 58091-56-8; 3-cyano-1-methylpyridinium ion, 15923-

33-8; 3-methoxy-1-methylpyridinium ion, 54560-57-5; 1,2,5-trimethylpyrazinium ion, 58091-57-9; 2-benzylisoquinolinium ion, 38602-73-2; 2-benzylphthalazinium ion, 46818-75-1; 3-carbamoyl-1-methylpyrazinium ion, 58091-58-0; nitromethide ion, 18137-96-7; ethanethiolate ion, 20733-13-5.

Supplementary Material Available. Additional NMR data and interpretation (2 pages). Ordering information is given on any current masthead page.

References and Notes

(1) J. A. Zoltewicz, T. M. Oestreich, J. K. O'Halloran, and L. S. Helmick, *J. Org. Chem.*, **38**, 1949 (1973).
(2) J. A. Zoltewicz and J. K. O'Halloran, *J. Am. Chem. Soc.*, **97**, 5531 (1975).
(3) E. A. Oostveen, H. C. van der Plas, and H. Jongejan, *Recl. Trav. Chim. Pays-Bas*, **93**, 114 (1974).
(4) J. A. Zoltewicz, L. S. Helmick, and J. K. O'Halloran, *J. Org. Chem.*, preceding paper in this issue.
(5) J. A. Zoltewicz and J. K. O'Halloran, *J. Org. Chem.*, **39**, 89 (1974).
(6) W. Kiel, F. Kröhnke, and G. Schneider, *Justus Liebigs Ann. Chem.*, **766**, 45 (1972).
(7) H. Ahlbrecht and F. Kröhnke, *Justus Liebigs Ann. Chem.*, **717**, 96 (1968).
(8) F. Kröhnke and K. Ellegast, *Justus Liebigs Ann. Chem.*, **600**, 176 (1956); F. Kröhnke and I. Vogt, *ibid.*, **600**, 211 (1956); W. R. Schleigh, *J. Heterocycl. Chem.*, **9**, 675 (1972).
(9) J. Hine and R. D. Weimar, Jr., *J. Am. Chem. Soc.*, **87**, 3387 (1965); J. Hine, *ibid*, **93**, 3701 (1971); C. D. Ritchie, *Acc. Chem. Res.*, **5**, 348 (1972).
(10) M. R. Crampton, *J. Chem. Soc. B*, 1208 (1968); M. R. Crampton and M. El. Gharini, *ibid.*, 1043 (1971); G. Biggi and F. Pietra, *J. Chem. Soc., Chem. Commun.*, 229 (1973); J. W. Larsen, K. Amin, S. Ewing, and L. L. Magio, *J. Org. Chem.*, **37**, 3857 (1972); M. J. Strauss, *Chem. Rev.*, **70**, 667 (1970).
(11) T. Matsmi and L. G. Hepler, *Can. J. Chem.*, **51**, 1941 (1973).
(12) W. G. Schneider, H. J. Bernstein, and J. A. Pople, *Ann. N.Y. Acad. Sci.*, **70**, 806 (1958); M. Saunders and E. H. Gold, *J. Org. Chem.*, **27**, 1439 (1962).
(13) T. Severin, H. Lerche, and D. Batz, *Chem. Ber.*, **102**, 2163 (1969).
(14) Note that in adducts VII, VIII, and IX annular positions are numbered differently from those in aromatic starting materials.
(15) T. H. Siddall and W. E. Stewart, *Prog. Nucl. Magn. Reson. Spectrosc.*, **5**, 33 (1969); A. Rauk, L. C. Allen, and K. Mislow, *Angew. Chem., Int. Ed. Engl.*, **9**, 400 (1970).
(16) H. Albrecht and F. Kröhnke, *Justus Liebigs Ann. Chem.*, **704**, 133 (1967); T. K. Chen and C. K. Bradsher, *Tetrahedron*, **29**, 2951 (1973).
(17) J. A. Zoltewicz and R. E. Cross, *J. Chem. Soc., Perkin Trans. 2*, 1363 (1974); J. A. Zoltewicz and L. S. Helmick, *J. Am. Chem. Soc.*, **93**, 5475 (1971).
(18) J. A. Zoltewicz and C. L. Smith, *Tetrahedron*, **25**, 4331 (1969).
(19) G. B. Barlin and J. A. Benbow, *J. Chem. Soc., Perkin Trans. 2*, 790 (1974).

The Nature of the Carbonium Ion. XII. The *N*-*p*-Toluenesulfonyl-2-aza-5-norbornyl Cation[1a]

Robert D. Gleim[1b] and Langley A. Spurlock*[2]

Metcalf Research Laboratories, Brown University, Providence, Rhode Island 02912

Received April 8, 1975

The syntheses of several C_5-substituted *N*-*p*-toluenesulfonyl-2-azabicyclo[2.2.1]heptanes are described. Solvolytic studies carried out on the *exo*- and *endo*-*p*-bromobenzenesulfonates **13** and **16**, respectively, in buffered acetic acid indicate a 10^{-4}–10^{-5}-fold rate retardation for either isomer as compared with the acetolysis rate of its corresponding 2-norbornyl analogue. The **13**:**16** (exo/endo) rate ratio is 5. The endo acetate **15**, formed in a relatively high proportion, and the anticipated exo acetate **9** were primary acetolysis products from both **13** and **16**. A mechanistic interpretation of the results is presented.

In connection with our interest in heterocyclic analogues of the norbornyl skeleton, we commenced a synthetic sequence leading to the incorporation of a nitrogen atom into a two-carbon bridge of the bicyclo[2.2.1]heptane skeleton. We elected to investigate those derivatives which possess functional groups attached to the opposite bridge such that they are separated from the nitrogen atom by a minimum of three carbons. The strong structural resemblance of these derivatives to the analgetic agents meperidine and prodine suggested a potential for physiological activity in a manner originally suggested by Portoghese.[4] In addition, for most dissociation reactions of secondary 2-norbornyl derivatives which lead to carbonium ions, it is uncertain whether the C_6–C_1 σ bond is directly involved in ionization, affording a delocalized cation, or only involved in a subsequent Wagner–Meerwein shift interconverting two localized cations.[5,6] In the case of the 2-sulfonyl-2-aza 5-substituted compound, the proximity of the electron-withdrawing sulfonamide function to the C_3–C_4 ethylene bond (analogous to the C_6–C_1 bond in the 2-substituted carbocyclic compounds) promised to shed light on the electronic requirements for involvement of this bond in cation forming reactions on the opposite two-carbon bridge.

As the syntheses of C_5-substituted 2-azanorbornyl systems are rather complex, only a few derivatives with this substitution pattern have been reported.[4,7]

Results

The *N,O,O'*-tri-*p*-toluenesulfonate ester of hydroxy-L-prolinol (**1**) was prepared by the method of Portoghese[4] and employed as the chief precursor to the 2-azabicyclo-[2.2.1]hept-5-yl derivatives.[8] (See Scheme I.) Reaction of the triarenesulfonate ester **1** with sodiomalonic ester in ethanol or in diglyme effected ring closure to bicyclic diester **2**. Hydrolysis in ethanol or in diglyme afforded the corresponding geminal diacid **3**. The crude diacid was effectively decarboxylated in pyridine at reflux to yield a mixture of the epimeric monoacids **4** and **5**. The acids were shown to be in an endo/exo ratio of 80:20 by GC analysis of their methyl esters. As the endo acid **5** was substantially more hindered than its epimer, a partial purification was achieved by preferential reaction of exo acid **4** with *tert*-butylamine, generating the acid salt **6**. Regeneration of the acid and crystallization from benzene gave pure exo acid **4**. The endo acid **5** was recovered from the mother liquors of the salt forming reaction.

In an attempt to further verify the stereochemical assignments about C_5, the methyl esters **7** and **8** were pre-