Leaving Group Efficacy in the Generation of Nitrenium Ions from Hydroxylamine Derivatives[1]

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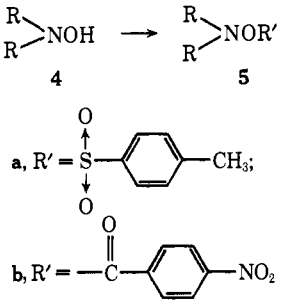
Abstract: *N,N*-Dialkylhydroxylamines, which are readily available from the corresponding secondary amines, have been shown to be useful precursors for the generation of nitrenium ions. The conversion of the hydroxyl group of the hydroxylamine into a suitable leaving group has been accomplished by its conversion to either a benzoate or sulfonate ester. *O*-Sulfonate esters of most hydroxylamines were found to be too unstable for convenient handling. 3,5-Dinitrobenzoates were found to be the most useful derivatives for subsequent heterolytic cleavage of the N–O bond to produce a nitrenium ion. These observations were placed on a more quantitative basis by the observation of a ρ of +0.68 for the methanolysis of a series of piperidin-1-yl benzoates, in comparison with a value of *ca.* +1.34 for the ρ determined for methanolysis of a series of 1-phenylcyclohexyl benzoates, indicating that the transition state for heterolytic cleavage of an N–O bond to generate a nitrenium ion occurs earlier in the bond breaking process than for heterolytic cleavage of a C–O bond to produce a tertiary carbonium ion.

The last few years have witnessed the firm establishment of divalent positive nitrogen (the nitrenium ion) as the mechanistic species involved in the rearrangement, synthesis, and cleavage of a variety of nitrogen containing compounds. The growing interest of theoretical[2-4] and synthetic organic chemists[5-7] in the reaction of nitrenium ions[8] has dictated the need for a more thorough knowledge of basic nitrenium ion chemistry. For instance, a more detailed knowledge of how nitrenium ions can be generated would be particularly useful. Most of the published reactions of nitrenium ions utilized the solvolytic heterolytic cleavage of the N–Cl bond of chloramines. Recently, it has been demonstrated that nitrenium ions can be generated from bromamines,[9] unsymmetrical hydrazines,[10] and, in a few isolated cases, hydroxylamine derivatives.[6,7,11,12] Since *N,N*-dialkylhydroxylamines are readily prepared from the corresponding secondary amines *via* the procedure of Rogers,[13] the latter route to nitrenium ions is particularly attractive. We now wish to report the results of our study of the effect of the leaving group in the generation of nitrenium ions from hydroxylamine derivatives.

Secondary amines can be transformed into *p*-toluenesulfonates and *p*-nitrobenzoates of hydroxylamines by a general sequence of reaction. Addition of a secondary amine, **1**, to ethyl acrylate in a Michael-type reaction produced tertiary amine **2**. Oxidation of **2** with peracid gave an *N*-oxide, **3**, which on heating with base gave hydroxylamine **4** and ethyl acrylate.[13] Treatment of **4** with 1 equiv of *n*-butyllithium followed by 1 equiv of *p*-toluenesulfonyl chloride gave **5a**, while the reaction of **4** with an ethereal solution of *p*-nitrobenzoyl chloride and sodium hydroxide at −50° gave **5b**. We have found this synthetic sequence to be a general route to nitrenium ion precursors.



As a specific example, **6** gave **7** in 76% yield. The Michael adduct, **7**, was converted to **8** through oxidation with *m*-chloroperbenzoic acid, and **8** was immediately dissolved in 1 *M* sodium hydroxide and heated to 90° for 1.5 hr. This procedure gave a 54% yield of **9** (based on **7**) as a white waxy solid.[14] Mixing of **9** and *p*-nitrobenzoyl chloride in ether at −50° followed by the slow addition of powdered sodium hydroxide gave **10**, in 75% yield.

By analogy to carbonium ion chemistry, it might be anticipated that the conversion of dialkylhydroxylamines into the corresponding tosylates should provide a simple route to nitrenium ions. This idea was supported by the investigation of Biehler and Fleury,[7] who prepared **11** (R = strong electron-withdrawing

(1) Paper XXVII of a series on The Chemistry of Nitrenium Ions. For the previous paper in this series, see P. G. Gassman, R. L. Cryberg, and K. Shudo, *J. Amer. Chem. Soc.*, **94**, 7600 (1972).

(2) R. G. Weiss, *Tetrahedron*, 27, 271 (1971).

(3) S. T. Lee and K. Morokuma, *J. Amer. Chem. Soc.*, **93**, 6863 (1971); S. Y. Chu, A. K. Q. Siu, and E. F. Hayes, *ibid.*, **94**, 2969 (1972).

(4) For the postulated existence of nitrenium ions in the gas phase, see W. T. Huntress, Jr., and D. D. Elleman, *ibid.*, **92**, 3565 (1970).

(5) D. C. Horwell and C. W. Rees, *Chem. Commun.*, 1428 (1969); V. Rautenstrauch, *ibid.*, 1122 (1969); P. Kovacic, J.-H. Liu, P. D. Roskos, and E. M. Levi, *ibid.*, 1034 (1970); P. Kovacic, J. -H. Liu, E. M. Levi, and P. D. Roskos, *J. Amer. Chem. Soc.*, **93**, 5801 (1971).

(6) H. H. Wasserman, H. W. Adickes, and O. E. de Ochoa, *ibid.*, **93**, 5586 (1971).

(7) J. -M. Biehler and J. -P. Fleury, *Tetrahedron*, 27, 3171 (1971).

(8) For a recent review of nitrenium ion chemistry, see P. G. Gassman, *Accounts Chem.Res.*, **3**, 26 (1970).

(9) P. G. Gassman, K. Shudo, R. L. Cryberg, and A. Battisti, *Tetrahedron Lett.*, 875 (1972).

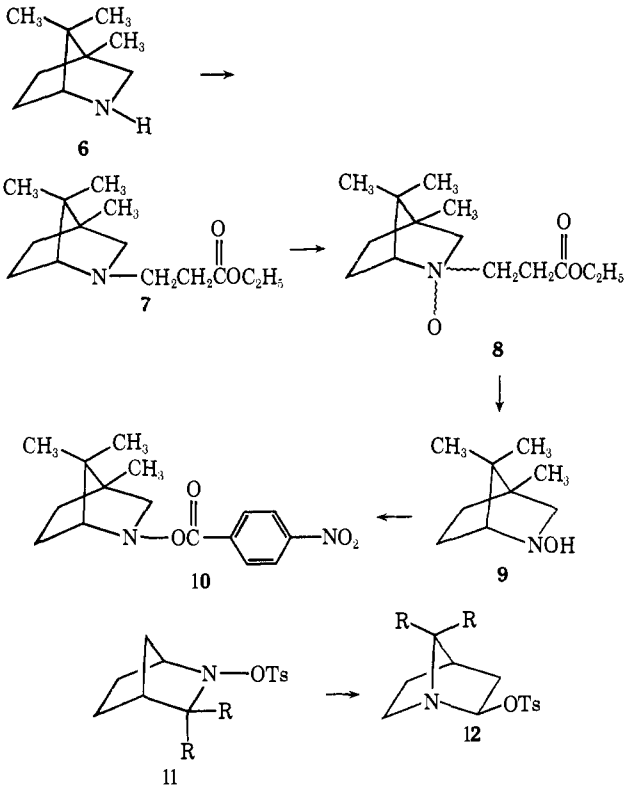
(10) P. G. Gassman and K. Shudo, *J. Amer. Chem. Soc.*, **93**, 5899 (1971).

(11) P. G. Gassman, K. Shudo, and G. Hartman, 2nd Central Regional Meeting of the American Chemical Society, June 3-5, 1971, Columbus, Ohio, Abstracts, p 55.

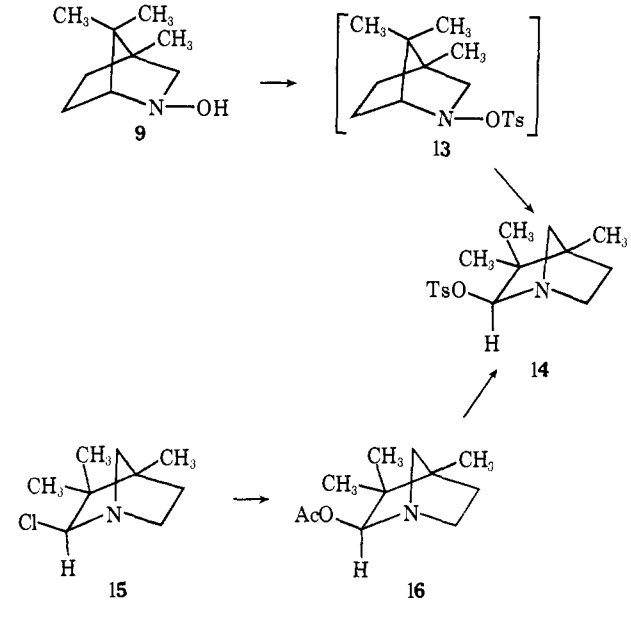
(12) We have recently been informed by Professor C. F. Wilcox of the unpublished results of Pohl on the solvolysis of *p*-nitrobenzoate and trichloroacetate esters of *N,N*-dialkylhydroxylamines in ethanol–water mixtures (K. K. Pohl, Ph.D. Thesis, Cornell University, 1963). Their preliminary results seemed to be more complex than ours, presumably due to the solvent system chosen. We wish to thank Professor Wilcox for this information. See also R. N. Keller and P. A. S. Smith, *J. Amer. Chem. Soc.*, **66**, 1122 (1944); **68**, 899 (1946); and P. Kovacic, R. P. Bennett, and J. L. Foote, *ibid.*, **84**, 759 (1962).

(13) M. A. T. Rogers, *J. Chem. Soc.*, 769 (1955).

(14) Infrared and nmr spectral data were consistent with the assigned structures. See Experimental Section for details.



substituents) and studied its solvolytic activity. They found that **11** rearranged readily to **12** at 25° in aqueous dioxane but was stable at room temperature in nonpolar media. Unfortunately, the practical use of the *p*-toluenesulfonate anion as a leaving group was limited to specific molecules in which the hydroxylamine function was flanked by strong electron-withdrawing groups. We have found that, in the absence of such electron-withdrawing groups, the initially formed sulfonate esters are extremely unstable. For example, reaction of **9** with 1 equiv of *n*-butyllithium followed by 1 equiv of *p*-toluenesulfonyl chloride failed to give **13**



as an isolable compound. Instead, **14** was obtained from the reaction mixture. The structure of **14** was verified both by spectral evidence and by independent synthesis. The nmr spectrum of **14** correlated excellently with that of **15**.[15] Reaction of **15** with silver acetate in refluxing acetic acid for 1.5 hr gave **16** as the major product.[16] When **16** was treated with 2 equiv of methyllithium followed by *p*-toluenesulfonyl chloride, a sample of **14** was obtained which was identical in all respects with the product obtained from **9**.[16]

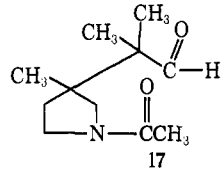
The formation of **14** under the conditions used to react **9** with *p*-toluenesulfonyl chloride demonstrates the extremely reactive nature of hydroxylamine tosylates.[17] We had previously shown[15] that the *N*-chloramine derived from **6** readily ionized to an ion pair, which underwent internal return to produce **15**. Available evidence indicated that the formation of **15** involved the formation of a nitrenium ion as a discrete intermediate.[19] In view of our data on the rearrangement of *N*-chloramines, we feel that the most likely mechanistic path from **9** to **14** involves the initial formation of **13** followed by ionization of **13** to form a nitrenium ion and tosylate anion. Internal return of this pair of ions would give **14**.

The facile rearrangement of **13** to **14** indicates that hydroxylamines, which have had their hydroxyl function converted into a suitable leaving group, should serve as excellent nitrenium ion precursors. Unfortunately, the extremely reactive nature of most *N,N*-dialkylhydroxylamine sulfonates makes these derivatives experimentally impractical. For this reason we turned our attention to the use of benzoate anions as leaving groups in the generation of nitrenium ions from hydroxylamine derivatives.

In order to evaluate the effect of using various benzoate anions as leaving groups, we studied the methanolysis of the piperidin-1-yl benzoates listed in Table I. Despite the good pseudo-first-order kinetics obtained conductometrically, the rates were anomalous in that all of the compounds listed in Table I appeared to solvolyze at about the same rate, although there was a drastic difference in the nature of the leaving groups. This result was distressing until a product analysis revealed that two competing reactions were occurring, one, which gave a nitrenium ion (**24**) and a benzoate anion (**25**), and a second, which produced *N*-hydroxypiperidine (**26**) and the appropriate methyl benzoate (**27**) *via* a simple transesterification reaction. In

(15) P. G. Gassman and R. L. Cryberg, *J. Amer. Chem. Soc.*, **90**, 1355 (1968); **91**, 2047 (1969).

(16) In addition to **16** a small amount of **17** was formed in this reaction. It was found that **16** could be thermally converted to **17**. We wish to thank Dr. Koichi Shudo for carrying out this interconversion: P. G. Gassman and K. Shudo, unpublished work.

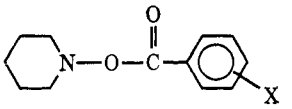


(17) An indication of the reactivity to be expected of hydroxylamine sulfonates was provided by the report[18] that *N,N*-diethylhydroxylamine reacts with benzenesulfonyl chloride to give an unstable compound which *explodes* in preparation or upon isolation. The products of this violent decomposition were identified as acetaldehyde and ethylamine. These products would be expected from the nitrenium ion intermediate generated in the heterolytic cleavage of the N–O bond of the intermediate hydroxylamine sulfonate.

(18) A. Ya. Berlin, M. N. Shchukina, and E. D. Sazonova, *Zh. Obshch. Khim.*, **14**, 249 (1944).

(19) P. G. Gassman and R. L. Cryberg, *J. Amer. Chem. Soc.*, **91**, 5176 (1969).

Table I. Methanolysis Rates of Piperidin-1-yl Benzoates at 50°



Compd	*p*-X	$k \times 10^6$ sec^{-1}	k_{rel}	Partial rate factor ($k_N \times 10^6$ sec^{-1}) for nitrenium ion formation[a]	k_{rel} for partial rate factors
18	OCH_3	23.6 ± 0.5	1.16	2.36	1.0
19	CH_3	15.5 ± 0.3	0.76	2.80	1.2
20	H	20.4 ± 0.5	1.00	4.50	1.9
21	Cl	16.2 ± 0.3	0.79	6.15	2.6
22	NO_2	13.7 ± 0.2	0.67	11.8	5.0
23	$3,5\text{-}(NO_2)_2$	43.8 ± 0.7	2.14	37.6	15.9

[a] Partial rate factors were determined by multiplying the overall rates by the product ratio for **26** and **28** shown in Table II (*vide post*).

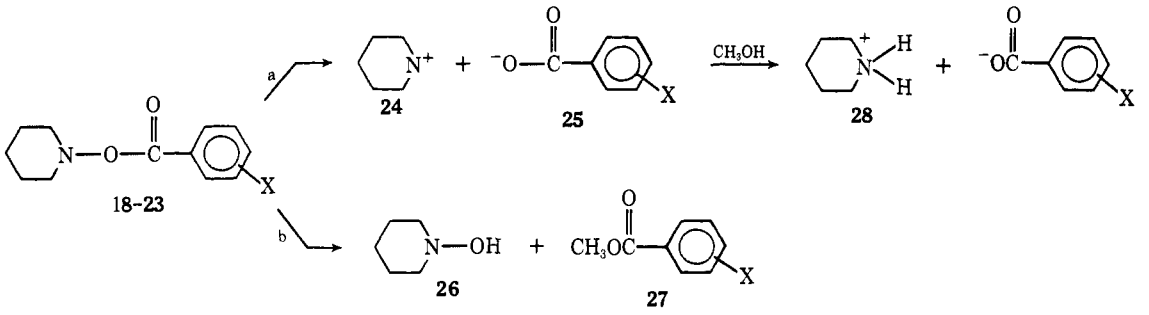
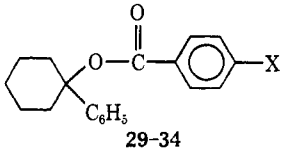


Table II. Products from the Methanolysis of **18–23**

Starting benzoate	Combined yield (vpc) of piperidine and *N*-hydroxypiperidine, %	Ratio of piperidine to hydroxypiperidine	Combined yield (isolated) of benzoic acid and methyl benzoate, %	Ratio of benzoic acid to methyl benzoate
18	96	10:90	83	10:90
19	95	18:82	88	15:85
20	92	22:78	86	25:75
21	94	38:62	86	39:61
22	88	86:14	82	83:17
23	94	86:14	90	85:15

methanol, the conversion of **24** into **28** was readily rationalized in terms of a singlet to triplet interconversion of the nitrenium ion, followed by hydrogen abstraction.[19-21] Table II lists the yields and ratios of products obtained in these solvolyses. Use of the ratio of piperidine to *N*-hydroxypiperidine allowed us to determine the partial rate factors, k_N, for path a (Table I). Figure 1 shows a plot of log k_N *vs.* σ. This gave a ρ of +0.68 (correlation coefficient 0.995) which is somewhat less than the value of +1.37 determined for the ionization of para-substituted benzoic acids in methanol.[22] For a more suitable comparison, we prepared and solvolyzed **29–34** (X = same substituents as utilized in **18–23**). A plot of log k *vs.* σ for the rates of methanolysis of **29–34** gave a ρ of +1.34 (correlation coefficient 0.969).



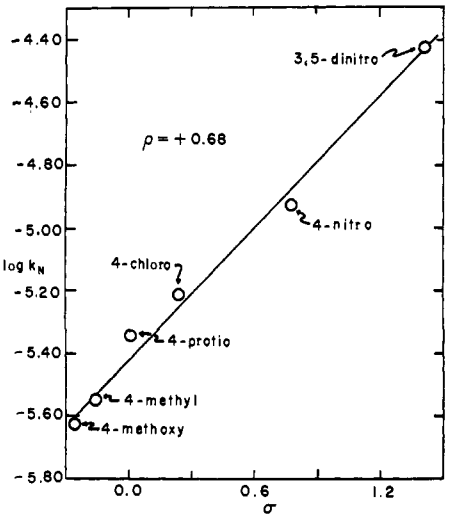


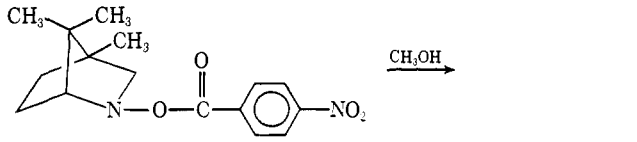
Figure 1. σ-ρ plot for the formation of benozic acids from 1-hydroxypiperidine benzoates in methanol.

(20) For examples of such singlet to triplet interconversions, see ref 19. Lee and Morokuma have recently calculated that the singlet nitrenium ion should be separated from the triplet nitrenium ion by about 45 kcal/mol, with the triplet being the ground state,[3] while Chu, Siu, and Hayes find an energy separation of 1.56 eV.

(21) Solvolysis of *N*-chloropiperidine in methanol also yields piperidine, as the only isolable product: P. G. Gassman and J. E. Trent, unpublished results.

(22) E. Grunwald and B. J. Berkowitz, *J. Amer. Chem. Soc.*, 73, 4939 (1951).

This value correlated quite well with the ρ of +1.34 obtained for the ionic rearrangement of perbenzoates.[23] In contrast, homolytic cleavages exhibit a negative ρ, as in the unimolecular free radical decomposition of benzoyl peroxide (ρ = −0.38)[24] and of *tert*-butyl-perbenzoate esters (ρ = −0.90).[25] The positive ρ observed for the methanolysis of **18–23** to yield **25** and **28** strongly supports the ionic nature of the bond cleavage involved in path a. In addition, we have found that **30** was formed as a major product in the methanolysis of **10**, which provides further evidence that the heterolytic cleavage of the N–O bond of benzoates esters of hydroxylamines occurs to yield nitrenium ions and the appropriate benzoate anion. In addition to **30**, **10** gave starting amine, **6**, and *p*-nitrobenzoic acid *via* the nitrenium ion route. The combined yield of **30** and **6** accounted for 33% of **10**.



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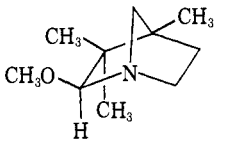

30

The competing reaction of transesterification afforded equivalent amounts of **9** and of methyl *p*-nitrobenzoate. This path was followed to the extent of 67% by **10**. The rate of disappearance of **10** was followed conductometrically. The observed pseudo-first-order rate constant was found to be 7.80 ± 0.37 × 10^{-6} sec^{-1} at 50°. This would result in a partial rate factor (k_N) for nitrenium ion formation from **10** of 2.36 × 10^{-6} sec^{-1} at 50°.

The smaller ρ observed for the generation of nitrenium ions from **18–23** indicates to us that the transition state for ionization of an N–O bond occurs earlier in the bond-breaking process than the transition state for ionization of a comparable C–O bond. This is presumably related to the weaker nature of the N–O bond (48 kcal/mol) relative to the C–O bond (78 kcal/mol).[26]

In summary, we have demonstrated that benzoate anions offer significant advantage over *p*-toluenesulfonate anions as leaving groups in the generation of nitrenium ions from derivatives of *N,N*-dialkylhydroxylamines. The use of 3,5-dinitrobenzoates of *N,N*-dialkylhydroxylamines offers particular advantage because these esters solvolyze readily and tend to minimize the side reaction due to transesterification.

Experimental Section[27]

***N*-(2-Carboethoxyethyl)-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane (7).** To a stirred solution of 3.0 g (0.0216 mol) of 4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane[15] in 20 ml of tetrahydrofuran was added dropwise 3.3 g (0.033 mol) of freshly distilled ethyl acrylate in 15 ml of tetrahydrofuran over the course of 1 hr at room temperature. The clear reaction solution was heated at reflux for 2 days and then cooled; the solvent was removed on the rotary evaporator. The clear, viscous residue was distilled through a short-path condenser to give 3.9 g (76%) of **7** as a clear oil: bp 85–87° (0.2 mm); ir (neat) 1050, 1148, 1180, 1290, 1380, 1385, 1460, 1740 cm^{-1}; nmr (CCl_4) τ 9.24 (3 H, s), 9.17 (3 H, s), 9.03 (3 H, s), 8.82 (3 H, t), 7.45 (6 H, m), 5.98 (2 H, q).

Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.47; H, 10.60; N, 5.82.

***N*-Hydroxy-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane (9).** To 1.0 g (0.0042 mol) of *N*-(2-carboethoxyethyl)-2-azabicyclo[2.2.1]-heptane (**7**) in 20 ml of methylene chloride cooled to 0–10° in an ice bath was added dropwise a solution of 1.0 g (0.0058 mol) of *m*-chloroperbenzoic acid in 15 ml of methylene chloride. After the addition was complete, the ice bath was removed and the reaction solution stirred at room temperature for 12 hr. The solvent was removed under vacuum to leave a clear oil, which was then dissolved in 20 ml of 1 *N* aqueous sodium hydroxide solution and heated with stirring at 85–90° for 1.5 hr.[13] The reaction solution was cooled and extracted with four 100-ml portions of ether. The extracts were combined, dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed on the rotary evaporator to leave a waxy, white solid. This solid was sublimed at 110° (10 mm) to give 0.35 g (54%) of pure **9**: mp 153–154°; ir (KBr) 825, 1382, 1385, 1460, 3170 cm^{-1}; nmr (acetone-d_6) τ 9.22 (3 H, s), 9.13 (3 H, s), 8.98 (3 H, s), 8.5 (2 H, m).

Anal. Calcd for $C_9H_{17}NO$: C, 69.63; H, 11.04; N, 9.02. Found: C, 69.71; H, 10.85; N, 8.75.

Attempted Preparation of *N*-Hydroxy-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane *p*-Toluenesulfonate (13). To 100 mg (0.69 mmol) of 2-hydroxy-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane (**9**) in 20 ml of hexane or ether was added 0.43 ml (0.69 mmol) of a 1.6 *N* solution of *n*-butyllithium in hexane under a nitrogen atmosphere at room temperature. This solution was added dropwise to a stirred solution of 0.134 g (0.69 mmol) of *p*-toluenesulfonyl chloride in 15 ml of hexane at 0–10°. A white precipitate appeared almost immediately and after 5 min the reaction was filtered and the solvent removed under vacuum at room temperature to yield 195 mg (98%) of 3,4,4-trimethyl-2-tosyloxy-1-azabicyclo[2.2.1]heptane (**14**), which was identical in all respects with an authentic sample.[16] The tosylate was purified by distillation on a molecular still at 105–110° (0.05 mm): mp 51–52°; ir (neat) 710, 848, 970, 1276, 1280, 1340 cm^{-1}; nmr (CCl_4) τ 9.10 (3 H, s), 9.07 (3 H, s), 9.02 (3 H, s), 7.60 (3 H, s), 5.32 (1 H, d), 2.42 (4 H, q).

Esterification of Hydroxylamine. General Procedure. To a vigorously stirred ethereal solution of 1 equiv of hydroxylamine at −55° was added an excess of powdered sodium hydroxide followed by the dropwise addition of an ethereal solution of 1 equiv of the requisite benzoyl chloride. Reaction at higher temperatures led to spontaneous discoloration and decomposition. The suspension was stirred for 1.5 hr, poured onto ice water, and quickly extracted with ether. The ether extract was dried over anhydrous magnesium sulfate and filtered, and the solvent was removed on the rotary evaporator to yield in all cases either a yellow solid or an oil which crystallized upon cooling.

***N*-Hydroxy-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane *p*-Nitrobenzoate (10).** Recrystallization from hexane afforded a 75% yield of **10** as a white solid: mp 114–116°; ir (KBr) 716, 854, 872, 1199, 1275, 1350, 1530, 1730 cm^{-1}; nmr ($CDCl_3$) τ 9.06 (3 H, s), 9.01 (3 H, s), 8.79 (3 H, s), 8.22 (5 H, m), 6.42 (2 H, s), 1.70 (4 H, d).

Anal. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.14; H, 6.62; N, 9.21. Found: C, 63.18; H, 6.66; N, 9.11.

Piperidin-1-yl 3,5-Dinitrobenzoate (23). Recrystallization from hexane afforded the desired ester in 55% yield as a white solid which turned pink within 15 min after exposure to the atmosphere: mp 119–120°; ir (CCl_4) 715, 920, 1145, 1250, 1348, 1540, 1760 cm^{-1}; nmr (CCl_4) τ 8.15 (6 H, m), 6.77 (4 H, m), 0.7 (3 H, m); mass spectrum: parent peak at *m/e* 295.

Piperidin-1-yl *p*-Nitrobenzoate (22). Recrystallization from hexane afforded a 90% yield of **22**: mp 69–71°; ir (KBr) 718, 848,

(23) P. D. Bartlett and J. L. Kice, *J. Amer. Chem. Soc.*, 75, 5591 (1953).

(24) C. G. Swain, W. H. Stockmayer, and J. T. Clarke, *ibid.*, 72, 5426 (1950).

(25) A. T. Blomquist and I. A. Berstein, *ibid.*, 73, 5546 (1951).

(26) T. L. Cottrell, "The Strength of Chemical Bonds," 2nd ed, Butterworths, London, 1958; for slightly different values see L. Pauling, "Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960.

(27) Melting points and boiling points are uncorrected. Infrared spectra were recorded on a Perkin–Elmer Model 137 Infracord spectrophotometer as neat liquids, solutions in carbon tetrachloride, or powdered solids in potassium bromide disks. Nuclear magnetic resonance spectra were obtained on a Varian Associates Model A-60 A spectrometer and are reported in tau (τ) units relative to tetramethylsilane (τ = 10.00) as the interval standard. Elemental analyses were performed by the Scandanavian Microanalytical Laboratory, Herlev, Denmark.

1094, 1250, 1355, 1540, 1750 cm^{-1}; nmr ($CDCl_3$) τ 8.10 (6 H, m), 6.70 (4 H, s), 1.67 (4 H, d).

Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.61; H, 5.77; N, 11.12.

Piperidin-1-yl *p*-Chlorobenzoate (21). Recrystallization from hexane gave a 78% yield of **21** as pure white needles: mp 67–68°; ir (CCl_4) 845, 1010, 1080, 1240, 1585, 1750 cm^{-1}; nmr (CCl_4) τ 8.12 (6 H, m), 5.90 (4 H, m), 2.37 (4 H, q).

Anal. Calcd for $C_{12}H_{14}NO_2Cl$: C, 60.38; H, 5.91; N, 5.87. Found: C, 60.07; H, 5.89; N, 5.72.

Piperidin-1-yl Benzoate (20). Recrystallization from hexane gave **20** as a white solid in 63% yield: mp 63–64°; ir (CCl_4) 703, 1015, 1060, 1070, 1175, 1240, 1450, 1755 cm^{-1}; nmr (CCl_4) τ 8.20 (6 H, m), 6.32 (4 H, m), 2.65 (5 H, s).

Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.40; H, 7.23; N, 6.58.

Piperidin-1-yl *p*-Methylbenzoate (19). Recrystallization from hexane afforded a 71% yield of **19**: mp 64–65°; ir (CCl_4) 1015, 1030, 1075, 1175, 1250, 1610, 1750 cm^{-1}; nmr (CCl_4) τ 8.25 (6 H, m), 7.60 (3 H, s), 6.90 (4 H, m), 2.50 (4 H, q).

Anal. Calcd for $C_{13}H_{17}NO_2$: C, 71.20; H, 7.82; N, 6.39. Found: C, 71.43; H, 7.83; N, 6.39.

Piperidin-1-yl *p*-Methoxybenzoate (18). Recrystallization from hexane gave an 85% yield of **18**: mp 35–36°; ir (CCl_4) 1040, 1080, 1173, 1250, 1512, 1620, 1755 cm^{-1}; nmr ($CDCl_3$) τ 8.27 (6 H, m), 6.95 (4 H, m), 6.20 (3 H, s), 2.60 (4 H, q).

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.45; H, 7.34; N, 5.77.

Conductometric Kinetics. Solvolysis of each piperidin-1-yl benzoate was carried out in methanol which had been distilled from anhydrous magnesium sulfate, stored over molecular sieves, and degassed with nitrogen immediately prior to each kinetic run. A 0.01 *M* solution of benzoate ester in methanol was prepared and the solution pipetted into a 3-ml conductivity cell which was then sealed. The conductivity cell was placed in an oil bath equilibrated at 50 ± 0.01°, attached to a YSI Model 31 conductivity bridge, and the changing conductance of the solution was monitored and recorded. First-order rate constants, obtained from a least-squares treatment of the appropriate conductance parameters,[28] varied by less than 3% in duplicate runs.

Control experiments carried out subsequent to the products analysis indicated that none of the four products individually had a significant conductance and that the benzoic acid–amine combination was responsible for almost all of the observed conductance increment.

Product Analysis. General Procedure. The requisite piperidin-1-yl benzoate was solvolyzed in methanol for at least 5 half-lives, the reaction solution then made acidic with concentrated hydrochloric acid, and the solvent removed on the rotary evaporator. The gummy residue was extracted with several portions of hexane to remove the methyl benzoate component and then with ether to remove the benzoic acid component. The residue was then made basic with aqueous sodium hydroxide solution and extracted with several portions of ether. The ethereal extracts were combined, dried over anhydrous magnesium sulfate, and filtered, and the solution was concentrated by distillation through a 6-in. Vigreux column. Vpc analysis on a 10-ft 10% Carbowax 20M–KOH on 60–80 Chromosorb W column indicated two components, samples of which were obtained *via* isolation from a 10-ft 10% Carbowax 20M–KOH on Chromosorb W preparative vpc column. The two components were shown to be piperidine and *N*-hydroxypiperidine through comparison with authentic samples. Indicated yields of these compounds are from vpc analysis of crude reaction mixtures utilizing *N*-methylaniline as an internal standard.

Synthesis of Benzoate Esters of 1-Phenylcyclohexanol. In a three-neck flask equipped with nitrogen inlet, serum cap, and addition funnel was placed a solution of 1 equiv of 1-phenylcyclohexanol[29] in dry ether under nitrogen atmosphere. With ice-bath cooling, 1 equiv of *n*-butyllithium in hexane was added through the serum cap, followed by enough tetrahydrofuran to dissolve the resulting precipitate. To this cooled, homogeneous solution was added dropwise 1.1 equiv of the requisite acid chloride dissolved in tetrahydrofuran, and the resulting suspension was stirred for 1 hr at room temperature. The reaction mixture was then poured into a saturated aqueous sodium chloride solution and quickly extracted twice with ether. The ether extracts were combined, dried over anhydrous magnesium sulfate, and filtered, and the solvent was removed on the rotary evaporator to yield in each case an oil which crystallized readily upon cooling.

1-Phenylcyclohexyl 3,5-Dinitrobenzoate (34). Recrystallization from carbon tetrachloride gave **34** in 86% yield: mp 117–119°; ir (CCl_4) 690, 715, 1125, 1160, 1235, 1265, 1275, 1338, 1540, 1740 cm^{-1}; nmr (CCl_4) τ 8.18 (8 H, s), 7.20 (2 H, m), 2.61 (5 H, d), 0.89 (3 H, m).

Anal. Calcd for $C_{19}H_{18}N_2O_6$: C, 61.61; H, 4.90; N, 7.56. Found: C, 61.44; H, 4.96; N, 7.52.

1-Phenylcyclohexyl *p*-Nitrobenzoate (33). Recrystallization from carbon tetrachloride gave **33** in 71% yield as a white solid: mp 133–135°; ir (CCl_4) 693, 717, 1098, 1118, 1245, 1265, 1290, 1350, 1534, 1740 cm^{-1}; nmr (CCl_4) τ 8.32 (8 H, s), 7.33 (2 H, m), 2.74 (5 H, s), 1.85 (4 H, s).

Anal. Calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89; N, 4.31. Found: C, 70.09; H, 5.93; N, 4.29.

1-Phenylcyclohexyl *p*-Chlorobenzoate (32). Recrystallization from hexane afforded an 84% yield of **32** as clear crystals: mp 98–99°; ir (CCl_4) 695, 850, 1015, 1100, 1240, 1272, 1290, 1438, 1596, 1732 cm^{-1}; nmr (CCl_4) τ 8.28 (8 H, s), 7.36 (2 H, m), 2.72 (5 H, s), 2.38 (4 H, q).

Anal. Calcd for $C_{19}H_{19}O_2Cl$: C, 72.49; H, 6.08; Cl, 11.26. Found: C, 72.36; H, 6.23; Cl, 11.44.

1-Phenylcyclohexyl Benzoate (31). Recrystallization from hexane gave **31** in 79% yield as clear crystals: mp 76–77°; ir (CCl_4) 693, 709, 1105, 1240, 1267, 1282, 1305, 1445, 1730 cm^{-1}; nmr (CCl_4) τ 8.38 (8 H, s), 7.43 (2 H, m), 2.77 (8 H, m), 2.10 (2 H, m).

Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.39; H, 7.19. Found: C, 81.19; H, 7.19.

1-Phenylcyclohexyl *p*-Methylbenzoate (30). Recrystallization from hexane afforded an 83% yield of **30** as clear crystals: mp 104–105°; ir (CCl_4) 690, 1098, 1235, 1264, 1280, 1728 cm^{-1}; nmr (CCl_4) τ 8.33 (8 H, s), 7.66 (3 H, s), 7.37 (2 H, m), 2.84 (7 H, m), 2.15 (2 H, d).

Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.48; H, 7.56.

1-Phenylcyclohexyl *p*-Methoxybenzoate (29). Recrystallization from hexane afforded an 80% yield of **29** as clear crystals: mp 70–72°; ir (CCl_4) 691, 1030, 1098, 1158, 1248, 1274, 1290, 1605, 1730 cm^{-1}; nmr (CCl_4) τ 8.34 (8 H, s), 7.40 (2 H, m), 6.29 (3 H, s), 2.82 (5 H, d), 2.69 (4 H, q).

Anal. Calcd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14. Found: C, 77.13; H 7.10.

Titrimetric Kinetics. Reagents. Reagent grade absolute methanol was stirred over anhydrous magnesium sulfate and then distilled at atmospheric pressure.

Procedure. The standard ampoule technique was used with slight modification. Either a standard solution of ester in methanol was made up with equal aliquots taken and carefully pipetted into different ampoules, or the same amount of ester was individually weighed and placed in each ampoule, followed by dilution with methanol. Trial runs showed these techniques to give rate constants within experimental error. The titrant was 0.01 *N* aqueous sodium hydroxide solution and titrations were performed on a Metrohm Herisan potentiograph, Model E 436. Rate constants were determined by the process of linear regression and the computations were carried out on a Wang 360 K programable calculator.

Product Study of the Methanolysis of *N*-Hydroxy-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane *p*-Nitrobenzoate (10). A 5.0-g quantity of **10** was solvolyzed in purified methanol for *ca.* 10 half-lives. The cooled reaction solution was then made acidic with concentrated hydrochloric acid and the solvent was removed on the rotary evaporator. The gummy residue was extracted with several portions of hexane; the extracts were combined and the solvent was evaporated to yield 0.87 g (31.9%) of methyl *p*-nitrobenzoate as a white solid. The gummy residue was then extracted with several portions of ether; the ether extracts were combined, dried over anhydrous magnesium sulfate, and filtered and the solvents removed to yield 1.98 g (64.0%) of *p*-nitrobenzoic acid as a white solid. The residue was then made basic with aqueous sodium hydroxide solution and extracted with four 30-ml portions of ether. The ethereal extracts were combined, dried over anhydrous magnesium sulfate, and filtered; the solution was concentrated on the rotary evaporator and the resulting oil subjected to vpc analysis on a 10 ft 20% Apiezon L–KOH on Firebrick preparative column.

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There were three components and in order of collection off the column these were shown to be 4,7,7-trimethyl-2-azabicyclo[2.2.1]-heptane (**6**), *N*-hydroxy-4,7,7-trimethyl-2-azabicyclo[2.2.1]heptane (**9**), and 2-*exo*-methoxy-3,3,4-trimethyl-1-azabicyclo[2.2.1]heptane (**30**). The reaction was repeated and analysis by vpc on a 10-ft 20% Apiezon L-KOH on 60–80 Chromosorb P analytical column (*vs. N,N*-dimethylaniline as internal standard) gave 13.4% of **6**, 60.4% of **9**, and 15.3% of **30**.

Acknowledgment. We are indebted to the National Cancer Institute of the Public Health Service for a grant which supported this investigation.

Diffusion-Controlled Proton Transfer and Heavy-Atom Reorganization in the General Acid, Specific Base Catalyzed Hydrolysis of Amides[1]

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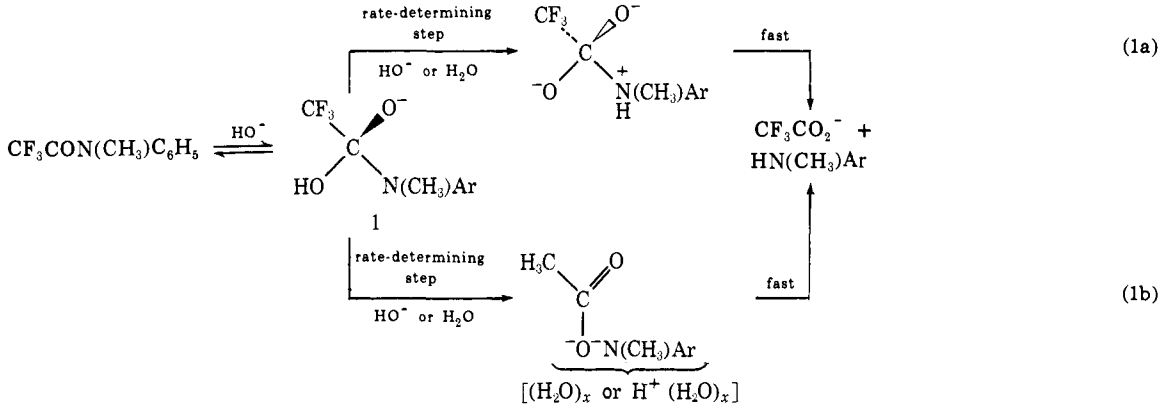
Abstract: The acyl-activated amide $CF_3CON(CH_3)C_6H_5$ adds hydroxide ion without general catalysis to form a tetrahedral intermediate which decomposes to *N*-methylaniline and trifluoroacetate ion with general acid and general base catalysis. General acids have $\delta_{BH} \log k_{BH} \simeq \delta_{BH} \log K_{BH}$ and thus are completely dissociated in the transition state. The glycine-catalyzed reaction is accelerated twofold by either a *p*-CH_3 or a *m*-Br substituent in the anilide ring, indicating two parallel pathways for catalysis, one with average negative charge and one with average positive charge on the transition state nitrogen, relative to its reactant charge. The former is presumably a diffusion process, the latter spectator catalysis.

In the action of acyl-transfer enzymes, protons are often transferred to and from intermediate tetrahedral carbonyl adducts in the course of their formation or decomposition.[4] The role of these proton shifts in the catalytic process is unknown, although in one proposal, the presumed capacity of the enzyme for precise orientation of the proton donor and acceptor along a highly preferred line for proton transfer is viewed as the origin of a major part of the catalytic power of the enzyme.[5] In the closely related nonenzymatic hydrolysis of amides (eq 1), we found simple proton transfer to the leaving group in the tetrahedral intermediates to be rate determining for poor leaving groups ($pK_b < 9$, eq 1a) with C–N bond cleavage subsequent and fast, while good leaving groups ($pK_b > 9$, eq 1b) suffered rate-limiting fission of the C–N bond, followed by fast proton transfer.[6] This result, although it is in close agreement with other studies of different amides[7] and with substituent-effect and isotope-effect data on α-chymotrypsin,[8] refers only to catalysis by water and hydroxide ion. Because of the undoubted part played by general acid–base catalysis in enzyme action, we have examined the same system in the presence of ten buffers of $pK_a = 8.3$–10.6. The kinetic complexity of



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