Effect of Solvent, Temperature, and Nature of the Sulfonate Group on the Azide Displacement Reaction of Sugar Sulfonates

Ming-Chi Wu, Laurens Anderson,* Charles W. Slife, and (in part) Lois J. Jensen

Department of Biochemistry, College of Agricultural and Life Sciences, University of Wisconsin—Madison, Madison, Wisconsin 53706

Received March 13, 1974

The effect of variation in the solvent, temperature, and nature of the sulfonate group on the rate of the azide–sulfonate displacement reaction was studied with series of sulfonate esters of diisopropylidenegalactose, diisopropylidenepinitol, and methyl tri-*O*-acetyl-D-gluco- and D-galactopyranosides. The order of rates with respect to solvent, calculated for pseudo-first-order conditions, is HMPT > DMSO > DMF. For four primary *p*-toluenesulfonates in DMF ΔH^* ranges from 16.7 to 20.3 kcal/mol, and ΔS^* from −16 to −21.5 eu. The order of rates with respect to sulfonate group is *p*-bromobenzenesulfonate > benzenesulfonate > *p*-toluenesulfonate > methanesulfonate. *p*-Nitrobenzenesulfonates in part give the parent alcohols and *p*-azidonitrobenzene, which is converted by inorganic azide to *p*-nitroaniline. Both direct attack by N_3^- on the aromatic ring and an indirect path beginning with attack on the sulfur must be considered as possible routes to *p*-azidonitrobenzene. The ready replacement by azide of the bromine in *p*-bromobenzenesulfonates was demonstrated.

The displacement of sulfonate groups by azide ion has been much used during the past decade as a means of introducing eventual amino groups into carbohydrate molecules.[1] The method is widely but not universally applicable, being subject to the restrictions which generally govern the displacement of secondary sulfonate groups. These restrictions, which involve conformational and electronic factors, have been particularly well delineated by Richardson[2a] and by Ball and Parrish.[2b]

Among the successful cases of displacement by azide there is great variation in the time required to complete the reaction and in the yield of product obtained. Such variations must be due in part to subtle steric and electronic effects, and in part to factors readily subject to control by the investigator, including the solvent used, the temperature, and the nature of the sulfonate leaving group. There is a body of qualitative knowledge about the effects of these latter variables,[2b] but they have had little systematic investigation. In the present paper quantitative data are given which should aid the synthetic chemist, in the carbohydrate and other fields, in choosing the sulfonate ester to be employed and arranging optimal reaction conditions.

Results

Effect of the Solvent. It is well known that the rates of the displacement of sulfonate groups by azide, like those of other bimolecular displacements involving anionic nucleophiles, are enhanced in dipolar aprotic solvents.[3] Thus, *N,N*-dimethylformamide (DMF) and methyl sulfoxide (DMSO) are frequently used in the preparation of carbohydrate azides. Also used is hexamethylphosphortriamide (HMPT), which is regarded as a superior medium for displacement reactions,[4,5] and 2-methoxyethanol, a protonic solvent. Some workers employ the anhydrous solvents, while others add water.

To study the effects of these variations in the solvent the rates of reaction with sodium azide were measured at 110° for two sulfonate esters which undergo displacement with moderate difficulty. One of these, 1,2:3,4-di-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-galactopyranose (1-Ts), is a primary sulfonate; the other, 1D-1,2:5,6-di-*O*-isopropylidene-3-*O*-methyl-4-*O*-*p*-tolylsulfonyl-*chiro*-inositol ("diisopropylidenetosylpinitol," 2-Ts), is a secondary sulfonate. Measurements were made in the nominally dry solvents, and in the presence of 1 and 10% (v/v) added water.

In Table I it may be seen that for each substrate the second-order rate constants are about the same in dry DMF and DMSO, and about tenfold greater in HMPT. The addition of water depressed the rates in all cases, the effect being greatest with HMPT. For the most part the data appear to fit the relationship log k proportional to the mole fraction of organic solvent.[6] Qualitative tests showed that, with both sulfonates, the reaction proceeds much more slowly in 2-methoxyethanol than in the dipolar aprotic solvents.

The observed second-order rate constants are measures

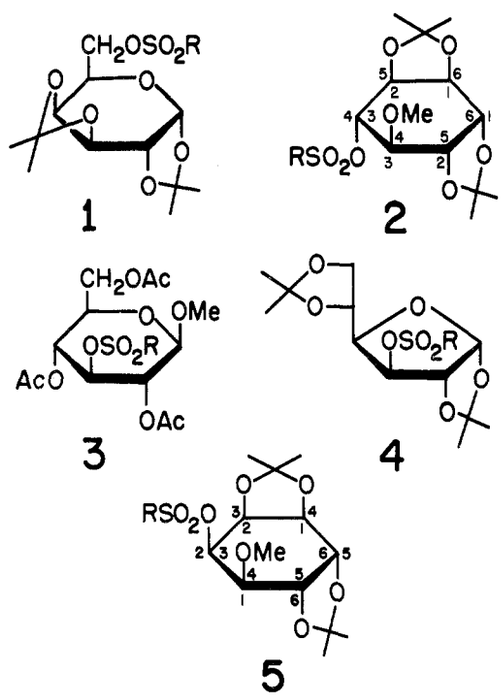

Table I
Second-Order Rate Constants for the Azide Displacement Reaction of Tosylates 1-Ts and 2-Ts in the Common Dipolar Aprotic Solvents

Sulfonate	Solvent	$10^2 k_2$, M^{-1} min^{-1}, at 110° [a] Dry	1% H_2O	10% H_2O
Gal (1-Ts)	DMF	2.60 ± 0.07	1.98 ± 0.10	0.83 ± 0.05
	DMSO	2.30 ± 0.10	2.00 ± 0.10	0.98 ± 0.03
	HMPT	20.0 ± 0.5	14.9 ± 0.4	3.4 ± 0.4
Pin (2-Ts)	DMF	0.97 ± 0.03	0.86 ± 0	0.36 ± 0.01
	DMSO	0.84 ± 0.02	0.56 ± 0.06	0.35 ± 0
	HMPT	8.2 ± 0.2	6.7 ± 0.1	1.74 ± 0.11

[a] Values are means ± range or, where three or more runs were made, ± standard deviation.

Table II
Solubility of Sodium Azide in the Solvents Used for Sulfonate Displacements

Solvent	Solubility, mol/l. Dry	1% H_2O (110°)	5% H_2O (110°)	10% H_2O (110°)
2-Methoxyethanol	0.31 (124°)			
DMF	0.10–0.12 (25–150°)	0.17	0.28	0.48
DMSO	1.5–1.6 (95–150°)	1.6	1.8	1.9
HMPT	0.43 (110–150°)	0.45	0.48	0.51

of the ability of the respective solvents to promote the azide displacement. However, the reaction is frequently run with excess solid sodium azide present, making it a pseudo-first-order process. Under these conditions the rate is also a function of the solubility of the reagent. Measurements of solubility show that sodium azide is much more soluble in DMSO than in the other two solvents (Table II). For the dry solvents, at least, there is remarkably little variation in solubility with temperature. The addition of water up to 10% greatly increases the solubility of the reagent in DMF, but has only a small effect with DMSO and HMPT.

When the observed second-order rate constants are converted to pseudo-first-order constants by reckoning in the solubility, the values shown in Table III are obtained. The times required for 97% completion of the reaction are also shown. Under pseudo-first-order conditions the reaction proceeds 13–15 times more rapidly in dry DMSO than in dry DMF. An additional two- to threefold gain in rate is achieved by going to dry HMPT. In DMF containing 10% water the rate is 1.5–2 times greater than in the dry solvent, but the addition of water decreases the first-order rates in the other two solvents.

Table III
Pseudo-First-Order Rate Constants and Times Required for 97% Completion of the Azide Displacement of Tosylates 1-Ts and 2-Ts at 110°

Sulfonate	Solvent	Dry $10^3 k_1$, min^{-1}	Dry $t_{97\%}$, hr	10% H_2O $10^3 k_1$, min^{-1}	10% H_2O $t_{97\%}$, hr
Gal (1-Ts)	DMF	2.6	22	4.0	14
	DMSO	39	1.5	18	3.2
	HMPT	86	0.67	17	3.3
Pin (2-Ts)	DMF	1.0	59	1.7	33
	DMSO	13	4.4	6.5	8.8
	HMPT	35	1.6	8.9	6.5

Effect of Temperature. The variation of the rate of the azide displacement reaction with temperature was studied on a series of primary *p*-toluenesulfonates in DMF. The compounds examined and the activation parameters calculated from the data are listed in Table IV. Since this part of the study was designed to provide numbers for the synthetic chemist to use in approximating the effect of temperature on the rate of the reaction, the data are not as extensive or as precise as in the usual physical organic study. Nevertheless they permit qualitative comparisons with the activation parameters of related reactions.

Effect of the Sulfonate Group. In synthetic work in the carbohydrate field methanesulfonate (mesylate) and *p*-toluenesulfonate (tosylate) esters are the most commonly used substrates for displacement reactions. It is generally recognized that toluenesulfonate is a better leaving group

Table IV
Activation Parameters for the Azide Displacement of Some Primary Sugar Tosylates in DMF at 80°

Sulfonate	Registry no.	$10^4 k_2$, M^{-1} sec^{-1}	Measurements made at °C	ΔH^*, kcal/mol[a]	ΔS^*, eu/mol[b]
Methyl 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-α-D-glucopyranoside	23661-33-8	166	60, 70, 80	16.7	−19.6
Methyl 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-β-D-glucopyranoside	13032-69-4	120	60, 70, 80, 100	18.5	−15.9
Methyl 2,3,4-tri-*O*-acetyl-6-*O*-*p*-tolylsulfonyl-α-D-galactopyranoside	52109-81-6	5.2	80, 100, 110	20	−17
1,2:3,4-Di-*O*-isopropylidene-6-*O*-*p*-tolylsulfonyl-α-D-galactopyranose (1-Ts)		0.42	80, 100, 110	20.3	−21.5

[a] Estimated accuracy ±1 kcal/mol. [b] Estimated accuracy ±3 eu.

Table V
Variation of the Rate of the Azide Displacement Reaction with Variation of the Sulfonate Group

Sulfonate group	Diisopropylidene-galactose sulfonates (1), $10^2 k_2$, M^{-1} min^{-1}, at 110° in DMF [a]	Diisopropylidene-pinitol sulfonates (2), $10^2 k_2$, M^{-1} min^{-1}, at 110° in DMF [a]	Methyl 2,4,6-tri-*O*-acetyl-β-D-glucopyranoside sulfonates (3), $10^2 k_2$, M^{-1} min^{-1}, at 110° in DMF [a]
Methanesulfonate	1.1 ± 0.1		
p-Toluenesulfonate	2.6 ± 0.1	0.97 ± 0.03	7.9 ± 0.6
Benzenesulfonate	3.4 ± 0.1		
p-Bromobenzenesulfonate	12 ± 0	3.0 ± 0.1	30.4 ± 0.8
p-Chlorobenzenesulfonate		3.6 ± 0.1	

[a] Values are means ± range or, where three or more runs were made, ± standard deviation.

than methanesulfonate. The use of *p*-bromobenzenesulfonates (brosylates) is occasionally reported, and displacements of *p*-nitrobenzenesulfonates (nosylates) have also been attempted.

To compare the efficacy of the various sulfonate groups in the azide displacement reaction, series of sulfonate esters, **1**, of diisopropylidene-α-D-galactopyranose and **2**, of diisopropylidenepinitol, were prepared. Rate measurements were then carried out on all the esters which appeared to be transformed cleanly to azido products. Two sulfonates (**3**) of methyl 2,3,6-tri-*O*-acetyl-β-D-glucopyranoside were also included in the study. The measurements were made in DMF at 110°.

It would be expected on theoretical grounds that the rate of the bimolecular displacement of sulfonate groups, RSO_3^-, would increase with increasing electron-withdrawing power of the R group. Indeed this has been demonstrated in the case of the alkoxide displacement of ethyl sulfonates.[7] The results of the present work (Table V) are also in accord with these expectations. In the diisopropylidenegalactose series the tosylate reacted 2.4 times faster than the mesylate, and the brosylate was 11 times faster. A comparison of tosylate with brosylate can be made for all three of the parent sugars, whereupon the rates of displacement of the brosylate group are seen to be 3.0–4.6 times those of tosylate. The *p*-chlorobenzenesulfonate of diisopropylidenepinitol had a slight rate advantage over the corresponding brosylate. No rate measurements were made with the nitrobenzenesulfonates **1**-Ns, **2**-Ns, and **2**-CNs because these compounds reacted with azide ion in two ways, giving the parent alcohols in addition to the normal displacement products. The nature of the side reaction is further discussed below.

In view of the notorious resistance to displacement of the tosylate group in 1,2:5,6-di-*O*-isopropylidene-3-*O*-*p*-tolylsulfonyl-α-D-glucofuranose (**4**-Ts) it seemed of interest to study the corresponding brosylate and nosylate. It had been shown[8] that when the brosylate **4**-Bs is treated with dimethylamine the bromine is displaced from the aromatic ring. Also, it had been reported[9] that the nosylate **4**-Ns gave much tar and some of the parent alcohol (diisopropylideneglucose) on treatment with methanolic ammonia at 165°. In our hands the reaction of **4**-Bs with sodium azide under the conditions used for the kinetic measurements gave a crystalline product which could be characterized, by its spectral properties and elemental analysis, as 3-*O*-*p*-azidophenylsulfonyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose. The reaction of the nosylate **4**-Ns with azide also gave some of the *p*-azidobenzenesulfonate, as well as the parent alcohol.

The foregoing results raised the question whether the displacement of the brosylates **1**-Bs, **2**-Bs, and **3**-Bs might be proceeding, in part, *via* azidobenzenesulfonates. On refinement of the tlc system used for following the reaction we could demonstrate the formation of some *p*-azidobenzenesulfonate during the displacement of **1**-Bs, and enough of the compound was isolated for a single measurement of its displacement rate. A value of 0.06 M^{-1} min^{-1} in DMF at 110° was found, which is about half the overall rate measured for **1**-Bs. We could not detect azidobenzenesulfonates from **2**-Bs and **3**-Bs, but since the displacement rate for **2**-Bs is lower than that for **1**-Bs, **2**-Bs probably also undergoes some replacement of bromine.

The complexity of the reaction of the brosylates with azide did not strongly affect the kinetic measurements, for plots of 1/substrate concentration *vs.* time were linear out to 2 half-lives. Beyond that point the precision of our analyses was too low to permit any conclusions as to whether the kinetics were complex. Nevertheless the measured rate constants must be considered as composite constants for the direct displacement of brosylate and the simultaneous displacement of azidobenzenesulfonate formed from a portion of the brosylate.

It seemed of interest to investigate the process whereby the nitrobenzenesulfonates are converted, in part, to parent alcohols during attempted displacement with azide ion. Under solvolysis conditions some sugar nosylates have given products suggestive of dissociation to nosylate and sugar carbonium ions.[10,11] If this were happening in the present case the carbonium ions might combine with the solvent to give labile intermediates which would be hydrolyzed to parent alcohols on work-up. To test this possibility compound **1**-Ns and the cyclitol nosylate **5**-Ns were prepared with ^{18}O in the ester oxygen. The labeled compounds were then treated with sodium azide in DMF at 110° for 24 hr, and the alcoholic products were isolated. These products retained all of the ^{18}O of the nosylates from which they were derived. The product from **1**-Ns was identified as 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (formula **1**, H in place of SO_2R). The pmr spectrum of the product from **5**-Ns was identical with that of 1D-1,2:5,6-di-*O*-isopropylidene-4-*O*-methyl-*allo*-inositol (formula **5**, H in place of RSO_2) and the product from (unlabeled) **2**-Ns was rigorously characterized as the pinitol derivative (formula **2**, H in place of RSO_2). These cyclitols are indeed the parent alcohols of **5**-Ns and **2**-Ns; hence there was retention of configuration at the sulfonate-bearing carbons. Compound **1**-Ns gave parent alcohol when heated alone in DMF.

Further investigation of the reactions of the nosylates with azide showed that a major aromatic product was *p*-nitroaniline. In search of immediate precursors of this compound, samples of *p*-azidonitrobenzene and *p*-nitrobenzenesulfonyl azide were synthesized. When the sulfonyl azide was heated for a short time with sodium azide in DMF it was converted to *p*-azidonitrobenzene. The latter, or the sulfonyl azide, when heated for 24 hr with sodium

azide gave *p*-nitroaniline as the principal product. The presence of sodium azide was necessary for the formation of the *p*-nitroaniline. *p*-Nitrobenzenesulfonic acid was unaltered under these conditions, except for salt formation.

In a final experiment the reaction of compound **2**-Ns with sodium azide was interrupted after 3 hr. Chromatographic and pmr spectroscopic examination of the rather complex reaction mixture showed that *p*-azidonitrobenzene, but not *p*-nitrobenzenesulfonyl azide, was present.

Azido Products. Reference samples of all the azido products were obtained by making preparative runs with the respective *p*-toluenesulfonates. The 6-sulfonates gave the expected 6-azido-6-deoxy compounds. Of these, 6-azido-6-deoxy-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose[12] and methyl 2,3,4-tri-*O*-acetyl-6-azido-6-deoxy-α-D-glucopyranoside[13] have been reported in the literature. The product from **3**-Ts and **3**-Bs is assumed to be methyl 2,4,6-tri-*O*-acetyl-3-azido-3-deoxy-β-D-allopyranoside on the basis that, in view of its second-order kinetics, the displacement took place with inversion of configuration.

Inversion of configuration was demonstrated to occur in the formation of azidocyclitols from sulfonates of series **2** and **5**. The characterization of these products will be described in a forthcoming paper.

Discussion

The data reported here reveal the extent to which the rates of azide–sulfonate displacements are affected by changes in the sulfonate group and the solvent used as reaction medium. For the compounds studied, with sodium azide as reagent under pseudo-first-order conditions in the common dipolar aprotic solvents, a *ca.* 35-fold range of variation could be shown to result from variation of the solvent, and an 11-fold change from variation of the sulfonate group. Combination of these two factors gives an overall variation in rates, at a given temperature, of nearly 400-fold. It is thus evident that considerable savings in the time required to prepare azido carbohydrate derivatives may be realized by proper choice of solvent and sulfonate ester. These savings will be significant in cases where the parent sugar structure is one which makes displacement inherently slow.

Our results confirm the superiority of HMPT as a solvent for azide–sulfonate displacements. The advantage of HMPT over DMSO is not great, however, owing to the better solubility of the reagent in DMSO. Accordingly DMSO may well be chosen when it is more readily available, or if it is found to be more easily removed from the reaction mixture during work-up. Where maximal rates are not required DMF is to be preferred because it is more easily removed than either of the other two solvents. The addition of up to 10% (perhaps more) of water to DMF increases the solubility of the reagent enough to more than offset the intrinsic rate-depressing effect of the water, and hence is to be recommended. Both DMSO and HMPT give better rates when dry.

Among the sulfonate groups brosylate has a clear advantage over mesylate and tosylate. The fact that a portion of a brosylate may be converted to azidobenzenesulfonate is not a drawback, for it appears that azidobenzenesulfonates undergo displacement at good rates. Under the conditions of our experiments the reaction of the very resistant diisopropylideneglucose derivative **4**-Bs stopped at the azidobenzenesulfonate stage. However, the azide displacement of the tosylate of diisopropylideneglucose has recently been accomplished by prolonged reaction at 115° in DMF,[14] or by treatment for 18 hr at 120° in HMPT.[15] Much elimination product was formed in the latter case.

The hope of achieving further gains in rate by using the still more electron-withdrawing nitrophenyl group in the sulfonate moiety was frustrated by the tendency of the nitrobenzenesulfonates to undergo a side reaction which regenerates the parent alcohols. This reaction was found to proceed with retention of configuration and, when ^{18}O-labeled nosylates were used, retention of label. These findings rule out mechanisms involving C–O cleavage, such as dissociation to *p*-nitrobenzenesulfonate and carbonium ions, or attack by the solvent on the esterified carbon. Since parent alcohol is generated in the absence of sodium azide, there may be some attack by the solvent (or traces of water therein) on the sulfonate sulfur, with the eventual formation of *p*-nitrobenzenesulfonate ion. However, this cannot be the major pathway when azide is present, for it does not explain the formation of *p*-nitroaniline (nosylate ion is inert to sodium azide). Rather, what is indicated is attack by N_3^- either on the sulfur or on the aromatic ring carbon bonded to sulfur. In the former case *p*-nitrobenzenesulfonyl azide would be formed, and the SO_2N_3 group would be displaced by a second N_3^- ion as shown in the present work to give the observed intermediate *p*-azidonitrobenzene. In the second case the *p*-azidonitrobenzene would be produced directly. The final conversion to *p*-nitroaniline may be rationalized as a reduction of *p*-azidonitrobenzene by azide ion.

In summary, the use in a contemplated azide displacement of a sulfonate with a too strongly electron-withdrawing R group can divert the attack of the azide to the sulfonate moiety. In the nitrobenzenesulfonate case, in addition to the points of attack just cited, the nitro group may also suffer displacement, as seen with **4**-Ns. This side reaction, unlike the others, may be followed by the normal displacement of the sulfonate group from the carbon to which it is esterified. Another case of the displacement of the nitro group from **4**-Ns is that observed by Rosenthal and Nguyen,[16] where the alkoxide of diisopropylideneglucose was the displacing species.

A virtue of choosing the solvent and sulfonate group which will give the maximal rate of azide displacement is that this permits lowering the reaction temperature. Since carbohydrate sulfonates and azides are both subject to elimination and other reactions of decomposition at high temperature, the best yields should in general be obtained by operating at the lowest temperature that gives a reasonable reaction rate. Thus, the yield of displacement product from diisopropylideneglucose sulfonates (**4**) could probably be improved by using the brosylate in DMSO (less basic then HMPT) at a temperature somewhat lower than 115°. An estimate of the effect of a change in temperature may be made from the data in Table IV or, more conveniently, by taking 2.2 as the factor by which the reaction rate increases with a 10° increase in temperature (the "Q_{10}" of the older literature).

Our data on the enthalpies and entropies of activation of the azide–sulfonate displacement reaction show no marked differences from other types of bimolecular displacements.[17] In a study of a closely related reaction, the displacement of primary sugar benzenesulfonates by iodide ion in 2,5-hexanedione, Sugihara and Teerlink[18] found 20–25 kcal/mol for ΔH^* and −6 to −15 eu for ΔS^*. These values are, respectively, a little higher and a little less negative than those found in Table IV.

It will be noted that although the diisopropylidenegalactose derivatives (**1**) are primary sulfonates, their reaction rates are in the same range as those of the secondary sulfonates **2** and **3** (Table V). The contrast between **1**-Ts and the more typical primary tosyl derivatives of glucose is

highlighted in Table IV, which also shows a comparatively low reaction rate for the 6-tosylate of methyl tri-*O*-acetyl-α-D-galactopyranoside. This low reactivity of the galactose primary sulfonates, particularly those derived from diisopropylidenegalactose,has been known for many years.[19] It has been attributed both to steric effects[20] and to field effects.[18,21] An explanation based on the interaction of dipoles in the transition state has also been advanced.[2b]

Experimental Section

General. Thin layer chromatography plates were prepared from silica gel G (Merck) and column chromatography was performed on silica gel (Merck). Chromatograms of both types were developed with ethanol–Skellysolve B, 1:9, v/v (solvent A) or benzene–acetone–ether, 14:3:1, v/v/v (solvent B). Compounds and reaction mixtures were routinely checked by tlc in solvent A; solvent B was used only as expressly noted. Melting points were determined in Pyrex glass capillaries immersed in a heated oil bath equipped with a calibrated thermometer. Proton magnetic resonance spectra were recorded with Varian A-60 or T-60 spectrometers, and are referenced to tetramethylsilane as internal standard. Infrared spectra were recorded on a Beckman IR-5. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Mass spectra were obtained with an AEI MS-902 instrument.

2-Methoxyethanol and hexamethylphosphortriamide from Eastman Organic Chemicals were redistilled, the latter under reduced pressure. Methyl sulfoxide, anhydrous grade, and *N,N*-dimethylformamide, spectroquality grade, were from Matheson Chemicals. All these solvents were stored over Linde type 4A molecular sieves.

Sulfonate Esters. Diisopropylidenegalactose,[22] diisopropylidenepinitol,[23] and diisopropylideneglucose were treated with sulfonyl chlorides under the conditions described by Tipson.[22] The acetylated 3-sulfonates of methyl β-D-glucopyranoside were prepared from the corresponding diisopropylideneglucose sulfonates according to Ahluwahlia, *et al.*[24] The following were recrystallized until their melting points and specific rotations agreed closely with those in the literature: 1-Ms,[25] 1-Ps,[18] 1-Ts,[26,27] 2-Ts,[28] 4-Ts,[29] 4-Bs,[8] 4-Ns,[9] and 3-Ts.[30] The acetylated 6-*p*-toluenesulfonates of methyl α-D-glucopyranoside,[31] methyl β-D-glucopyranoside,[32] and methyl α-D-galactopyranoside[33] were prepared by Cramer's procedure.[34]

6-*O*-*p*-Bromophenylsulfonyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (1-Bs) was recrystallized from ethanol: yield 92%; mp 92–93°; $[\alpha]_{589}$ −45.8° (*c* 2, DMF); pmr ($CDCl_3$) τ 2.23 and 2.32 ppm (q_{AB}, 4, J = 9 Hz, aromatic H).

Anal. Calcd for $BrC_{18}H_{23}O_8S$ (479.35): C, 45.10; H, 4.84. Found: C, 45.37; H, 4.90.

1,2:3,4-Di-*O*-Isopropylidene-6-*O*-*p*-nitrophenylsulfonyl-α-D-galactopyranose (1-Ns) was recrystallized from ethanol: yield 78%; mp 101–102°; $[\alpha]_{589}$ −48.9° (*c* 2, DMF); pmr ($CDCl_3$) τ 1.60 and 1.85 ppm (q_{AB}, 4, J = 9 Hz, aromatic H).

Anal. Calcd for $C_{18}H_{23}NO_{10}S$ (445.44): C, 48.53; H, 5.20. Found: C, 48.59; H, 5.19.

1,2:3,4-Di-*O*-isopropylidene-6-*O*-*p*-nitrophenylsulfonyl-[6-^{18}O]-α-D-galactopyranose ([6-^{18}O]-1-Ns). [^{18}O]Benzoic acid was prepared by treating 0.75 ml of $H_2{}^{18}O$ (40 atom %) in 25 ml of dry pyridine with a 0.96 molar portion of benzoyl chloride (78% yield). Sodium [^{18}O]benzoate made by neutralizing the acid with sodium hydroxide was recrystallized from ethanol–water. Compound 1-Ts (1.27 g, 3.1 mmol) and the labeled sodium benzoate (0.89 g, 6.2 mmol) were refluxed in 25 ml of dry DMF for 65 hr. The reaction mixture was then diluted with 50 ml of water and extracted twice with ether (50 ml each). The ether extract, washed twice with water and dried ($MgSO_4$), was evaporated to dryness under vacuum. The syrupy product was identical (tlc in solvent B, pmr) with the substance obtained by benzoylating 1,2:3,4-di-*O*-isopropylidenegalactose with benzoyl chloride, and the pmr spectra had the expected features. Hence the compound was **1-[^{18}O]benzoyl-1,2:3,4-di-*O*-isopropylidene-[6-^{18}O]-α-D-galactopyranose** (yield 0.95 g, 85%).

The labeled benzoate ester was catalytically saponified (sodium methoxide, methanol) to **1,2:3,4-di-*O*-isopropylidene-[6-^{18}O]-α-D-galactopyranose** containing, according to mass spectrometric analysis, 17.1 atom % excess ^{18}O in the labeled position (expected, 20 atom %). The calculations[35] were based on the peaks at *m/e* 245 and 247 (M − 15). The bulk (0.65 g, 2.5 mmol) of the [^{18}O]diisopropylidenegalactose was converted to **[6-^{18}O]-1-Ns** by treatment with two molar portions of *p*-nitrobenzenesulfonyl chloride according to the Tipson method,[22] yield 0.82 g (73%), mp 103–104°.

6-*O*-*p*-Azidophenylsulfonyl-1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose (1-As). To a solution of 1-Bs (4.8 g, 10 mmol) in HMPT (50 ml), excess sodium azide (5 g) was added. The solution was heated at 110° for 30 min, then distilled under high vacuum (80°, 0.05 Torr) to remove all the solvent. The residue was extracted with chloroform and the extract was evaporated to a thick syrup. Tlc in solvent A showed three spots, R_f 0.8 (6-azido-6-deoxydiisopropylidenegalactose), 0.55 (starting material), and 0.53 (title compound). These components were separated by column chromatography (solvent A), which yielded 0.2 g of pure title compound as a yellowish syrup: ir (film) 2100 cm^{-1} (N_3); pmr ($CDCl_3$) τ 2.19 and 2.82 ppm (q_{AB}, 4, J = 9 Hz, aromatic H).

Anal. Calcd for $C_{18}H_{23}N_3O_8S$ (441.45): C, 48.97; H, 5.25; N, 9.52. Found: C, 49.03; H, 5.49; N, 9.25.

1D-3-*O*-*p*-Bromophenylsulfonyl-1,2:5,6-di-*O*-isopropylidene-4-*O*-methyl-*chiro*-inositol (2-Bs)[36] was recrystallized from ethanol: yield 90%; mp 115–116°; $[\alpha]_{589}$ +22.7° (*c* 2, DMF); pmr ($CDCl_3$) τ 2.21 and 2.36 ppm (q_{AB}, 4, J = 9 Hz, aromatic H).

Anal. Calcd for $BrC_{19}H_{25}O_8S$ (493.37): C, 46.25; H, 5.11. Found: C, 46.55; H, 5.37.

1D-3-*O*-*p*-Chlorophenylsulfonyl-1,2:5,6-di-*O*-isopropylidene-4-*O*-methyl-*chiro*-inositol (2-Cs) was recrystallized from ethanol: yield 80%; mp 110–111°; $[\alpha]_{589}$ +59.7° (*c* 1, $CHCl_3$); pmr ($CDCl_3$) τ 2.12 and 2.53 ppm (q_{AB}, 4, J = 9 Hz, aromatic H).

Anal. Calcd for $C_{19}ClH_{25}O_8S$ (448.91): C, 50.83; H, 5.61. Found: C, 50.22; H, 5.52.

1D-1,2:5,6-Di-*O*-isopropylidene-3-*O*-methyl-4-*O*-*p*-nitrophenylsulfonyl-*chiro*-inositol (2-Ns) was recrystallized from ethanol: yield 89%; mp 129–131°; $[\alpha]_{589}$ +64.5° (*c* 1, $CHCl_3$); pmr ($CDCl_3$) τ 1.64 and 1.89 ppm (q_{AB}, 4, J = 9 Hz, aromatic H).

Anal. Calcd for $C_{19}H_{25}NO_{10}S$ (459.46): C, 49.66; H, 5.48. Found: C, 49.61; H, 5.36.

1D-3-*O*-(4-Chloro-2-nitrophenylsulfonyl)-1,2:5,6-di-*O*-isopropylidene-4-*O*-methyl-*chiro*-inositol (2-CNs) was recrystallized from ethanol: yield 80%; mp 118–119°; $[\alpha]_{589}$ +49.3° (*c* 1, $CHCl_3$); pmr ($CDCl_3$) τ 1.87–2.38 ppm (m, 3, aromatic H).

Anal. Calcd for $C_{19}ClH_{24}NO_{10}S$ (493.91): C, 46.20; H, 4.90. Found: C, 46.75; H, 5.29.

Methyl 2,4,6-tri-*O*-acetyl-3-*O*-*p*-bromophenylsulfonyl-β-D-glucopyranoside (3-Bs) was recrystallized from ethanol: yield 35%; mp 102–103°; $[\alpha]_{589}$ −15.1° (*c* 2, $CHCl_3$); pmr ($CDCl_3$) τ 7.93 (s, 3), 8.00 (s, 3), and 8.03 (s, 3) ($COCH_3$), 6.50 (s, 3, OCH_3), and 2.35 ppm (s, 4, aromatic H).

Anal. Calcd for $BrC_{19}H_{23}O_{11}S$ (539.36): C, 42.31; H, 4.30. Found: C, 42.85; H, 4.50.

3-*O*-*p*-Azidophenylsulfonyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (4-As) was obtained from 3-*O*-*p*-bromophenylsulfonyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (4-Bs) by a procedure similar to that used for the preparation of compound 1-As. Recrystallized from ethanol, it had mp 109–110°; $[\alpha]_{589}$ −77.7° (*c* 1, $CHCl_3$); ir (KBr) 2100 cm^{-1} (N_3); pmr ($CDCl_3$) τ 8.53 (s, 3), 8.70 (s, 3), 8.79 (s, 3), and 8.85 (s, 3) (isopropylidene CH_3), 4.10 (d, 1, J = 4 Hz, H-1), 2.19, and 2.82 ppm (q_{AB}, 4, J = 9 Hz, aromatic H).

Anal. Calcd for $C_{18}H_{23}N_3O_8S$ (441.45): C, 48.97; H, 5.25; N, 9.52. Found: C, 48.93; H, 5.31; N, 9.73.

1D-1,2:5,6-Di-*O*-isopropylidene-4-*O*-methyl-3-*O*-*p*-nitrophenylsulfonyl-*allo*-inositol (5-Ns) (Including [3-^{18}O]-5-Ns).[36] 1L-2-*O*-Benzoyl-3,4:5,6-di-*O*-isopropylidene-1-*O*-methyl-*allo*-inositol[37] was catalytically saponified (sodium methoxide, methanol) and 0.54 g of the resulting syrupy hydroxy compound was treated with three molar portions of *p*-nitrobenzenesulfonyl chloride according to the Tipson procedure.[22] The title compound was recrystallized from absolute ethanol: yield 50%; mp 137°; $[\alpha]_{589}$ + 8°, $[\alpha]_{436}$ + 17° (*c* 0.7, $CHCl_3$); pmr ($CDCl_3$) τ 1.61 and 1.83 ppm (q_{AB}, 4, J = 9.3 Hz, aromatic H).

Anal. Calcd for $C_{19}H_{25}NO_{10}S$ (459.46): C, 49.66; H, 5.48; N, 3.04; S, 6.97. Found: C, 49.40; H, 5.59; N, 2.99; S, 7.01.

An amount of 1.36 g (3.2 mmol) of compound 2-Ts was treated with the above-described sodium [^{18}O]benzoate (0.91 g, 6.3 mmol) by the procedure of Angyal and Stewart.[37] The resulting **1L-2-*O*-[^{18}O]-benzoyl-3,4:5,6-di*O*-isopropylidene-1-*O*-methyl-[2-^{18}O]-*allo*-inositol** (0.89 g, 74%) was catalytically saponified to **1D-1,2:5,6-di-*O*-isopropylidene-4-*O*-methyl-[3-^{18}O]-*allo*-inositol** (0.54 g, 84%). Calculation (see above) based on the mass spectral peaks at *m/e* 259 and 261 (M − 15) showed 17.1 atom % excess ^{18}O in this product. Conversion to **[3-^{18}O]-5-Ns** was accomplished as for the unlabeled material. The purity of the intermediate and

the final product was checked by tlc in solvent B.

Reaction Rate Measurements. Bacteriological culture tubes (1.8 × 15 cm) with screw caps, equipped with 0.5-in. magnetic stirring bars, were used as reaction vessels. A solution of sodium azide in the desired solvent was adjusted to 0.100 *M* (titration). Sulfonate sufficient to give a concentration of 0.100 *M* was weighed into a volumetric flask and dissolved in the azide solution. Aliquots (2.00 ml) of the mixture were then distributed to the tubes and these tubes were immersed to 5 cm in a preheated oil bath regulated to ±0.1°. The oil bath was mounted on a magnetic stirrer. Tubes were removed at intervals and quenched by adding 20 ml of ice water, and the remaining azide ion was titrated with 0.010 *M* silver nitrate with potassium chromate as indicator.[38] Two or more runs were made with each ester in each solvent used.

Solubility of Sodium Azide. Sodium azide (5 g) and the solvent (40 ml) were stirred magnetically in a stoppered flask at the desired temperature for 4 hr. Stirring was discontinued, and after the solid sodium azide had settled, 2 ml of the clear solution was taken by a volumetric pipette and titrated with 0.010 *M* silver nitrate.

Azido Products. The desired *p*-toluenesolfonate was heated with excess sodium azide in DMF at 110° for a suitable time. The reaction mixture was then evaporated to dryness under reduced pressure. The residue was extracted with ether, the extract was evaporated, and the crude azide was purified by the appropriate means.

Product from 3-Ts and 3-Bs. The reaction time was 2 days. Purification by column chromatography gave a colorless syrup: $[\alpha]_{589}$ −25° (*c* 2, $CHCl_3$); ir (film) 2100 cm^{-1} (N_3); pmr ($CDCl_3$) τ 7.90 (s, 3) and 8.00 (s, 6) ($COCH_3$), 6.58 (s, 3, OCH_3), and 4.9–6.2 ppm (m, 7, sugar ring H).

Methyl 2,3,4-Tri-*O*-acetyl-6-azido-6-deoxy-β-D-glucopyranoside. The reaction time was 30 min. The product was recrystallized from ethanol: mp 80–82°; $[\alpha]_{589}$ −38.5° (*c* 2, $CHCl_3$); ir (KBr) 2100 cm^{-1} (N_3); pmr ($CDCl_3$) no aromatic H.

Anal. Calcd for $C_{13}H_{19}N_3O_8$ (345.31): C, 45.22; H, 5.55. Found: C, 45.34; H, 5.40.

Methyl 2,3,4-Tri-*O*-acetyl-6-azido-6-deoxy-α-D-galactopyranoside. The reaction time was 30 min. The product was recrystallized from ethanol–Skellysolve B: mp 85–86°; $[\alpha]_{589}$ +137.3° (*c* 2, $CHCl_3$); ir (KBr) 2100 cm^{-1} (N_3); pmr ($CDCl_3$) no aromatic H.

Anal. Calcd for $C_{13}H_{19}N_3O_8$ (345.31): C, 45.22; H, 5.55. Found: C, 45.39; H, 5.07.

Azide Displacement of the *p*-Nitrobenzenesulfonates. Samples (about 0.8 g) of compounds **1**-Ns, **2**-Ns, and **5**-Ns were heated with an eightfold molar excess of sodium azide in 20 ml of dry DMF at 110° for 24 hr. The solutions were diluted with 50 ml of water and extracted thrice with ether (50 ml each). The combined ether extracts were washed twice with water, dried ($MgSO_4$), examined by tlc (solvent B), and concentrated to dryness. Chromatography of the residues on silica gel columns (3.3 × 60 cm, solvent B) gave in each case three fractions. The first fractions to emerge from each column were shown by comparison (tlc, pmr) with authentic samples to be the azidodeoxydi-*O*-isopropylidene derivatives of galactose, 1-*O*-methyl-*allo*-inositol, and pinitol, respectively. The second fraction in each case was identified as *p*-nitroaniline by comparison (tlc, pmr, ir, and mixture melting point) with an authentic sample.

The third fractions were indistinguishable (tlc, pmr) from the respective parent alcohols of **1**-Ns, **2**-Ns, and **5**-Ns. The product from **2**-Ns was heated with 50% aqueous acetic acid to hydrolyze off the isopropylidene groups, and the residue was trimethylsilylated and subjected to glc[39] on a column of 5% SE-30 on Chromosorb W. This column clearly separated the TMS ethers of 1-*O*-methyl-*allo*-inositol and pinitol. The product from **2**-Ns chromatographed with penta-*O*-trimethylsilylpinitol.

Treatment of [6-^{18}O]-**1**-Ns and [3-^{18}O]-**5**-Ns as just described gave parent alcohol fractions which were analyzed by mass spectrometry (see above). Values of 16.8 and 17.6, respectively, were found for the atom per cent excess ^{18}O in the labeled positions.

A sample (0.23 g) of **2**-Ns was heated for 3.5 hr with sodium azide in DMF and worked up as just described. Tlc (solvent B) of the ether extract showed five components, with the R_f's, respectively, of *p*-azidonitrobenzene, unknown, the azidocyclitol product, *p*-nitroaniline, and the parent alcohol. Partial separation of the mixture was accomplished by column chromatography. In the aromatic region of the pmr spectrum of the residue from the early fractions the characteristic doublets (τ 1.71, 2.83, $CDCl_3$) due to *p*-azidonitrobenzene were clearly evident.

Conversion of Aromatic Intermediates to *p*-Nitroaniline. Samples of *p*-azidonitrobenzene[40] (0.064 g) and *p*-nitrobenzenesulfonyl azide[41] (0.11 g) were heated in 5 ml of dry DMF at 110° for 24 hr. After evaporation of the solvent under vacuum the residues were examined by tlc (solvent B) and pmr. The *p*-azidonitrobenzene was recovered unchanged. The *p*-nitrobenzenesulfonyl azide was converted to a product which was not *p*-azidonitrobenzene or *p*-nitroaniline, but which was not further characterized.

These experiments were repeated with the addition of sodium azide (eightfold molar excess) to the reaction mixtures. Ether extracts were obtained as described in the previous section. The residue in both cases was primarily *p*-nitroaniline (tlc, pmr).

p-Nitrobenzenesulfonyl azide was treated with sodium azide as just described for 1 hr. Examination (tlc, pmr) of the residue from the ether extract showed complete disappearance of the starting material. The major product was *p*-azidonitrobenzene, accompanied by a substantial portion of *p*-nitroaniline.

Acknowledgments. This work was supported by the College of Agricultural and Life Sciences, University of Wisconsin—Madison, and by Grant AM-10588 from the National Institute of Arthritis, Metabolism, and Digestive Diseases, National Institutes of Health. L. J. J. was an NSF Undergraduate Summer Research Participant. The authors thank Professors M. H. O'Leary and S. F. Nelsen of the Department of Chemistry for helpful discussions.

Registry No.—**1**-Bs, 52109-71-4; **1**-Ns, 52109-72-5; **1**-Ns (6-^{18}O), 52109-73-6; **1**-Ts, 4478-43-7; **1**-As, 52109-74-7; **2**-Bs, 52109-75-8; **2**-Cs, 52109-76-9; **2**-Ns, 52109-77-0; **2**-CNs, 52109-78-1; **2**-Ts, 18391-45-2; **3**-Bs, 52109-79-2; **4**-As, 52109-80-5; **4**-Bs, 20581-78-6; **5**-Ns, 52154-18-4; methyl 2,3,4-tri-*O*-acetyl-6-azido-6-deoxy-β-D-glucopyranoside, 52109-82-7; methyl 2,3,4-tri-*O*-acetyl-6-azido-6-deoxy-α-D-galactopyranoside, 52109-83-8.

References and Notes

(1) A. K. Chatterjee, D. Horton, and J. S. Jewell, *Carbohyd. Res.*, **7**, 212 (1968).
(2) (a) A. C. Richardson, *Carbohyd. Res.*, **10**, 395 (1969); (b) D. H. Ball and F. W. Parrish, *Advan. Carbohyd. Chem.*, **24**, 139 (1969).
(3) A. C. Richardson, *Annu. Rep. Progr. Chem.*, **63**, 493 (1966).
(4) J.-J. Delpuech, *Tetrahedron Lett.*, 2111 (1965); *Bull. Soc. Chim. Fr.*, 1624 (1966).
(5) Y. Ali and A. C. Richardson, *J. Chem. Soc. C*, 1764 (1968).
(6) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969).
(7) M. S. Morgan and L. H. Cretcher, *J. Amer. Chem. Soc.*, **70**, 375 (1948).
(8) D. Horton, J. S. Jewell, and H. S. Prihar, *Can. J. Chem.*, **46**, 1580 (1968).
(9) B. Coxon and L. Hough, *J. Chem. Soc.*, 1643 (1961).
(10) P. W. Austin, J. G. Buchanan, and R. M. Saunders, *J. Chem. Soc. C*, 372 (1967).
(11) P. W. Austin, J. G. Buchanan, and D. G. Large, *Chem. Commun.*, 418 (1967).
(12) W. A. Szarek and J. K. N. Jones, *Can. J. Chem.*, **43**, 2345 (1965).
(13) F. Cramer, H. Otterbach, and H. Springmann, *Chem. Ber.*, **92**, 384 (1959).
(14) U. G. Nayak and R. L. Whistler, *J. Org. Chem.*, **34**, 3819 (1969).
(15) R. L. Whistler and L. W. Doner, *J. Org. Chem.*, **35**, 3562 (1970).
(16) A. Rosenthal and L. Nguyen, *Can. J. Chem.*, **46**, 3751 (1968).
(17) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, p 22.
(18) J. M. Sugihara and W. J. Teerlink, *J. Org. Chem.*, **29**, 550 (1964).
(19) R. S. Tipson, *Advan. Carbohyd. Chem.*, **8**, 107 (1953).
(20) M. Akagi, S. Tejima, and M. Haga, *Chem. Pharm. Bull.*, **11**, 559 (1963).
(21) S. Nadkarni and N. R. Williams, *J. Chem. Soc.*, 3496 (1965).
(22) R. S. Tipson, *Methods Carbohyd. Chem.*, **2**, 246 (1963).
(23) S. J. Angyal and C. G. Macdonald, *J. Chem. Soc.*, 686 (1952). Prepared by the procedure of S. J. Angyal and R. M. Hoskinson, *J. Chem. Soc.*, 2985 (1962), using dimethoxypropane as reagent.
(24) R. Ahluwahlia, S. J. Angyal, and M. H. Randall, *Carbohyd. Res.*, **4**, 478 (1967).
(25) B. Helferich, H. Dressler, and R. Griebel, *J. Prakt. Chem.*, **261**, 285 (1939).
(26) K. Freudenberg and R. M. Hixon, *Ber.*, **56**, 2119 (1923).
(27) A. B. Foster, W. G. Overend, M. Stacey, and L. F. Wiggins, *J. Chem. Soc.*, 2542 (1949).
(28) S. J. Angyal and N. K. Matheson, *J. Amer. Chem. Soc.*, **77**, 4343 (1955).
(29) K. Freudenberg and O. Ivers, *Ber.*, **55**, 929 (1922).
(30) S. Peat and L. F. Wiggins, *J. Chem. Soc.*, 1088 (1938).
(31) B. Helferich and E. Himmen, *Ber.*, **61**, 1825 (1928).
(32) J. Compton, *J. Amer. Chem. Soc.*, **60**, 395 (1938).
(33) H. Ohle and H. Thiel, *Ber.*, **66**, 525 (1933).
(34) F. D. Cramer, *Methods Carbohyd. Chem.*, **2**, 244 (1963).
(35) S. R. Thorpe and C. C. Sweeley, *Biochemistry*, **6**, 887 (1967).
(36) The cyclitol derivatives described here are named and numbered according to the IUPAC-IUB Tentative Cyclitol Nomenclature Rules, *J. Biol. Chem.*, **243**, 5809 (1968). It will be noted that in some cases the methy-

lated position of pinitol is assigned the number 3, and the sulfonylated position the number 4, while in other cases the opposite is true. Similar numbering shifts occur with the *allo*-inositol derivatives, accompanied by a change in the designation of configurational series (D or L). These unfortunate variations result from the necessity of choosing between the two equivalent numberings inherent in the stereochemistry of each of the parent inositols. The choice is made by the principle of "lowest number to the substituent first in alphabetical order," which seems the least undesirable of the alternatives available for dealing with this situation. Confusion is best avoided by constant reference to formulas **2** and **5**.

(37) S. J. Angyal and T. S. Stewart, *Aust. J. Chem.*, **20**, 2117 (1967).
(38) J. W. Arnold, *Ind. Eng. Chem., Anal. Ed.*, **17**, 215 (1945). We did not find it necessary to remove the bulk of the precipitated silver azide by filtration before completing the titration.
(39) F. Loewus and R. H. Shah, *Methods Carbohyd. Chem.*, **6**, 14 (1972).
(40) H. H. Hodgson and W. H. H. Norris, *J. Chem. Soc.*, 762 (1949).
(41) M. T. Reagan and A. Nickon, *J. Amer. Chem. Soc.*, **90**, 4096 (1968).

Kinetics and Mechanism of Alkyl Ether Oxidation by Peroxydisulfate Ion

Ruggero Curci,[1a] George Delano,[1b] Fulvio DiFuria,[1a] John O. Edwards,[1a] and Andrew R. Gallopo*[1b]

Departments of Chemistry, Brown University, Providence, Rhode Island 02912, and Montclair State College, Upper Montclair, New Jersey 07043

Received June 20, 1974

The oxidation of three ethers (*p*-dioxane, tetrahydrofuran, and diethyl ether) by peroxydisulfate ion in aqueous solution has been investigated. The rate law is $-d[S_2O_8^{2-}]/dt = k_{obsd}[S_2O_8^{2-}]^{3/2}$ with the value of k_{obsd} depending on the nature of the ether. The rate law, rate constants, influences of oxygen gas and cupric ion, and activation energies indicate a radical chain mechanism closely similar to that known for the oxidation of primary alcohols by peroxydisulfate. Chain lengths have been evaluated, and the influences of aldehydes on rates were investigated. Some of the products of ether oxidation (vinyl ethers and their oligomers) are different from those found in alcohol oxidation. Similarities in and differences between the reactions for the two classes of organic oxygen compounds are discussed.

The general features of the peroxydisulfate oxidation of primary and secondary alcohols have been elucidated in the work of this group[2,3] and in other laboratories.[4] Evidence was reported for a free-radical chain mechanism which involves as initiation step the unimolecular homolytic dissociation of $S_2O_8^{2-}$

$$S_2O_8^{2-} \xrightarrow[\Delta]{k_1} 2SO_4\cdot^- \qquad (1)$$

and the following as propagation steps

$$SO_4\cdot^- + H-\underset{\displaystyle R}{\overset{\displaystyle R'}{\overset{|}{\underset{|}{C}}}}-OH \xrightarrow{k_2} HSO_4^- + \cdot\underset{\displaystyle R}{\overset{\displaystyle R'}{\overset{|}{\underset{|}{C}}}}-OH \qquad (2)$$

$$\cdot\underset{\displaystyle R}{\overset{\displaystyle R'}{\overset{|}{\underset{|}{C}}}}-OH + S_2O_8^{2-} \xrightarrow{k_3} \underset{\displaystyle R}{\overset{\displaystyle R'}{\diagdown\!\!\diagup}}C=O + HSO_4^- + SO_4\cdot^- \qquad (3)$$

where R′ = R′ = H; R = H and R′ = CH_3; and R = R′ = CH_3. Nevertheless, the exact nature of the third step of the chain was not understood because two reasonable transition state configurations can be visualized. Both of these two pathways seem consistent with the formation of the observed products. One pathway involves the formation of an hemiacetal-like intermediate by carbon attack on peroxide oxygen

$$S_2O_8^{2-} + \cdot\underset{\displaystyle R}{\overset{\displaystyle R'}{\overset{|}{\underset{|}{C}}}}-OH \longrightarrow {}^-OS(=O)_2-O-\underset{\displaystyle R}{\overset{\displaystyle R'}{\overset{|}{\underset{|}{C}}}}-OH + SO_4\cdot^- \qquad (3a)$$

and its subsequent breakdown.

$$\begin{matrix}O\\ \|\\ {}^-OS-O-\underset{\displaystyle R}{\overset{\displaystyle R'}{\overset{|}{\underset{|}{C}}}}-OH\\ \|\\ O\end{matrix} \xrightarrow[H_2O]{k_4} HSO_4^- + \underset{\displaystyle R}{\overset{\displaystyle R'}{\diagdown\!\!\diagup}}C=O \qquad (4)$$

The other mechanism involves the direct breaking of the oxygen–hydrogen bond (*i.e.*, hydrogen atom transfer) during attack on peroxide oxygen.

$$S_2O_8^{2-} + H-O-\underset{\displaystyle R}{\overset{\displaystyle R'}{\overset{|}{\underset{|}{C}}}}\cdot \xrightarrow{k_{3b}} SO_4\cdot^- + HSO_4^- + \underset{\displaystyle R}{\overset{\displaystyle R'}{\diagdown\!\!\diagup}}C=O \qquad (3b)$$

The termination step for ethanol involves two organic radicals (reacting by either disproportionation or dimerization).

$$2CH_3\dot{C}HOH \longrightarrow \text{products} \qquad (5)$$

It was deemed worthwhile to carry out a kinetic study of the peroxydisulfate oxidations of ethers. Assuming that the alcohol and ether oxidations proceed by analogous mechanisms, in the case of the ethers the latter pathway (eq 3b) proposed for the third step is clearly impossible. A comparison of the relative rates for alcohols and ethers could then lead to better understanding of the behavior of the reaction of the α-oxyalkyl radical and the peroxydisulfate anion.

Moreover, in the general field of peroxide oxidation of the ethers, very interesting characteristics have been found.[5] A free-radical chain mechanism for the ether-induced decomposition of benzoyl peroxide has been demonstrated. The propagation steps are believed to be the formation of an α-oxyalkyl radical from the ether and the reaction of this radical with the peroxide.

The production of dioxanyl radicals by reaction of the sulfate radical ion $SO_4\cdot^-$ (from peroxydisulfate ion) with dioxane and the subsequent dioxanylation of some heteroaromatic bases have been recently reported by Minisci and coworkers,[6] and a kinetic study of the peroxydisulfate oxidation in the presence of silver ion has been carried out by Mishra and Ghosh.[7]

On the other hand, the kinetic behavior of the reaction of ethers and peroxydisulfate alone has never been studied extensively. This investigation was undertaken in order to elucidate the general features of the reaction mechanism as well as to compare the results with those obtained for the peroxydisulfate oxidation of alcohols.