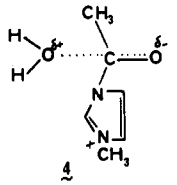
tonitrile when $[H_2O] < 1.0$ M. In that case the transition state of the reaction may be **4**. The water molecule bound



4

to the positive site should produce fractionation factors for both of its hydrogenic sites with values between ϕ = 1 (the reactant value) and ϕ = 0.69 (the product value). A value of ϕ^* = 0.92 substituted into eq 5, the appropriate

$$k_n = k_0 (1 - n + n\phi^*)^2 \quad (5)$$

form of the Gross–Butler equation for **4**, reproduces the isotope effect. The proton inventory should show some slight curvature, but it is beyond the limits of detection with our experimental data (Figure 1 inset).

Conclusion

We have shown that the transition-state structure for the hydrolysis of 1-acetyl-3-methylimidazolium ion varies little as a function of the composition of an acetonitrile–water solvent system over a wide range. However, at very low water concentrations the transition-state structure does change due to a change in the molecularity of the reaction with respect to water. This result may be of importance in mechanistic studies of enzymes with very hydrophobic active sites.

Experimental Section

Materials. 1-Acetyl-3-methylimidazole was prepared and purified by the method of Wolfenden and Jencks.[12] 1-Acetyl-d_3-3-methylimidazole was prepared by the same method by using acetyl-d_3 chloride (Aldrich). Acetonitrile was distilled twice from phosphorus pentoxide and stored under nitrogen. Deuterium oxide (99.75 atom % deuterium, Bio-Rad) was used as obtained. Water was doubly distilled. Sodium chloride (Fischer certified) was dried in an oven at 120 °C for 24 h.

Reaction Solutions. The solutions containing 0.5 and 0.9 volume fraction of acetonitrile in water were prepared by mixing appropriate volumes of acetonitrile and water, adjusting their pH to 3.0 by the addition of HCl, and dissolving the required amount of NaCl. Similarly, solutions of acetonitrile in D_2O were prepared as above except that the solutions were adjusted to pD 3.0 (pH meter reading 2.6). The solutions for proton-inventory studies in 0.5 and 0.9 volume fractions of acetonitrile in H_2O–D_2O of atom fraction of deuterium n were prepared by mixing appropriate volumes of H_2O and D_2O solutions in CH_3CN. The atom fraction of deuterium of exchangeable protons was calculated from the results of an analysis by Joseph Nemeth[23] on a sample of "100%" D_2O–acetonitrile solution. The solvent mixtures for the water order studies were prepared gravimetrically.

Kinetics. The instrumentation employed has been described elsewhere.[4] Experiments were conducted in thermostated cell holders and were initiated after thermal equilibration. Initiation of reaction was accomplished by injection of 25 μL of a 9.0×10^{-3} M 1-acetyl-3-methylimidazole in acetonitrile solution into 3.00 mL of buffer contained in a cuvette. A decrease in absorbance was monitored at 245 nm by directly registering the absorbance at 1-s intervals with a microcomputer interfaced with a Cary 118C UV-vis spectrophotometer. The rate constants were calculated by using a nonlinear least-squares program.

Registry No. **1b**, 31399-05-0; deuterium, 7782-39-0.

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(23) Urbana, IL.

Pyridinium Halide Promoted Ring-Opening Reactions of *exo*-Norbornene Oxide

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Ring opening of **1** with pyridinium chloride or pyridinium iodide in chloroform and/or pyridine gives significant amounts of halohydrins **2a** or **2b**, reflecting partial suppression of the Wagner–Meerwein rearrangement that occurs on ring-opening with hydrogen halides. Opening with pyridinium iodide (but not with pyridinium chloride) in acetonitrile gave considerable amounts of the 2-*endo*-iodohydrin **4b**. Pyridinium poly(hydrogen fluoride) or triethylammonium tris(hydrogen fluoride) gave only rearranged products.

Vicinal *trans*-norbornane halohydrins are difficult to obtain by treatment of epoxides with either hydrochloric or hydrobromic acid because of the tendency of this bicyclic system to undergo the Wagner–Meerwein rearrangement.[1] In fact, several processes can be observed in the acid-induced ring opening of *exo*-norbornene oxide (**1**), as shown in Figure 1.

Suppression of the Wagner-Meerwein rearrangement has been reported where R (Figure 1) is CH_2Cl, presumably because this group leads to formation of a relatively stable chloronium ion intermediate (route d),[2] and via a stable dioxolenium ion in related systems.[3] We have reported that this rearrangement is also partly suppressed in the reaction of **1** with pyridinium chloride (PyHCl), with **2a** being one of the products (Table I, entries 2 and 4).[4]

We here report on the ring opening of **1** with several pyridinium halides and with the corresponding hydrogen halides. The results are summarized in Table I. Product

(1) (a) Berson, J. A. In "Molecular Rearrangements"; De Mayo, P., Ed.; Wiley-Interscience: New York, 1963; Vol. 1, p 111. (b) Brown, H. C. "The Nonclassical Ion Problem"; Plenum Press: New York, 1977.

(2) Chollet, A.; Hagenbuch, J. P.; Vogel, P. *Helv. Chim. Acta* **1979**, *62*, 511.

(3) Bazbouz, A.; Christol, H.; Coste, J.; Plenat, F. *Tetrahedron* **1980**, *36*, 2745.

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Table I. Distribution of Products Obtained by the Reaction of *exo*-Norbornene Oxide with Pyridinium Halides and Related Reagents

reagent	solvent	time, h	temp, °C	product relative yield[a,b] by GLC, % 1	2	3	4	5	6
PyHCl	dioxane	13	101	nd	19	46			35
	$CHCl_3$	8	61	nd	17	40			37
	CH_3CN	13	82	nd	8	60			32
	Py	5	115	nd	45	20			31
HCl	Et_2O[c]		0	nd	nd	44			26
	H_2O[d]		10	nd	nd	69			nd
PVPHCl[e]	dioxane	20	101	20	14	49			2
	$CHCl_3$	20	61	30	7	37			10
PyHI	$CHCl_3$	24	61	nd	79	15	nd		2
	CH_3CN	17	61	nd	27	23	32		nd
	CH_3CN	17	20	33	26	23	nd		18
HI	H_2O	2	10	nd	nd	65	nd		8
$Py(HF)_x$	$CHCl_3$	23	20	nd		48		46	nd
	Py	23	20	90		4		4	nd
$Et_3N \cdot 3HF$	$CHCl_3$	20	55	4		48		19	19

[a] The difference from 100% represents unidentified products. Typically, isolated yields for compounds **2b**, **3b**, **3c**, and **5c** were ±5%, 8%, 20%, and 25%, respectively (reactions run in $CHCl_3$). [b] nd = not detected. [c] Reference 2, footnote 2. [d] In agreement with the results previously reported by: McDonald, R. N.; Tabor, T. E. *J. Org. Chem.* **1968**, *33*, 2934. [e] PVPHCl = poly(4-vinylpyridinium chloride).

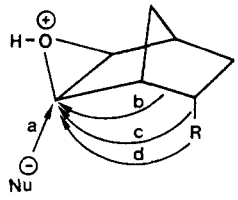


Figure 1. a, normal product; b, Wagner-Meerwein rearrangement; c, hydride shift (R = H); d, nucleophilic participation (R = Nu).

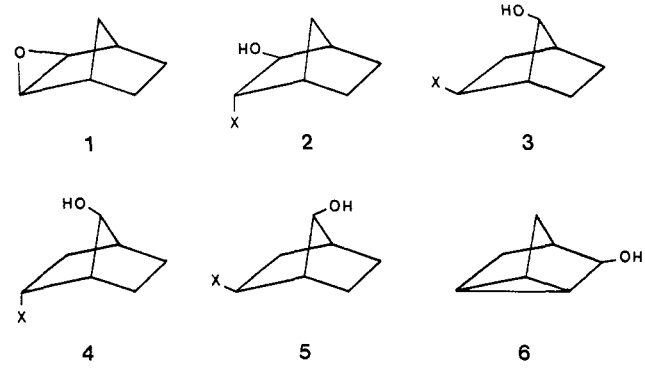
distributions in reactions with PyHCl and PyHI were not affected by changing the concentration of reagent from 1 to 10^{-2} M. Product structures **2–6** (Chart I) were deduced from spectral data compared with authentic samples or literature data.

Of the reagents tested, PyHI in $CHCl_3$ provided the greatest suppression of the Wagner–Meerwein rearrangement, with about 80% of the product being **2b**. With the same reagent in the more polar CH_3CN, only one-third of the product was the unrearranged isomer **2b**, and an additional 32% was the rearranged **4b**, also with an endo iodine atom. In separate experiments, we found that the rearranged exo isomer **3b** was converted into *endo*-**4b** on heating in CH_3CN at 61 °C, whereas this isomerization did not occur in CH_3Cl at the same temperature.

Reports of equilibrations of norbornanes with no substituent in the 7-position, such as 2-norbornyl acetate,[5] indicate exo/endo ratios of 6–10. Other nucleophilic displacements have been reported in which *endo*-2-norbornanes are the principal products.[6] Our results with PyHI in CH_3CN probably reflect the fact that this polar solvent favors ionic processes that allow equilibration of exo and endo isomers.

The Wagner–Meerwein rearrangement was not suppressed appreciably with poly(4-vinylpyridinium chloride)[7] and not at all with HCl, HI, pyridinium poly(hydrogen fluoride) (Olah's reagent),[8] or triethylammonium tris(hydrogen fluoride).[9] The principal products from the last

Chart I



a, X = Cl b, X = I c, X = F

two reagents were **3c** and **5c** in roughly comparable amounts. Nortricyclanol (**6**) was a significant product in all reactions except those with HCl/H_2O, PyHI/CH_3CN (at 61 °C), and Olah's reagent.

The structures of **3c** and **5c** were assigned on the basis of ^1H and ^{13}C NMR spectra. The ^1H NMR spectra are similar to those of the 2-*exo*-fluoro-7-halobicyclo[2.2.1]-heptanes.[10] The endo C-2 proton shows a large geminal coupling with the fluorine atom, vicinal couplings with the C-3 protons, a small vicinal coupling with the C-1 proton, and a long-range coupling with the anti C-7 proton in the syn compounds. The splitting patterns of the C-2 protons in both **3c** and **5c** are similar to those of *syn*-7-azido-*exo*-2-fluorobicyclo[2.2.1]heptane, before and after irradiation, respectively, at the frequency of absorption of the C-7 proton.[11] The ^{13}C NMR spectra of **3c** and **5c** (Table II) agree with the assigned structures, taking into account the reported coupling constants for *exo*-2-fluorobicyclo-[2.2.1]heptane[12] and the expected perturbation of the chemical shift values due to the introduction of a hydroxyl group at C-7.[13]

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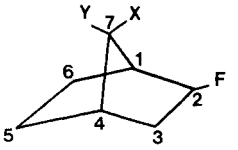
(12) Grutzner, J. B.; Jautelat, M.; Dence, J. B.; Smith, R. A.; Roberts, J. D. *J. Am. Chem. Soc.* **1970**, *92*, 7107.

Table II. ^{13}C NMR Resonances of *exo*-2-Fluoronorbornanes



compd	chemical shift[a] (J_{CF}, Hz)						
	C-1	C-2	C-3	C-4	C-5	C-6	C-7
X = Y = H[b]	42.1 (20.2)	95.6 (182.0)	39.8 (20.4)	34.6 (2.3)	28.0 (<1)	22.3 (9.8)	35.0 (<1)
X = OH, Y = H	45.1 (17.5)	97.8 (179.7)	37.2 (19.5)	40.5[c]	24.7[c]	20.2 (10.0)	80.7[c]
X = H, Y = OH	46.5 (19.2)	94.5 (182.1)	37.6 (21.3)	38.8[c]	24.9[c]	20.0 (9.8)	76.7[c]

[a] Chemical shifts reported in parts per million downfield from Me_4Si with in $CDCl_3$ as the solvent. [b] Reference 13 (dioxane). [c] J_{CF} less than 2.0 Hz.

In summary, ring-opening reactions of 1 with PyHCl or PyHI give significant amounts of unrearranged products, which suggests the partial occurrence of an S_N2 mechanism (Figure 1, route a) that does not involve a free carbenium ion. An ion-pair intermediate or a borderline mechanism (where bond breaking is further advanced than bond making) may account for our results in different solvents, although controversy remains about the pathway of acid-catalyzed ring opening of oxiranes.[14]

Experimental Section

IR spectra were recorded on a Perkin-Elmer 257 Infracord, and values are given in reciprocal centimeters. ^1H NMR spectra were obtained on a Perkin-Elmer R32 or a JEOL C-60 HL spectrometer with Me_4Si as an internal standard. ^{13}C NMR spectra were taken on a Varian CFT-20 or XL-100 spectrometer with Me_4Si as an internal standard and $CDCl_3$ as the solvent. Mass spectra were obtained on an AEI MS12 spectrometer at an ionization potential of 70 eV. High-resolution mass spectra were obtained on a VG ZAB 2F spectrometer (10000 resolution, 5% valley). GLC analyses were carried out with a Carlo-Erba Fractovap GI gas chromatograph with 2 m × 2 mm glass columns packed with OV-17 (2%) on Chromosorb W or PEG 20M (2%) on H_2T-Carbopack C (Supelco). Pyridinium chloride (Fluka), pyridinium poly(hydrogen fluoride) (Fluka), triethylammonium tris(hydrogen fluoride) (Fluka), and *exo*-norbornene oxide (1) (EGA) were commercial products. Pyridinium iodide,[15] nortricyclanol,[16] and poly(4-vinylpyridinium chloride)[7] were prepared by using the reported procedures.

Reactions of *exo*-Norbornene Oxide with Pyridinium Halides. A mixture of the oxirane 1 (5 mmol) and pyridinium chloride or iodide (10 mmol) in 13 mL of dry solvent was stirred for variable times at the reported temperature (see Table I). The reaction mixture was poured into cold water and extracted several times with chloroform. After organic layer was washed with water and dried over anhydrous sodium sulfate, the solvent was distilled, and the residue was chromatographed (silica gel; hexane/diethyl ether, 7:3), giving the products and yields shown in Table I. The following physical properties, yet unreported, are given below (products in order of elution).

***endo*-3-Iodo-*exo*-bicyclo[2.2.1]heptan-2-ol (2b)**: bp 66–68 °C (18 mmHg; external bath); IR ($CHCl_3$)ν_{OH} 3560,3360; ^1H NMR ($CDCl_3$) δ 0.8–2.4 (m, 8 H), 2.5 (s, 1 H, OH), 3.9 (br s, 2 H, CHI and CHOH); ^{13}C NMR (multiplicity in SFORD) δ 24.6 (t), 27.1 (t), 32.7 (t), 41.1 (d), 44.1 (d, two unresolved peaks), 85.7 (d); mass spectrum, m/z (relative intensity) 238 (31, M^+), 111 (100). The acetyl derivative gave spectral data in agreement with those reported.[17] Cyclization of **2b** in a basic medium[18] led to the oxirane 1.

***exo*-2-Iodo-*syn*-bicyclo[2.2.1]heptan-7-ol (3b)**: mp 72–73 °C (lit.[19] 72–73.5 °C); IR and ^1H NMR spectra are in agreement with those reported;[19] ^{13}C NMR δ 23.0, 24.6, 28.5, 41.9, 43.0, 49.5, 80.6; mass spectrum, m/z (relative intensity) 238 (3, M^+), 110 (100).

***endo*-2-Iodo-*syn*-bicyclo[2.2.1]heptan-7-ol (4b)**: white crystals mp 54–55 °C (petroleum ether); IR ($CHCl_3$) ν_{OH} 3570, 3380; ^1H NMR ($CDCl_3$) δ 1.2–2.9 (m, 9 H, containing the sharp s of OH at 1.9), 4.05 (br s, 1 H, CHOH), 4.7 (m, 1 H, CHI); ^{13}C NMR (multiplicity in SFORD) δ 24.2 (t), 24.3 (t), 27.9 (d), 38.4 (t), 38.8 (d), 46.4 (d), 77.8 (d); mass spectrum, m/z (relative intensity) 238 (5, M^+), 111 (100); high-resolution mass spectrum, calcd for $C_7H_{11}OI$ m/z 237.9856, found m/z 237.9854.

Reaction of *exo*-Norbornene Oxide with Hydriodic Acid. To 1 mL of a solution of 46% hydriodic acid at −10 °C was slowly added the oxirane 1 (5 mmol). After being stirred at 10 °C for 2 h, the reaction mixture was extracted several times with ether. After the organic layer was washed with water and dried over anhydrous sodium sulfate, the solvent was evaporated, giving the iodohydrin **3b** in 65% yield.

Reaction of 3b with Pyridinium Iodide. A mixture of **3b** (1 mmol) and pyridinium iodide (2 mmol) in 2.5 mL of dry acetonitrile (or chloroform) was stirred for 20 h at 61 °C. The reaction mixture was worked up as usual. GLC and NMR analyses of the mixture showed the iodohydrins **3b** and **4b** in a 1:2 ratio (in acetonitrile) or only the starting material (in chloroform).

Reaction of 1 with Poly(4-vinylpyridinium chloride). A mixture of the oxirane 1 (5 mmol) and poly(4-vinylpyridinium chloride) (2.5 g) in 5 mL of dry chloroform or dry dioxane was stirred for 20 h at the reflux temperature. The reaction mixture was poured into ether and filtered, and the filtrate was washed with water and dried over anhydrous sodium sulfate. GLC analysis of the reaction mixture showed the products in the reported yield (see Table I).

Reaction of *exo*-Norbornene Oxide with Pyridinium Poly(hydrogen fluoride). To a stirred solution of the oxirane 1 (2 mmol), 2.4 mL of pyridine, and dry $CHCl_3$ or dry pyridine (2.8 mL) in a polyethylene bottle was slowly added pyridinium poly(hydrogen fluoride) (3.2 mL) at 0 °C. After being stirred at room temperature for 23 h, the reaction mixture was poured into cold water and extracted several times with chloroform. After the organic layer was washed with sodium carbonate solution and with water and dried over anhydrous sodium sulfate, the solvent was distilled off through a Vigreux column. The residue was chromatographed (silica gel; hexane/diethyl ether, 6:4), giving the products in the relative yields reported in Table I. The GLC retention time of **3c** is shorter than that of **5c**, but this order is reversed in column chromatography.

***exo*-2-Fluoro-*syn*-bicyclo[2.2.1]heptan-7-ol (3c)**: mp 77–79 °C (hexane); IR (CCl_4) ν_{OH} 3620, 3410; ^1H NMR (CCl_4) δ 0.8–2.5 (m, 8 H), 2.6 (s, 1 H, OH), 3.9 (br s, 1 H, CHOH), 4.6 (2 unsym m, J_{HF} = 57 Hz, 1 H, CHF); ^{13}C NMR, see Table II; mass spectrum, m/z (relative intensity) 130 (M^+, traces), 110 (31), 79 (100);

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high-resolution mass spectrum, calcd for $C_7H_{11}OF$ m/z 130.0794, found m/z 130.0785.

***exo*-2-Fluoro-*anti*-bicyclo[2.2.1]heptan-7-ol (5c)**: mp 111-113 °C (hexane); IR (CCl_4) ν_{OH} 3610, 3420; ^1H NMR (CCl_4) δ 0.8-2.5 (m, 8 H), 3.5 (s, 1 H, OH), 4.2 (br s, 1 H, CHOH), 4.4 (2 unsym q, J_{HF} = 57 Hz, 1 H, CHF); ^{13}C NMR, see Table II; mass spectrum, m/z (relative intensity) 130 (M^+, traces), 110 (17), 79 (100); high resolution mass spectrum, calcd for $C_7H_{11}OF$ m/z 130.0794, found m/z 130.0789.

Reaction of *exo*-Norbornene Oxide with Triethylammonium Tris(hydrogen fluoride). To a stirred solution of 1 (2 mmol) in 5 mL of dry $CHCl_3$ was slowly added 0.6 mL of triethylammonium tris(hydrogen fluoride). After being stirred at 55 °C for 20 h, the reaction mixture was poured into a mixture of ice and concentrated ammonium hydroxide, extracted with ether, dried over anhydrous sodium sulfate, and analyzed by GLC, showing the products in the yields reported in Table I.

Registry No. 1, 3146-39-2; **2b**, 85551-24-2; **3b**, 31337-70-9; **3c**, 85507-31-9; **4b**, 85507-32-0; **5c**, 85507-33-1; PyHCl, 628-13-7; PyHI, 18820-83-2; HI, 10034-85-2; PVPHCl, 29323-87-3; $Py(HF)_x$, 62778-11-4; $Et_3N{\cdot}3HF$, 73602-61-6.

Structure-Reactivity Relationships and the Rate-Determining Step in the Nucleophilic Cleavage of Phenyl Salicylate with Primary and Secondary Amines

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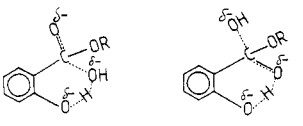
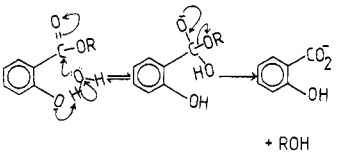
The kinetics of reactions of phenyl salicylate with piperidine, methylamine, morpholine, glycine, 1,2-diaminoethane, piperazine, and *N*-methylpiperazine have been studied at 30 °C. The respective values of bimolecular nucleophilic rate constants for the reactions of these amines with the ionized and nonionized forms of phenyl salicylate, k_1 and k_2, have been found to fit to the Brønsted equation with slopes, β_{nuc_1} and β_{nuc_2}, equal to 0.18 ± 0.02 and 0.82 ± 0.07, respectively. The low value of β_{nuc_1} is attributed to the intramolecular general-base-catalyzed nucleophilic attack as the rate-determining step while the high value of β_{nuc_2} is indicative of the expulsion of the leaving group as the rate-determining step. The extent of the enhanced reactivity produced by the intramolecular general-base catalysis depends upon the relative basicity of the nucleophiles and the phenolic group of the ester. The two Brønsted plots intersect each other at pK_a = 10.56. Thus, as the pK_a of the nucleophile decreases from 10.56, the ratio k_1/k_2 increases, while a decrease in k_1/k_2 takes place with an increase in the pK_a of the nucleophile from 10.56. The nonappearance of buffer catalysis in the cleavage of phenyl salicylate in buffer solutions of trimethylamine indicates that k_1 or k_1/k_2 should be very close to zero. Thus, the value of k_1/k_2 (0.38) for methylamine still displays an enhanced reactivity caused by intramolecular general-base catalysis. The buffer catalysis could not be detected in the nucleophilic cleavage of methyl salicylate in the presence of piperidine buffer solution. This observation has been ascribed to the expulsion of the leaving group as the rate-determining step for the cleavage of ionized methyl salicylate. The present study has supported our conclusion that the enhanced reactivity due to intramolecular general-base catalysis could be detected in such reactions only if the nucleophilic attack is the rate-determining step.

Intramolecular reactions and their mechanisms have become of immense importance since the awareness that intramolecular participation is one of the various factors which is responsible for the exceptionally high catalytic power of many enzymes.[1] Bender and his co-workers[2] have studied the hydrolytic cleavage of *p*-nitrophenyl salicylate and a few of its derivatives with the aim to find out quantitatively the rate facilitation produced by the neighboring hydroxyl group in the ester. They also attempted to differentiate between two kinetically indistinguishable probable mechanisms: (i) intramolecular general-base and (ii) general-acid catalysis involving transition states 1 and 2, respectively. But their deuterium



1 2

Scheme I



oxide solvent technique could not ultimately differentiate between these two. However, they preferred 1 over 2 because they could not detect any rate acceleration for the reactions between salicylate esters and nucleophiles having no transferable proton. In an attempt to clarify further the mechanism involved in the hydrolytic cleavage of salicylate esters, Capon and Ghosh[3] have studied the hydrolysis of phenyl salicylate and several of its derivatives, but their studies could not produce any better evidence than that produced by earlier studies[2] to show a preference for either of the two alternative mechanisms. Capon and Ghosh have proposed a mechanism as shown in Scheme I. All these studies could not produce any evidence to support whether nucleophilic attack or expulsion of the leaving group is the rate-determining step.

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