protonation reaction the exothermicity of the reaction is retained by the MH^+ product but also it indicates that the fragmentation of MH^+ in these cases cannot have an activation energy significantly greater than the reaction endothermicity. This suggests that the effect of the bond dipole is to influence the site of protonation rather than the activation energy for fragmentation.

The charge distributions in Table V for the haloanilines show that $\mu(C\text{-}N) \simeq (C\text{-}F) > (C\text{-}Cl)$. This suggests that, if ion-bond dipole interactions influence the site of protonation, there should be significant protonation at the amino group. The MH^+ ion, which is the base peak in all spectra, probably represents those cases where protonation occurs at the amino substituent or on the aromatic ring. We suggest only that the magnitude of the carbon-halogen bond dipole determines the fraction of the protonation events which occur at halogen, one of the many possible protonation sites.

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Tosylate Oxygen Scrambling Associated with Ion-Pair Return in the *threo*-3-*p*-Anisyl-2-butyl System

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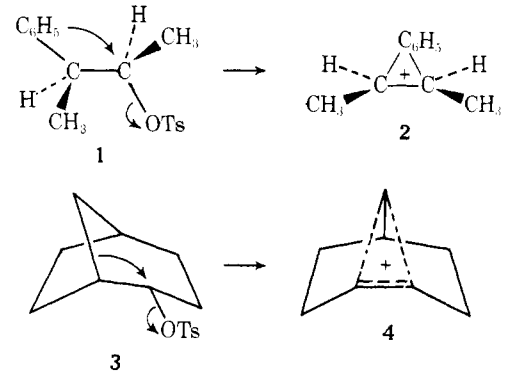
Abstract: Ion-pair return involved in acetolysis of *threo*-3-*p*-anisyl-2-butyl *p*-toluenesulfonate (**6**-OTs) results in racemization of optically active **6**-OTs (k_{rac}) and equilibration of the sulfonate oxygen atoms of ^{18}O-labeled **6**-OTs (k_{eq}). In this system external ion-pair return is involved. Presumably most, if not all, external ion-pair return is eliminated by 0.03 M $LiClO_4$. The oxygen equilibration to racemization (total measurable return) ratio for internal return, $(k_{eq}/k_{rac})_{in}$, is ~0.5 and the ratio for external ion-pair return, $(k_{eq}/k_{rac})_{ex}$, is ~1. Acetolysis of **6**-OTs is accompanied by some exchange with added ^{14}C-labeled *p*-toluenesulfonic acid. Exchange is lowered, but not eliminated, by 0.03 M $LiClO_4$ and does not result in loss of diastereomeric configuration, which rules out an S_N2-type exchange process. The residual exchange in the presence of $LiClO_4$ presumably results from external ion-pair return induced by the accumulating *p*-toluenesulfonic acid produced by acetolysis.

In an earlier investigation[1] we determined the amount of sulfonate oxygen scrambling (eq 4) associated with ion-pair return involved in acetolysis of ^{18}O-labeled *threo*-3-phenyl-2-butyl (**1**) and *endo*-bicyclo[3.2.1]octan-2-yl *p*-toluenesulfonate (**3**). These systems were selected because the type of ion-pair return had been characterized previously[2-4] as internal return, and the rate of total ion-pair return can be determined independently. Both **1**[5,6] and **3**[3] give symmetrical cations (**2** and **4**)—initially formed products are racemic. Thus, with optically active substrates the rate of loss of optical activity (eq 1) corresponds to total ionization and the rate of re-formation of racemic substrate (eq 3) corresponds to total ion-pair return (in these cases internal return) providing that the intimate ion pair, as well as the unperturbed cation, is symmetrical. The rate of racemization of the unsolvolyzed ester (eq 3) can be determined indirectly from the difference between rates of ionization (k_α) and solvolysis (k_t, eq 2), i.e., $k_{rac} = k_\alpha - k_t$.[1,3]



The first-order constants for oxygen equilibration (k_{eq}) of ^{18}O-labeled **1** and **3** are about $\frac{1}{2}k_{rac}$. This means that in each case the sulfonate oxygen atoms are not equilvalent in the

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Table I. Polarimetric (k_α), Titrimetric (k_t), Racemization (k_{rac}), and Sulfonate Oxygen Equilibration (k_{eq}) Rate Constants for Acetolysis of *threo*-3-*p*-Anisyl-2-butyl *p*-Toluenesulfonate (**6**-OTs)[a] at 25.00 °C

$[LiClO_4]$, 10^2 M	k_α,[b] 10^6 s^{-1}	k_t,[c,d] 10^6 s^{-1}	k_{rac},[e] 10^6 s^{-1}	k_{eq}, 10^6 s^{-1}
none	25.5 ± 0.4[f]	5.52 ± 0.08[g]	20.0 ± 0.4	17.2 ± 0.6[h]
1.10		18.5. ± 0.3		
1.83	32.7 ± 0.3[i]			
3.00	39.3 ± 0.4	29.5[j]	9.8 ± 0.7	5.4 ± 0.4[k]
3.67		32.7 ± 0.2		
4.58	44.8 ± 0.3[l]	37.2 ± 0.3	7.6 ± 0.6	
7.33		50.3 ± 0.6		
9.16	70.4 ± 0.6			
18.33	123. ± 1.5			

[a] $[6\text{-OTs}]_0$ = 0.03–0.05 M. [b] Unless indicated otherwise, uncertainty is average deviation for 10–12 integrated constants for 19–75% reaction. [c] Unless indicated otherwise, uncertainty is average deviation for 6–7 integrated constants for 20–70% reaction. [d] $k^0_{ext} = 15.8 \times 10^{-6}$ s^{-1} from extrapolation of the linear portion of a plot of k_t vs. $[LiClO_4]$. [e] Determined from $k_{rac} = k_\alpha - k_t$; uncertainties estimated from limiting values of k_α and k_t. [f] Average of five independent kinetic experiments each consisting of 10–12 integrated rate constants. [g] Average of four independent kinetic experiments each consisting of 6–7 integrated rate constants. [h] Average and average deviation for four independent experiments each consisting of a one-point determination at 45–77% equilibration. [i] Average of two independent kinetic experiments. [j] Value obtained by extrapolation of linear plot of three constants below vs. $[LiClO_4]$. [k] Average for four independent experiments each consisting of a one-point determination at 10–12% equilibration. [l] Average of two independent kinetic experiments.

symmetrical intimate ion-pair intermediate and k_{eq} corresponds to about one-half of the total measurable return. Both racemization (eq 3) and oxygen equilibration (eq 4) result from ion-pair return according to all criteria that were applied including intramolecularity (no exchange), kinetics (reactions 1–4 first order), and solvent effects.[1]

$$(+)\text{-ROTs} \xrightarrow{k_\alpha} \text{inactive products} \quad (1)$$

$$\text{ROTs} \xrightarrow{k_t} \text{solvolysis products} \quad (2)$$

$$(+)\text{-ROTs} \xrightarrow{k_{rac}} (\pm)\text{-ROTs} \quad (3)$$

$$\text{R-}^{18}\text{OSO}_2\text{Ar} \xrightarrow{k_{eq}} \text{R-}^{18}\text{OS}^{18}\text{O}_2\text{Ar} \quad (4)$$

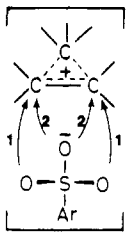
Evidently only internal return from an intimate ion-pair intermediate is involved with **1**[2] and **3**[3] because there is no special lithium perchlorate salt effect.[1-4] Thus the Winstein ion-pair scheme[4,7] reduces to eq 5. The measurable rate constants (eq 1–3) are related to those in eq 5 as shown by eq 6 and 7.

$$\text{ROTs} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [\text{R}^+\text{OTs}^-] \xrightarrow{k_2} \text{products} \quad (5)$$

$$k_\alpha = k_1 \quad (6)$$

$$k_{rac}/k_t = k_{-1}/k_2 \quad (7)$$

Acetolysis of ^{18}O-labeled optically pure **1** was investigated[1b] to distinguish between different possible orientations of the ions in the intimate ion-pair intermediate. With this doubly labeled substrate it was established that oxygen equilibration occurs to the same extent in both enantiomers of re-formed substrate. Or, to put it another way, the amount of mixing is the same for return to the original carbon atom (no rearrangement) as for return with rearrangement. The behavior of the intimate ion-pair intermediate in this system is illustrated by **5**, which



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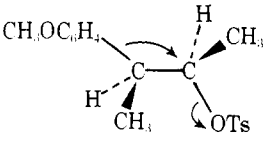
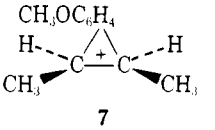
shows the relative rates of formation of the various carbon–oxygen bonds so as to give the observed k_{eq}/k_{rac} ratio of 0.5. Only a symmetrical arrangement is considered because k_{rac} measures return from a symmetrical intermediate—return from an unsymmetrical intermediate does not result in either racemization or oxygen equilibration.[8]

We have now extended our studies to a system that involves external ion-pair return. In this work we have investigated sulfonate oxygen scrambling (eq 4) associated with acetolysis of *threo*-3-*p*-anisyl-2-butyl *p*-toluenesulfonate (**6**-OTs). For this system, which has been studied in detail,[4,7,9] the Winstein ion pair scheme is shown by eq 8. In this connection it is noteworthy that (a) **6**-OTs shows a special salt effect whereas **1** does not,[7] (b) external ion return is not involved,[4a,9a] (c) acetolysis of **6** gives almost exclusively (99.7%) S_N1 product,[9b] and (d) the S_N1 product (>99.7% threo acetate) is formed with complete retention of diastereomeric configuration.[9b] These observations show that the main, if not only, product-forming intermediate is the solvent-separated ion-pair intermediate as shown in eq 8.

$$\text{ROTs} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} [\text{R}^+\text{OTs}^-] \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} [\text{R}^+||\text{OTs}^-] \xrightarrow{k_3} \text{product} \quad (8)$$



6-OTs



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The symmetry properties of substrate and cation are the same for **6**-OTs as for **1** and thus the first-order racemization of unsolvolyzed substrate (eq 3) provides an independent measure of total ion-pair return. Presumably external ion-pair return is eliminated by $LiClO_4$ and the Winstein ion-pair scheme reduces to eq 5. From measurable rate constants, total return can be dissected into the internal return and external ion-pair return components. Thus k_{eq}/k_{rac} can be determined for both internal return and total return. The k_{eq}/k_{rac} ratio for external ion-pair return can be determined indirectly from these ratios and the composition of total return.

Results and Discussion

The pertinent first-order rate constants for acetolysis of **6**-OTs at 25 °C are given in Table I. The titrimetric rate constants (k_t) were determined in the usual way[1-3] and good first-order behavior was observed in all cases. Reactions were

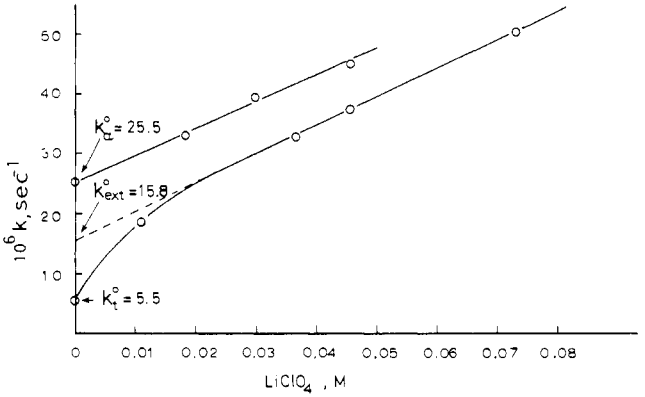

Figure 1. Special salt effect for acetolysis of *threo*-3-*p*-anisyl-2-butyl *p*-toluenesulfonate (**6**-OTs) at 25 °C.

followed to ~75% completion and infinity titers were in good agreement with calculated values.

For the polarimetric rates, reactions were carried out in an all-glass jacketed polarimeter tube and k_α was determined from the rate of loss of optical activity. These reactions were followed to ~75% completion and in all cases loss of optical activity was complete and good first-order behavior was observed.

Rate constants for equilibration of the sulfonate oxygen atoms (k_{eq}) were determined with discretely labeled sulfonyl-^{18}O **6**-OTs by the method developed earlier.[1] Unsolvolyzed ester was isolated at appropriate times and k_{eq} determined from the ^{18}O distribution. A modified Schutz-Unterzaucher method[1,10] was used to determine ^{18}O contents. The total ^{18}O content of the unsolvolyzed ester remained constant during the reaction. To determine the ^{18}O distribution the isolated ester was cleaved at the S-O linkage by reduction with sodium naphthalene,[11] the resulting **6**-OH reconverted to **6**-OTs, and the ^{18}O content of the latter determined. The latter value gives the ^{18}O abundance of the ether oxygen atom at the time of isolation of the unsolvolyzed ester. Pure samples of **6**-OTs were used for all ^{18}O measurements. In other work[12] we have found that apparent ^{18}O contents of alcohol derivatives are not always the same as for the alcohol from which they are derived. However, for each derivative, apparent ^{18}O contents are reproducible. Control experiments demonstrated that methods used to prepare ^{18}O-labeled **6**-OTs, isolate the unsolvolyzed ester, and determine the distribution of the label do not result in scrambling or loss of ^{18}O.

Oxygen equilibration (eq 4) could only be followed for a period corresponding to ~50% acetolysis because required amounts of pure samples of unsolvolyzed **6**-OTs could not be separated from the accumulating solvolysis products (**6**-OAc) beyond this point. The data in Table I show that, in the absence of $LiClO_4$, the return to solvolysis ratio is favorable (k_{rac}/k_t = 3.6) and equilibration can be followed to >75% completion—under these conditions 50% solvolysis corresponds to 92% racemization and 88% oxygen equilibration. In this case the kinetic order can be determined and good first-order behavior was observed.

In the presence of 0.03 M $LiClO_4$ the return to solvolysis ratio is decreased considerably because of the special salt effect (k_{rac}/k_t = 0.33) and the k_{eq}/k_{rac} also decreases. In this case 50% solvolysis corresponds to 21% racemization and 12% oxygen equilibration. Thus, under these conditions oxygen equilibration was only followed to 12% completion. The value of k_{eq} in Table I is the average of four independent experiments with all points taken at 10–12% completion.

Plots of k_α and k_t vs. [$LiClO_4$] are shown in Figure 1. These data are similar in all details to those reported by Winstein and Robinson[7a] except that all rate constants, including k^0_{ext}, are about 5% lower than the earlier values. In this work several independent experiments (8 for k_t and 12 for k_α) showed that both constants are reproducible to within 2% and insensitive to variation of substrate concentration over the range 0.03–0.06 M. From this we conclude that the discrepancy with the earlier work results from a temperature difference (~0.3 °C required) or solvent effect. It should also be noted that in the present work the same constant-temperature bath was used for all comparisons.

Dissection of ion-pair return with k^0_α and k^0_t in Table I[13] and k^0_{ext} from Figure 1 gives the same results as the earlier data[7a] with regard to (a) fraction of all ion-pair intermediates that return, $k_{-1}/(k_{-1} + k_3) = 0.78$, (b) fraction of [$R^+OTs^-$] that returns, $k_{-1}/(k_{-1} + k_2) = 0.38$, and (c) fraction of [$R^+||OTs^-$] that returns $k_{-2}/(k_{-2} + k_3) = 0.83$.

As illustrated by Figure 1, the k_t vs. [$LiClO_4$] plot shows a "special salt effect"[7] and becomes linear at about 0.03 M $LiClO_4$ at which point presumably external ion-pair return has been eliminated, leaving only internal return. Extrapolation of the linear portion of the k_t plot to zero salt concentration gives k^0_{ext}, the rate constant for formation of the solvent-separated ion-pair intermediate.[7] Or, to put it another way, this is what k^0_t would be if there were no external ion-pair return.

The total return that occurs in the absence of $LiClO_4$ can be separated into its two components with the rate constants shown in Figure 1. The fraction of total return (measured by $k^0_\alpha - k^0_t$) that is internal return (F_{in}) is given by eq 9 and the fraction that is external ion-pair return (F_{ex}) is given by eq 10. The present data give values of F_{in} = 0.48 and F_{ex} = 0.52. Thus, as observed earlier,[7] in this system, return involves about equal amounts of internal and external ion-pair return.

$$F_{in} = (k^0_\alpha - k^0_{ext})/(k^0_\alpha - k^0_t) \quad (9)$$

$$F_{ex} = (k^0_{ext} - k^0_t)/(k^0_\alpha - k^0_t) \quad (10)$$

The mechanism of the special salt effect involves an exchange reaction of the solvent-separated ion-pair intermediate.[7b] From this, exchange between unsolvolyzed ester and the HOTs produced by acetolysis would be expected. Or, to put it another way, ion-pair return is partly intermolecular and this part leads to complete oxygen equilibration. To determine the importance of the intermolecular component to total return, exchange between **6**-OTs and ^{14}C-labeled HOTs was investigated. In these experiments second-order rate constants for exchange between **6**-OTs and ^{14}C-labeled HOTs (k_{exc}, eq 11) were determined for acetolysis without $LiClO_4$ and with 0.03 M $LiClO_4$ (i.e., the conditions of the oxygen equilibration experiments except for the added acid). Samples of unsolvolyzed ester were isolated at appropriate times and the amount of radioactivity incorporated was determined by liquid scintillation counting.

$$\textbf{6}\text{-OTs} + \text{HOTs}^* \underset{k_{exc}}{\overset{k_{exc}}{\rightleftharpoons}} \textbf{6}\text{-OTs}^* + \text{HOTs} \quad (11)$$

Second-order exchange constants were calculated using an equation that is rigorous for a system of this type, i.e., exchange between two species with simultaneous conversion of one to the other by a first-order process.[10a] For acetolysis of **6**-OTs at 25 °C in the absence of $LiClO_4$, $k_{exc} = 31.0 \times 10^{-5}$ L M^{-1} s^{-1}, and in the presence of 0.03 M $LiClO_4$, $k_{exc} = 7.1 \times 10^{-5}$ L M^{-1} s^{-1}. With these constants the amount of exchange between remaining **6**-OTs and HOTs produced by acetolysis can be calculated for any stage of the reaction. Under these conditions the only HOTs present is that formed by solvolysis and the average HOTs concentration, $[HOTs]_{av}$, is a known function of time. As shown earlier,[10a] $k_{exc}[HOTs]_{av}$ is a pseudo-first-order constant that applies for the same period as $[HOTs]_{av}$.

The relative amounts of solvolysis, racemization, oxygen equilibration, and exchange at the time of isolation of ester in

Table II. Comparison of Amounts of Solvolysis, Racemization, Oxygen Equilibration, and Exchange for Acetolysis of **6**-OTs at 25 °C under Conditions for Key Oxygen Equilibration Experiments

$[LiClO_4]$, 10^2 M	time, 10^{-4} s	sol[a,b] %	rac[a,c] %	eq[a,d] %	exc[a,e] %
none	4.86	24	62	57	8.5
3.0	2.16	47	19	11	2.2

[a] Percent reaction calculated from appropriate rate constants, i.e., % reaction = $100(1 - e^{-kt})$. [b] Determined from k_t. [c] Determined from k_{rac}. [d] Determined from k_{eq}. [e] Determined from k_{exc}·$[HOTs]_{av}$.

key equilibration experiments are shown in Table II. These values were calculated from k_{eq}, k_{rac}, and k_t in Table I and $k_{exc}[HOTs]_{av}$. From these data it is apparent that racemization and oxygen equilibration are primarily intramolecular.

Rate constants for racemization (k_{rac}) and sulfonate oxygen equilibration (k_{eq}) can be corrected for the intermolecular contribution by subtraction of the pseudo-first-order constants for exchange using $[HOTs]_{av}$ for the time of isolation of unsolvolyzed ester for the oxygen equilibration experiments. These corrected values are shown in Table III.

The data in Table II show that exchange is decreased, but not completely eliminated, by 0.03 M $LiClO_4$. Evidently, under these conditions the accumulating HOTs restores a small amount of external ion-pair return. However, the amount of this return (2.2% during 47% solvolysis) is not sufficient to cause a detectable induced common ion rate depression.[7b] It is significant that, although added common ion salts do not cause a rate depression in the absence of $LiClO_4$[9a] (i.e., there is no external ion return), induced common ion rate depressions have been observed.[7b] Exchange resulting from induced external ion-pair return is presumably suppressed by higher concentrations of $LiClO_4$. However, 0.03 M $LiClO_4$ is the highest concentration that could be used because the unsolvolyzed ester could only be examined up to about 50% solvolysis and, as can be seen from Figure 1, the return to solvolysis ratio, $(k_\alpha - k_t)/k_t$, decreases rapidly with $LiClO_4$ concentration because of the normal positive salt effects.

According to this interpretation for the residual exchange in the presence of $LiClO_4$, exchange would not be expected in systems that do not show a special salt effect such as *threo*-3-phenyl-2-butyl *p*-toluenesulfonate (**1**). In such cases induced common ion rate depressions are not observed.[7b] In this work we have reexamined this system and find that the second-order exchange constant (k_{exc}, eq 11) for acetolysis of **1** in the presence of 0.015 M ^{14}C-labeled NaOTs and 0.116 M NaOAc at 74.8 °C is $2.4 \pm 0.5 \times 10^{-5}$ L M^{-1} s^{-1}. Thus the exchange constant for **1** is about 17 times smaller at 75 °C than for **6**-OTs at 25 °C. In this case, during acetolysis exchange with the accumulating HOTs is negligible. For example, there is only ~0.1% exchange at a point corresponding to 31% sulfonate oxygen equilibration and 50% racemization.

The observation that acetolysis of **6**-OTs is stereospecific (the **6**-OAc contains <0.1% of the erythro isomer)[9b] shows that exchange evidently occurs with preservation of diastereomeric configuration. We have confirmed this by examination of the unsolvolyzed ester at the time of isolation of the samples for the experiments in Table II. The ester was converted to the corresponding alcohol by reduction with sodium naphthalene[11] and the configuration of the alcohol was determined by capillary GC. Control experiments with synthetic mixtures showed that this method gives correct values for the configurational composition of the unsolvolyzed ester. At the time of isolation (8.5% exchange in one case and 2.2% in the other) the remaining **6**-OTs contained <0.3% erythro isomer. These experiments show that S_N2-type exchange processes are not important and support the view that exchange results from an exchange reaction of the solvent-separated ion-pair intermediate.

Table III. First-Order Rate Constants for Intramolecular Racemization (k^{cor}_{rac}) and Sulfonate Oxygen Equilibration (k^{cor}_{eq}) for Acetolysis of **6**-OTs at 25 °C, [**6**-OTs] = 0.04–0.6 M

$[LiClO_4]$, 10^2 M	k^{cor}_{rac}[a,b] 10^6 s^{-1}	k^{cor}_{eq}[b,c] 10^6 s^{-1}	$k^{cor}_{eq}/k^{cor}_{rac}$[b]
none[d]	18.2 ± 0.5	15.4 ± 0.6	0.85 ± 0.06
3.0[e]	8.8 ± 0.7	4.3 ± 0.4	0.49 ± 0.09

[a] Rate constant corrected for intermolecular component (exchange) as follows: $k^{cor}_{rac} = k_{rac} - k_{exc}[HOTs]_{av}$. [b] Uncertainties determined from limiting values of both constants. [c] Rate constants determined from $k^{cor}_{eq} = k_{eq} - k_{exc}[HOTs]_{av}$. [d] Reaction time, 4.86×10^4 s; $[ROTs]_0 = 0.048$ M; $[HOTs]_{av} = 0.0059$ M. [e] Reaction time, 2.16×10^4 s; $[ROTs]_0 = 0.056$ M; $[HOTs]_{av} = 0.0145$ M.

The sulfonate oxygen equilibration to ion-pair return ratios for total return $(k_{eq}/k_{rac})_{total}$ and internal return $(k_{eq}/k_{rac})_{int}$ are obtained directly from the appropriate rate constants for acetolysis in the absence and presence of 0.03 M $LiClO_4$. The ratios in Table III, 0.85 ± 0.06 and 0.49 ± 0.09, result from constants corrected for intermolecular contributions to racemization and oxygen equilibration. Ratios derived from the uncorrected rate constants in Table I are well within experimental error of the ratios in Table III. For example, the constants in Table I give ratios of 0.86 ± 0.05 and 0.55 ± 0.09 for total and internal return. Thus, intermolecular contributions to k_{eq} and k_{rac} do not have a significant effect on the k_{eq}/k_{rac} ratios.

The equilibration to return ratio for external ion-pair return, $(k_{eq}/k_{rac})_{ex}$, can be determined indirectly from the ratios for total return and internal return with eq 12. In this equation F_{in} and F_{ex} are the fractions of internal and external ion-pair return determined with eq 9 and 10. The $(k_{eq}/k_{rac})_{ex}$ ratio is 1.1 ± 0.2 and again there is no significant difference in the values obtained with uncorrected constants (Table I) and those corrected for intermolecular contributions (Table III).

$$(k_{eq}/k_{rac})_{total} = (k_{eq}/k_{rac})_{in} F_{in} + (k_{eq}/k_{rac})_{ex} F_{ex} \quad (12)$$

The $(k_{eq}/k_{rac})_{ex}$ ratio of ~1 shows that external ion-pair return results in complete randomization of the sulfonate oxygen atoms. This is consistent with other known properties of solvent-separated ion-pair intermediates that indicate weak attractive forces between counterions, viz., facile anion exchange reactions.[4a,7c]

The $(k_{eq}/k_{rac})_{in}$ ratio of ~0.5 is similar to that observed for internal return involved in acetolysis of **1** and **3**. This ratio shows that the sulfonate oxygen atoms are not equivalent in the symmetrical intimate ion-pair intermediate that returns to racemic substrate.

Various orientations of the ions in the intimate ion-pair that would result in excess rebonding to the original oxygen atom and lead to $k_{eq}/k_{rac} < 1$ were discussed in an earlier paper.[1b] As mentioned above, it has been shown that, for acetolysis of **1**, oxygen equilibration occurs to the same extent (~50%) for re-formation of either entantiomer. This was determined by acetolysis of optically pure ^{18}O-labeled **1**, isolation of the unsolvolyzed ester after substantial racemization, and determination of the ^{18}O distribution in each enantiomer.[1b] This method requires resolution of the isolated unsolvolyzed **1**. We were unable to apply this method in the present study because of the unfavorable return to solvolysis ratio (k_{rac}/k_t) for **6**-OTs under conditions where internal return is isolated from external ion-pair return. For example, the k_{rac}/k_t ratio for acetolysis of **1** is ~2.5 as compared to 0.33 for acetolysis of **6**-OTs in the presence of 0.03 M $LiClO_4$. Thus in the latter case most of the **6**-OTs is consumed by solvolysis before racemization or oxygen equilibration proceed very far. For example, 50% equilibration

corresponds to 98% solvolysis.

We presume that the remote methoxyl substituent in **6**-OTs does not change the nature of oxygen equilibration associated with internal return and that the behavior of the intimate ion-pair intermediate is the same as for acetolysis of **1** which is illustrated by **5**. As discussed previously,[1] it is not clear if there is a single intimate ion-pair intermediate or if **5** is a composite of two or more species which differ with regard to orientation and k_{eq}/k_{rac} ratios. In any case, the overall k_{eq}/k_{rac} ratio for the intermediate, or intermediates, not trappable with $LiClO_4$ is ~0.5.

The reason for preferential rebonding with the original oxygen atom is not clear. This memory effect could result from the three sulfonate oxygen atoms being solvated differently. For example, the two sulfoxyl oxygen atoms may be solvated and thus more encumbered than the oxygen atom involved in bond cleavage. It should also be noted that in the anion the three sulfonate oxygen atoms are not equivalent if there is a rotation barrier for the phenyl-sulfur bond. In this case the memory effect could be a consequence of the original oxygen atom being predisposed for rebonding relative to the other oxygen atoms for conformation or steric factors.

Experimental Section

Materials. ***threo*-3-*p*-Anisyl-2-butyl *p*-toluenesulfonate (6-OTs),** mp 49–50 °C (lit. mp 49–50 °C),[4a] was prepared from isomerically pure *threo*-3-*p*-anisyl-2-butanol (**6**-OH).[14] Optically active **6**-OTs, mp 68–70 °C, $[\alpha]^{30}_D$ 20.3° (*c* 1.1, $CHCl_3$), was obtained from optically active **6**-OH[7a] and ether ^{18}O-labeled **6**-OTs (4.0% ^{18}O) was obtained from ^{18}O-labeled **6**-OH (see below). Sulfonyl ^{18}O-labeled **6**-OTs was prepared from **6**-OH and ^{18}O-labeled *p*-toluenesulfonyl chloride (6.0% ^{18}O).[1] ***erythro*-3-*p*-Anisyl-2-butyl *p*-toluenesulfonate,** mp 51–52 °C, was obtained from the isomerically pure corresponding alcohol.[14] ***threo*-3-Phenyl-2-butyl *p*-toluenesulfonate,** mp 47–48 °C (lit. mp 47–48 °C),[1] was prepared as described earlier.

***threo*-3-*p*-Anisyl-2-butanol-^{18}O** was obtained as follows. 3-*p*-Anisyl-2-butanone was obtained by oxidation[15] of **6**-OH. In a typical preparation, a solution of 200 mL of water, 35.4 g (0.354 mol) of chromium trioxide, and 100 g (0.59 mol) of sulfuric acid was cooled to 2°C. After addition of 1 L of acetone a solution of 50 g (0.28 mol) of **6**-OH in 200 mL of acetone was added over a 10-min period. The temperature was maintained at 8 °C during the addition and the solution was stirred for 1 h at this temperature, after which 10 mL of methanol was added. The acetone solution was decanted from the brown semisolid insoluble material and the solids were washed with ether. The decanted acetone solution was concentrated to remove the acetone and the residue was combined with the ether washings. The ether solution was diluted to 1 L and washed with water, aqueous K_2CO_3, and saturated brine. After drying ($MgSO_4$) the solvent was removed, leaving 46.6 g (0.26 mol) of crude 3-*p*-anisyl-2-butanone (94% yield).

The above ketone was equilibrated with oxygen-18 enriched water as follows. A mixture of 15 g (0.084 mol) of ketone, 11 mL of ^{18}O water (5% ^{18}O), and ~0.1 g of *p*-toluenesulfonic acid in 100 mL of dioxane was stirred for 12 h at room temperature. After addition of 500 mL of hexane, the organic layer was separated, dried ($MgSO_4$), and concentrated. Distillation under reduced pressure gave 14 g (94% recovery) of ^{18}O-labeled 3-*p*-anisyl-2-butanone.

The ^{18}O-labeled ketone was converted to 3-*p*-anisyl-2-butanol in 85% yield by reduction with $LiAlH_4$.[16] Isomerically pure ^{18}O-labeled **6**-OH (4.0% ^{18}O) was obtained from the threo–erythro mixture via the acid phthalate derivative as previously described.[7a]

Anhydrous acetic acid was prepared by refluxing reagent grade acetic acid with sufficient acetic anhydride to consume the trace amounts of water. After distillation, this solvent, which was used for all kinetic experiments, contained ~0.5% acetic anhydride.[17] *p*-Toluenesulfonic acid-^{14}C was obtained from ^{14}C-labeled sodium *p*-toluenesulfonate[18] by mixing the labeled salt with a 20-fold excess of unlabeled HOTs. This mixture was dissolved in water and the resulting solution concentrated to near dryness. The labeled HOTs was purified by recrystallization from $CHCl_3$–ether and the degree of hydration determined from the neutralization equivalent.

Kinetic Experiments. A. Titrimetric Rates. All concentrations correspond to 25 °C. In a typical experiment, 1.31 g (3.92 mM) of **6**-OTs was dissolved in 100 mL of thermostated acetic acid containing 0.0458 M $LiClO_4$. The zero-point titer was determined after an additional 30 min of temperature equilibration at 25 °C. Subsequent samples were withdrawn at appropriate times, delivered into a chilled (0 °C) flask, and titrated to the bromphenol blue end point with sodium acetate (0.0450 M) in acetic acid. Three "infinity" ampules were placed in an 80 °C bath for about ten half-periods. The "infinity" titers were usually within 1–2% of the calculated values (4% maximum difference). The results of these experiments are summarized in Table I.

B. Polarimetric Rates. In a typical experiment, 0.0206 g (0.06 mM) of optically active **6**-OTs was dissolved in 2 mL of acetic acid and transferred by syringe to a jacketed, 1-dm polarimeter tube (ca. 1.1-mL capacity). The polarimeter tube was maintained at 25.00 (±0.02) °C by circulating water from a constant-temperature bath. After the solution was equilibrated for 45 min, polarimeter readings were recorded with a chart recorder (436, Hg line). The total change in rotation was ca. 0.6 °C and the results of these experiments are summarized in Table I.

C. Rates of Sulfonate Oxygen Equilibration. In a typical experiment, 240 mL of anhydrous acetic acid containing 0.03 M $LiClO_4$ was thermostated at 25.00 °C for 45 min. At zero time, 4.5 g (13.46 mM) of sulfonyl ^{18}O-labeled **6**-OTs (5.72% ^{18}O) was added, followed by vigorous shaking for 2 min. After 6 h, the reaction mixture was poured into 200 mL of ice water and the unsolvolyzed ester isolated as follows. The water-acetic acid solution was extracted with four 75-mL volumes of chloroform. The chloroform extracts were washed with potassium carbonate, sodium bicarbonate, water, and saturated brine and dried ($MgSO_4$). Crystallization of the ester from ether–chloroform–hexane gave 2.15 g (90% recovery) of TLC-pure tosylate.

The tosylate was reduced to the alcohol with sodium naphthalene by a method reported earlier.[11] Control experiments showed that reduction and recovery procedures do not result in loss or scrambling of the oxygen-18 label. In a typical reduction, a mixture of 6.2 g (0.048 M) of naphthalene, 1.00 g (0.043 g-atom) of sodium, and 100 mL of dry tetrahydrofuran was stirred at room temperature under oxygen-free, dry nitrogen for 20 h. A solution of 2.15 g (6.4 mM) of the recovered ester in 25 mL of tetrahydrofuran was added by syringe to the sodium naphthalene solution which had been cooled to −78 °C. After the solution was stirred for 8 min, 3 mL of water was added. After the solution was stirred for an additional 5 min, the dry ice bath was removed and 2 mL of water was added. After discharge of color (ca. 5 min), the reaction mixture was diluted with water and extracted with ether. The ether extracts were combined, washed with water, 10% sodium hydroxide, water, and saturated brine, and dried ($MgSO_4$). After filtration and removal of solvent, the crude *threo*-3-*p*-anisyl-2-butanol was reconverted to the tosylate with *p*-toluenesulfonyl chloride. The crude ester was placed on a silica gel column and eluted with 30% ether–hexane. The resulting tosylate was recrystallized twice from chloroform–hexane, yielding 0.170 g of TLC-pure **6**-OTs suitable for oxygen-18 analysis. Control experiments demonstrated that column chromatography does not result in loss of oxygen-18. Thus, the ^{18}O content of the final sample of **6**-OTs corresponds to the ^{18}O abundance of the ether oxygen of the recovered, unsolvolyzed **6**-OTs.

The rate constants for sulfonate oxygen equilibration were calculated from the ^{18}O distribution in the usual manner.[19]

In a control experiment, ether ^{18}O-labeled **6**-OTs was isolated from an acetic acid solution containing equivalent amounts of **6**-OAc and HOTs. This corresponds to the solvolysis solution at 50% reaction. The isolated **6**-OTs was converted to the alcohol, which was reconverted to **6**-OTs as described above. This sample had the same ^{18}O content as the original ester. This shows that preparation of the tosylate and the isolation and reduction procedures do not result in any scrambling or loss of label. The tosylates were analyzed for ^{18}O by a modification of the Schutze–Unterzaucher method.[11b,20]

D. Exchange Experiments. Exchange between 6-OTs and *p*-Toluenesulfonic Acid-^{14}C. In a typical experiment, 25 mL of anhydrous acetic acid containing 0.009 41 M *p*-toluenesulfonic acid-^{14}C (54.2 × 10^{-3} μCi/mmol) was thermostated at 25.00 °C for 45 min. At zero time, 0.4703 g (1.41 mM) of **6**-OTs was added, followed by vigorous shaking for 2 min. After 6.03 h, the solution was poured into 50 mL of ice water and the unsolvolyzed ester isolated as described for the sulfonate oxygen equilibration experiments. Two recrystallizations of the isolated **6**-OTs from chloroform–hexane gave 0.136 g of

TLC-pure product.

The activities (μCi/mmol) of the original labeled acid and of the recovered, unsolvolyzed tosylate were determined by liquid scintillation counting (toluene-2,5-diphenyloxazole for tosylates and toluene-2,5-diphenyloxazole–scintisol for *p*-toluenesulfonic acid).

The second-order exchange constants, k_{exc}, were calculated as described earlier for similar experiments.[10]

E. Exchange between *threo*-3-Phenyl-2-butyl *p*-Toluenesulfonate (1) and Sodium *p*-Toluenesulfonate-*4*-^{14}C. In a typical experiment, 50 mL of anhydrous acetic acid (0.1155 M sodium acetate, 0.0120 M sodium tosylate-^{14}C, 0.114 μCi/mmol) was thermostated at 74.8 °C for 1.5 h. At zero time, 1.55 g (4.64 mM) of **1** was added, followed by vigorous shaking for 2 min. After 1.25 h, the reaction was quenched by cooling and the solution was poured into 100 mL of ice water. After crystallization the tosylate was collected by filtration. The ester was dissolved in ether and washed with water and saturated sodium chloride. After drying ($MgSO_4$), recrystallization from ether–hexane gave 0.71 g of **1**.

The activities (μCi/mmol) of the original labeled salt and of the recovered, unsolvolyzed tosylate were determined by liquid scintillation counting.

Isomerization Studies. In a typical experiment, 25 mL of anhydrous acetic acid was thermostated at 25.00 (±0.02) °C for 1 h. At zero time, 0.5281 g (1.58 mM) of **6**-OTs was added, followed by vigorous shaking for 2 min. After 13.50 h, the solution was poured into 50 mL of ice water and the unsolvolyzed ester was isolated as described for the sulfonate oxygen equilibration experiments. Recrystallization of the isolated ester from chloroform–hexane gave 0.250 g of TLC-pure **6**-OTs.

The ester was reduced to the alcohol with sodium naphthalene as described above and the ether extracts were dried ($MgSO_4$) and used without further purification for the GC determinations of the isomeric compositions of the alcohols. These experiments showed that, under conditions of the experiments in Table II, the unsolvolyzed ester contained <0.3% of the erythro isomer.

In control experiments pure **6**-OTs and synthetic mixtures containing 3.3 and 13.4% erythro isomer were recovered from acetic acid and reduced to the alcohol as described for the isomerization studies. As shown by GC, the alcohols contained zero, 2.9, and 11.9% erythro isomer.

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Intra- and Intermolecular Cyclization of Olefinic Tosylhydrazones under Acidic Conditions. A Facile Synthesis of Bicyclic Azoalkanes

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Abstract: Tosylhydrazones of olefinic ketones and aldehydes have been observed to undergo a variety of unusual cyclizations under acidic conditions. The intramolecular version of this novel cyclization reaction has been applied in the synthesis of previously unaccessible bicyclo[3.2.1]- and bicyclo[2.2.1]azoalkanes. Of these two bicyclic systems, the less strained [3.2.1] system is formed with the greater ease, and in either system the intramolecular cyclization is favored by more nucleophilic olefins (isopropenyl better than vinyl). Those systems that do not undergo efficient azoalkane formation, either due to excessive ring strain or lack of olefin nucleophilicity, undergo novel intermolecular cyclizations instead. The assignments of structure to these products has been based upon 300-MHz NMR data and an X-ray crystal study of the most unusual of these condensation products, **9**. From this structural information an internally consistent mechanistic framework for the formation of these products has been developed. Thus, while these intermolecular condensation reactions produce a structurally diverse set of products, all of these products seem to originate from an initial cyclization between a molecule of tosylhydrazone and its highly nucleophilic enamine tautomer.

Introduction

During our studies of the photochemical conversion of azoalkanes into peroxides,[1] we have found it necessary to seek new methods for the synthesis of bicyclo[*n*.2.1]azo compounds (**1** in Scheme I).[2] One such approach involved the decomposition of olefinic tosylhydrazone salts under basic conditions. For years this method has provided one of the standard routes to diazoalkanes and the carbenes which frequently arise from the decomposition of these diazo intermediates.[3] It was hoped

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