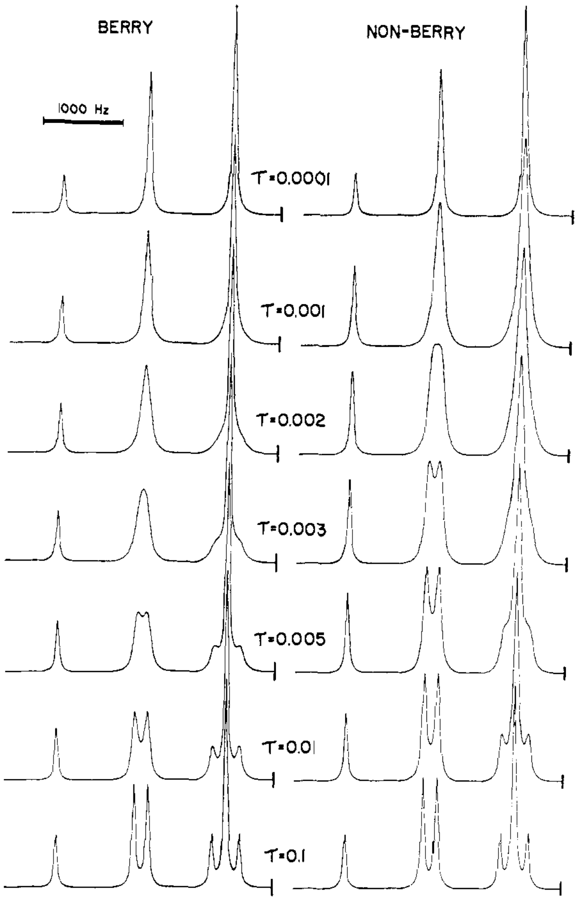

Figure 3. Spectra calculated for pseudorotation by Berry and non-Berry mechanisms. To save space, only the kinetic behavior of lines 1-6 is shown.

correspond with the lines of the observed static spectrum. Spectra calculated for a range of preexchange lifetimes τ are given in Figure 3.

$$\mathbf{K}_{\text{Berry}} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & -1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -1 & 0 & 1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 1 & 0 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -1 & 1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 1 & -1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \qquad (2)$$

$$\mathbf{K}_{\text{non-Berry}} = \begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -\frac{1}{2} & \frac{1}{2} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \frac{1}{2} & -\frac{1}{2} & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -1 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{1}{4} & -\frac{1}{2} & \frac{1}{4} & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & -1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\frac{1}{2} & \frac{1}{2} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & \frac{1}{2} & -\frac{1}{2} & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix} \qquad (3)$$

Comparisons of two features of these calculated and observed spectra clearly demonstrate that a Berry mechanism is responsible for pseudorotation in **1**. First, in agreement with spectra calculated assuming this mechanism, line 5 of the observed spectra remains sharp throughout the temperature range responsible for the broadening and complete collapse of lines 4 and 6; by contrast, line 5 is appreciably broadened for intermediate non-Berry exchange rates. Second, the *relative* rates of broadening and collapse of lines 2, 3, 4, and 6 are compatible with those calculated on the basis of a Berry mechanism, but are incompatible with relative rates based on a non-Berry process.

[10] National Institutes of Health Predoctoral Fellow, 1966–1969.

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Received June 2, 1969

The Solvolysis of Highly Unreactive Substrates Using the Trifluoromethanesulfonate (Triflate) Leaving Group

Sir:

Although it has been realized for some time that trifluoromethanesulfonates (triflates)[1] are remarkably reactive compounds[1–4] (ethyl triflate is capable of alkylating ether!) their solvolytic behavior has been studied in only a few primary cases. Methyl[4] and ethyl[1] triflates are approximately $10^{4.4}$ times more reactive than the corresponding tosylates, and the solvolysis of ethyl triflate has been shown to be an SN2 process.[1] We report in this paper and in a companion study from these laboratories[5a] kinetic results using the triflate leaving group in a variety of normally highly unreactive systems. We find that use of this extremely reactive leaving group extends significantly the spectrum of compounds whose reactivities can be examined solvolytically.

The triflates employed in this study (Table I) were prepared and purified using the usual procedure for tosylates:[6] equimolar amounts of the alcohol and trifluoromethanesulfonic acid anhydride[7] were mixed in pyridine solution at 0°. All of the derivatives prepared were liquids and were stable for several weeks at 5°. On solvolysis, all displayed good first-order kinetics to about 85% reaction.

Table I summarizes the results of our kinetic investigations on I–V. Included are the results previously reported for methyl[4] and ethyl[1] triflates, and data for the corresponding tosylates, where available. The triflate/tosylate rate ratios can be seen to fall in the range $10^{4.3}$–$10^{5.3}$; they are remarkably constant considering the variety of systems studied.[5b,9]

The rate constants presented here for *exo*-bicyclo[3.1.0]hex-6-yl triflate (I, X = OTf) and for 1-nortricyclyl triflate (II, X = OTf) represent the first measurable solvolytic reactivity reported for these systems. Although the thermal and solvolytic behavior of bicyclo[3.1.0]hex-6-yl derivatives has been investigated

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[1] Trivial name suggested by A. Streitwieser, Jr., C. L. Wilkins, and E. Kiehlmann, *J. Amer. Chem. Soc.*, 90, 1598 (1968).

[2] T. Gramstad and R. N. Haszeldine, *J. Chem. Soc.*, 4069 (1957).

[3] J. Burdon and V. C. R. McLoughlin, *Tetrahedron*, 21, 1 (1965).

[4] R. L. Hansen, *J. Org. Chem.*, 30, 4322 (1965).

[5] (a) P. J. Stang and R. Summerville, *J. Amer. Chem. Soc.*, 91, 4600 (1969); (b) also *cf.* W. M. Jones and D. D. Maness, *ibid.*, 91, 4314 (1969).

[6] L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley & Sons, Inc., New York, N. Y., 1967, p 1180.

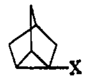
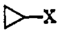
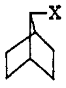
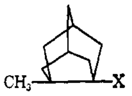
[7] Prepared by treatment of barium trifluoromethanesulfonate with fuming sulfuric acid, followed by dehydration with P_2O_5.[8] We are indebted to Dr. R. L. Hansen of the Minnesota Mining and Manufacturing Co. for the generous gift of barium trifluoromethanesulfonate and for supplying detailed procedures.

[8] J. Burdon, I. Farazmand, M. Stacey, and J. C. Tatlow, *J. Chem. Soc.*, 2574 (1957).

[9] This essential constancy in going from primary to tertiary bridgehead systems shows that OTf/OTs ratios, unlike OTs/Br ratios,[10] are not sensitive to changes in mechanism.

[10] H. M. R. Hoffmann, *J. Chem. Soc.*, 6753, 6762 (1965).

Table I. Rate Constants for Acetolysis of Triflates and Tosylates

Compound	X	Temp, °C	k_1, sec^{-1} [a]	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu	OTf/OTs, 25°
 I	OTf	150.0	$(2.23 \pm 0.03) \times 10^{-5}$	32.3	−4.3	
		175.0	$(2.01 \pm 0.04) \times 10^{-4}$			
		186.1	4.95×10^{-4} [b]			
		25.0	1.61×10^{-12} [b]			
		124.3[c]	$(3.17 \pm 0.05) \times 10^{-5}$	28.9	−7.0	
		150.0[c]	$(3.11 \pm 0.02) \times 10^{-4}$			
		186.1[c]	5.02×10^{-3} [b]			
 II	OTf	186.1[c]	$(5.98 \pm 0.20) \times 10^{-6}$			
 III	OTf	75.15	$(3.01 \pm 0.07) \times 10^{-5}$ [d]	26.3	−4.1	
		100.08	$(4.07 \pm 0.05) \times 10^{-4}$ [d]			
		186.10	3.81×10^{-1} [b]			
		25.0	4.35×10^{-8} [b]			$10^{4.9}$
	OTs	25.0	5.70×10^{-13} [b,e]	32.3[e]	−6.1[e]	
 IV	OTf	100.2[f]	$(3.94 \times 0.07) \times 10^{-5}$	29.5	0.0	
		124.98[f]	$(5.01 \pm 0.03) \times 10^{-4}$			
		25.0[f]	1.37×10^{-9} [b]			$10^{5.3}$
	OTs	25.0[g]	6.36×10^{-15}	35.7	−3.5	
 V	OTf	50.28[f]	$(6.52 \pm 0.15) \times 10^{-6}$	28.7	6.4	
		76.28[f]	$(1.96 \pm 0.04) \times 10^{-4}$			
		186.1[f]	5.10[b]			
		25.0[f]	1.36×10^{-7} [b]			$10^{4.8}$
	OTs	25.0[h]	2.17×10^{-12}	32.6	−2.6	
CH_3X	OTf	25.0[4]	7.13×10^{-5}			$10^{4.3}$
	OTs	25.0	3.42×10^{-9} [i]	22.2[i]	−22.7[i]	
CH_3CH_2X	OTf	25.0[1]	5.27×10^{-5}	17.4	−19.7	$10^{4.5}$
	OTs	25.0[j]	1.78×10^{-9}	24.4	−16.7	

[a] Determined titrimetrically unless otherwise noted. [b] Calculated from data at other temperatures. [c] 60% aqueous ethanol. [d] Determined conductometrically. [e] This work; *Cf.* ref 20. [f] Buffered HOAc, 0.032 *M* in NaOAc. [g] S. Winstein, M. Shatavsky, C. Norton and R. B. Woodward, *J. Amer. Chem. Soc.*, 77, 4183 (1955). [h] P. von R. Schleyer and E. Wiskott, *Tetrahedron Lett.*, 2845 (1967). [i] Calculated from data in footnote *j*. [j] S. Winstein and H. Marshall, *J. Amer. Chem. Soc.*, **74**, 1120 (1952).

several times,[11–14] the *exo* derivatives had previously proven inert. Thus, heating the *exo*-chloride I (X = Cl) at 250° for 4 hr led to no reaction.[13] The *exo*-tosylate I (X = OTs) was likewise unchanged after 3 months in acetic acid at 150°; at higher temperatures blackening occurred, possibly due to solvent attack on the cyclopropane ring.[14] No solvolytic data at all are available for II, although the deamination of 1-nortricyclylamine (II, X = NH_2) has been reported.[15] Both I and II (X = OTf) are remarkably unreactive substances, and high temperatures had to be used before solvolysis occurred at a conveniently measurable rate.

At 25°, the calculated rate of acetolysis of *exo*-bicyclo[3.1.0]hex-6-yl triflate, (I, X = OTf) is 26,000 times slower than that for cyclopropyl triflate (III, X = OTf).[16] I (X = OTf) is also 850 times less reactive than 7-norbornyl triflate (IV, X = OTf) in HOAc at 25°. Thus, I is the least reactive secondary system on record. The estimated rate constant for I (X = OTs) in acetic acid at 25°, 8×10^{-18} sec^{-1}, is nearly 10^{10} times slower than that of cyclohexyl tosylate under the same conditions![17]

1-Nortricyclyl triflate (II, X = OTf) is even less reactive than I (X = OTf). As side reactions caused k_1 to increase with time in HOAc, the solvolysis of II (X = OTf) was carried out in 60% ethanol. At 186.1°, II (X = OTf) was 840,000 times less reactive than 7-methyl-3-noradamantyl triflate (V, X = OTf), studied for comparison. If the II/I ratio of 830 (186.1°, 60% ethanol) can be extrapolated to HOAc at 25° for the tosylates, then a rate constant for II (X = OTs) of $\sim 10^{-20}$ sec^{-1} can be crudely estimated. Clearly, II is the least reactive tertiary system known; the former record holder, 1-norbornyl tosylate, has a calculated acetolysis rate of 9.3×10^{-15} sec^{-1} at 25°.[18]

Encouraged by our success with the constrained cyclopropyl systems, I and II, and by the discovery that vinyl triflates were also reactive on solvolysis,[5] we examined the behavior of some aryl triflates.[19] Phenyl tosylate is known not to react with acetic acid at 190°[20] nor with water at 100°.[21,22] The aryl triflates we

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(11) L. Ghosez, P. Laroche, and G. Slinckx, *Tetrahedron Lett.*, 2767 (1967).

(12) C. W. Jefford and R. Medary, *ibid.*, 2069, 6317 (1966); C. W. Jefford and W. Wojnarowski, *ibid.*, 199 (1968).

(13) M. S. Baird and C. B. Reese, *ibid.*, 1379 (1967).

(14) U. Schöllkopf, K. Fellenberger, M. Patsch, P. von R. Schleyer, T. Su, and G. W. Van Dine, *ibid.*, 3639 (1967).

(15) P. Lipp and C. Padberg, *Ber.*, **54**, 1316 (1921); H. Hart and R. A. Martin, *J. Amer. Chem. Soc.*, **82**, 6362 (1960).

(16) Because of the severe restrictions in I against concerted disrotatory ring opening, I (X = OTf) provides the best model yet available for the behavior of a classical secondary cyclopropyl system on solvolysis.[14]

(17) S. Winstein, B. K. Morse, E. Grunwald, H. W. Jones, J. Corse, D. Trifan, and H. Marshall, *J. Amer. Chem. Soc.*, 74, 1127 (1952).

(18) R. C. Fort, Jr., and P. von R. Schleyer, *Advan. Alicyclic Chem.*, 1, 283 (1966).

(19) For a review of disubstituted cations see H. G. Richey in "Carbonium Ions," Vol. II, G. Olah and P. von R. Schleyer, Ed., John Wiley & Sons, Inc., New York, N. Y., 1969.

(20) J. D. Roberts and V. C. Chambers, *J. Amer. Chem. Soc.*, 73, 5034 (1951).

examined proved similarly inert.[23] Both phenyl triflate and *p*-methoxyphenyl triflate[24] were stable to the action of acetic acid for 1 week at 200°; no trifluoromethanesulfonic acid was liberated, and the starting materials were recovered in good yields. Prolonged heating (>1 week) in trifluoroacetic acid at 125° caused complete destruction of the substrates, but less than 1% of the theoretical amount of triflic acid was liberated. Work-up after 4 days under the same conditions gave unreacted starting material as the only substance detectable by glpc. The observed inertness of these aryl triflates provides good evidence that the solvolyses recorded in Table I proceed by alkyl–oxygen and not sulfur–oxygen cleavage.

In summary, use of the triflate leaving group offers the following advantages: (1) systems that are sluggish with ordinary leaving groups can now be studied under less strenous conditions—conditions which avoid side reactions and permit more sensitive studies (*e.g.*, isotope effects) to be carried out; (2) a number of systems previously found "inert" can now be studied solvolytically.

Acknowledgments. We thank the National Science Foundation, the National Institutes of Health (AI-07766), and the Petroleum Research Fund, administered by the American Chemical Society, for support of this work. We are grateful to Mr. C. J. Lancelot for construction of a recording conductivity bridge used in this work.

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[21] R. V. Vizgert and E. K. Savchuk, *Zh. Obshch. Khim.*, **26**, 2268 (1956); *Chem. Abstr.*, **51**, 4984 (1957).

[22] Aryl benzenesulfonates do undergo hydrolysis under forcing conditions but by S_N2 processes involving sulfur–oxygen cleavage: S. Oae, T. Fukumoto, and R. Kiritani, *Bull. Chem. Soc. Jap.*, **36**, 346 (1963); S. Oae and R. Kiritani *ibid.*, **38**, 765 (1965).

[23] Professor A. Streitwieser has also found phenyl triflate to be unreactive in trifluoroethanol (private communication).

[24] Kindly prepared by Dr. G. W. McLay by the thallous salt method: E. C. Taylor, G. W. McLay, and A. McKillop, *J. Amer. Chem. Soc.*, **90**, 2422 (1968).

[25] American Chemical Society, Petroleum Research Fund Fellow, 1968–1969.

[26] American Machine and Foundry Fellow, 1967–1969.

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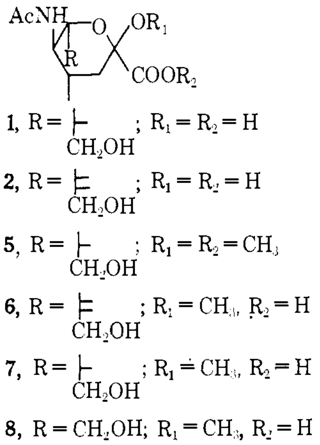
Received June 19, 1969

5-Acetamido-3,5-dideoxy-D-*galacto*-octulosonic Acid, an Eight-Carbon Analog of N-Acetylneuraminic Acid[1]

Sir:

We wish to report the synthesis of 5-acetamido-3,5-dideoxy-D-*galacto*-octulosonic acid (**1**), an eight-carbon analog of *N*-acetylneuraminic acid (NANA) (**2**), and the observation that **1** is a substrate for NANA aldolase.

The condensation of 2-acetamido-2-deoxy-D-lyxose[2] (**3**) with di-*t*-butyl oxaloacetate (**4**) by the general procedure of Kuhn and Baschang[3] gave 5-acetamido-3,5-dideoxy-D-*galacto*-octulosonic acid (**1**). The analog **1** had the following properties: mp 167–170° dec (microcrystalline powder from methanol–ether), $[\alpha]^{24}\mathrm{D}$ −53.2° (*c* 1.73, water). *Anal.* Found: C, 42.90; H, 6.23; N, 4.88. The pure analog **1** migrated as a single spot when subjected to paper chromatography (in two different solvent systems) or thin layer chromatography.



Assignment of structure **1** to the analog was based on the following data: (a) the analog reacted with methanol in the presence of Dowex-50 (H^+) resin to give a methyl ester, methyl glycoside derivative **5** (compound **5** was assigned the β configuration for the reasons described under e), mp 215° dec, $[\alpha]^{25}\mathrm{D}$ −64.3° (*c* 2.46, methanol) (*Anal.* Found: C, 46.61; H, 6.85; N, 4.42); (b) reaction of the analog with O-phenylenediamine yielded a 2-ketodihydroquinoxaline derivative,[4] mp 217–219° dec, $[\alpha]^{26}\mathrm{D}$ −111.9° [*c* 0.32, dimethyl sulfoxide–water (1:1)] (*Anal.* Found: C, 54.61; H, 6.17; N, 11.78); (c) the chromophores developed in the direct Ehrlich[5] and Warren[6] assays exhibited visible spectra essentially identical with those produced by NANA under similar conditions; (d) the infrared spectrum and periodate consumption were consistent with the assigned structure; and (e) the assignment of the configuration of C-4 and C-5[7] was based on the fact that the β-methyl glycoside of NANA (**6**) and the methyl glycoside of the eight-carbon analog **7** (obtained by dilute NaOH pretreatment of **4**) were degraded, by periodate treatment, then $NaBH_4$ reduction, to the same seven-carbon methyl glycoside **8** (previously reported by two groups[4,8]).

The eight-carbon analog **1**, very interestingly, has proven to be a substrate for the NANA aldolase isolated from *Clostridium perfringens*. The rate of enzymatic decomposition of the analog **1**, in preliminary experiments, was approximately one-fifth that of NANA.

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[1] Research supported by Grant P-441 from the American Cancer Society, the General Research Support Grant from the U. S. Public Health Service to the School of Medicine, State University of New York at Buffalo, and Grant No. MD 2803 from the Armed Forces Epidemiological Board.

[2] R. Kuhn and G. Baschang, *Ann.*, **628**, 193 (1959).

[3] R. Kuhn and G. Baschang, *ibid.*, **659**, 156 (1962).

[4] Kuhn and Gauhe prepared 2-ketodihydroquinoxaline derivatives of NANA and the N-acetylheptulosaminic acid obtained by periodate oxidation of NANA: R. Kuhn and A. Gauhe, *Ber.*, **98**, 395 (1965).

[5] I. Werner and L. Odin, *Acta Soc. Med. Upsalien.*, **57**, 230 (1952).

[6] L. Warren, *J. Biol. Chem.*, **234**, 1971 (1959).

[7] The possibility of epimerization at C-2 of 2-acetamido-2-deoxy-D-lyxose during the base-catalyzed condensation cannot be excluded *a priori*.

[8] R. K. Yu and R. Ledeen, *J. Biol. Chem.*, **244**, 1306 (1969).

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Received January 22, 1969