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A Special-Salt Effect upon the Hydride Shift during the Acetolysis of Cyclohexyl Tosylate

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Lambert and Putz[1b] have recently suggested from stereochemical studies that the substitution product formed during the acetolysis of cyclohexyl tosylate arises from nucleophilic attack on an intimate ion pair (IIP). This interpretation is based upon the observation that cyclohexyl acetate was selectively formed with inversion of configuration. To our knowledge, this is the only study of the intermediate(s) leading to substitution on an unsubstituted cyclohexyl system, although Winstein and Holness[2] had previously suggested similar behavior in the solvolysis of *trans*-4-*tert*-butylcyclohexyl tosylate. On the other hand, Elakovich and Traynham[3] concluded from a study of the special salt effect that the cyclohexyl acetate was formed from a solvent separated ion pair (SSIP) during a chlorinolysis in acetic acid. With the exception of the work discussed above, most reports on the cyclohexyl system have been oriented toward the study of the possible conformation of the transition state.[4]

In this paper we report studies involving the special-salt effect and hydride shifts which are directed toward the elucidation of the product determining intermediates in the acetolysis of cyclohexyl tosylate. The results of the acetolysis of 2,2,6,6-tetradeuteriocyclohexyl tosylate at 50 °C are summarized in Table I.

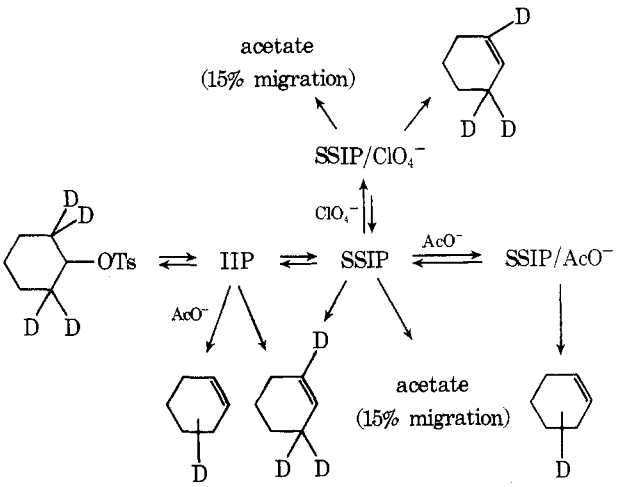
Substitution. The observation that the 0.13 D at position 1 of unreacted tosylate in the absence of $LiClO_4$ is suppressed by the presence of this salt clearly suggests the intermediacy of an external ion pair. Although Winstein[5] did not observe a special salt effect upon the rate of similar reactions, a contradiction does not necessarily exist. The special salt effect upon each of various reaction steps can sometimes be hidden in measurement of the overall rate since not all of the individual rate constants play a rate-determining role. Winstein, himself, recognized this as he admitted the possibility of external return, especially in the light of a very large normal salt effect ($b = 37.2$ at 50 °C). In terms of Winstein's[6] classic scheme

$$RX \underset{k_{-1}}{\overset{k_1}{\rightleftarrows}} \underset{\text{IIP}}{R^+X^-} \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} \underset{\text{SSIP}}{R^+//X^-} \underset{k_{-3}}{\overset{k_3}{\rightleftarrows}} R^+ + X^- \qquad (1)$$

this result indicates that the equilibrium goes at least as far as the SSIP, suggesting the possibility of a reaction involving such a species, even in the absence of $LiClO_4$.

The intermediacy of a SSIP in the substitution reactions seems logical upon consideration of the following results. There is no change in the extent of deuterium scrambling in the acetate buffered reaction upon the inclusion of $LiClO_4$ in the reaction mixture. Observation of two identical patterns of deuterium scrambling for products arising from two different kinds of ion pairs is unlikely.[7] Since addition of $LiClO_4$ presumably increases the SSIP/IIP rates, the observed increase in the substitution/elimination (S/E) ratio upon addition of this salt suggests that the SSIP is more prone to substitution than the IIP.

Scheme I

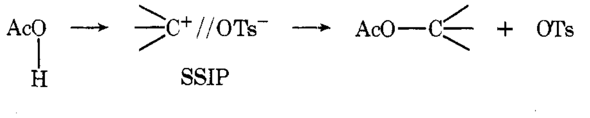


The present suggestion that the SSIP might be an intermediate in the substitution may, at first, seem in contradiction with the stereoselective inversion reported by Putz and Lambert.[1b] Nevertheless, there exists no definitive proof that a SSIP intermediate cannot react with such stereoselectivity, especially if the nucleophile is not the particular solvent molecule thought to separate the ions. In fact, reaction of a SSIP to form an inverted alcohol has been recently proposed by Shiner et al.[8] Such a possibility has also been recently suggested in two recent reformulations of the original Winstein equilibrium.[9,10]

We suggest two possible mechanisms that are consistent with substitution of a SSIP with inversion of configuration:

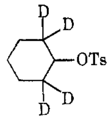
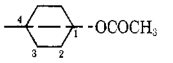
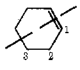
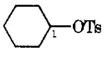
(a) The nucleophile could be an acetic acid that attacks the SSIP from the rear. This idea is in accord with a recent suggestion by Schleyer et al.[9]

(b) Another possibility is the simple collapse of the so-called anion–cation-stabilized intermediate (ACSI) which has recently been proposed by one of us as an alternative model for the SSIP[10] (reaction 3).

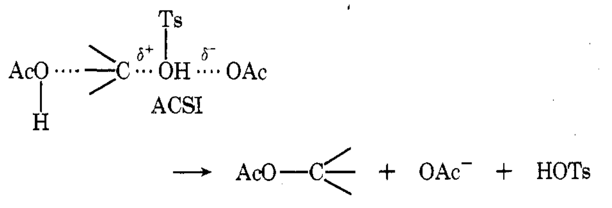


$$\underset{\text{H}}{\text{AcO}} \longrightarrow \underset{\text{SSIP}}{{>}C^+//OTs^-} \longrightarrow AcO{-}C{<} + OTs \qquad (2)$$

Table I. Extent of Migration during Acetolysis

0.03 M  $D_T{}^a$ = 3.95 7 days at 50 °C in 1.4 M anhydrous acetic acid		Number of atoms of deuterium per atom of hydrogen at position 1,2 . . . and total deuterium $D_T{}^a$												
		Cyclohexyl acetate 					Cyclohexene 				Recovered tosylate 		
	S/E^b	1	2	3	4	D_T	1	2	3	D_T	1	D_T	% ROTs recovered
With base 0.053 M CH_3COOK	10/90	0.15	0.86	0.07	0	3.96	0.40	0.38	0.21	3.17	0.13	3.97	10
With base and perchlorate 0.053 M CH_3COOK 0.0053 M ClO_4Li	45/55	0.15	0.86	0.07	0	3.96	0.51	0.49	0.03	3.08	0	3.97	10
Without base	30/70^c	0.26^c				3.75^c	0.50	0.47	0	2.89	0.05^c	3.84^c	60^c

[a] Quantitative isotopic distributions were done by NMR and MS errors are ± 3%. [b] Substitution/elimination ratio is determined chromatographically. [c] These results are not significant since both HOTs and HOAc add to cyclohexene under these conditions.



(3)

Elimination. The elimination reaction at 50 °C (in the presence of KOAc and absence of $LiClO_4$) yields cyclohexene that exhibits a substantially greater amount of hydride shift than for the substitution product. Addition of $LiClO_4$ suppresses these shifts to a great extent. The cyclohexene produced exhibits a deuterium distribution consistent with that observed for the cyclohexyl acetate if we assume that k_H/k_D for the proton transfer from carbocation to base is reasonably small. These results clearly suggest the intermediacy of different species for the eliminations in two cases. Analysis of the three different sets of reaction conditions used can be interpreted in terms of the different kinds of SSIP's which might serve as possible intermediates: (a) $R^+//OTs^-$ in the absence of KOAc and $LiClO_4$; (b) $R^+//OTs^-$ and $R^+//OAc^-$ in the presence of KOAc; (c) $R^+//ClO_4^-$ in the presence of both KOAc and $LiClO_4$.

The extensive migration observed in the presence of KOAc might be related to the relatively strong basicity of the OAc^- anion. This particular point will be developed in a further and more detailed paper.

In conclusion, the most important point to emphasize is that $LiClO_4$ and KOAc can have a significant effect upon the extent of hydride migration and the product distribution of the acetolysis of cyclohexyl tosylate. Furthermore, it seems reasonable that both the substitution and elimination products are formed via the intermediacy of a SSIP.

Experimental Section

The reaction products were analyzed by GLC on a Girdel Model 75 chromatograph using a 3 m × 2 mm column of 20% PEG 20M on 60–80 mesh Chromosorb W NAW.

Cyclohexyl acetate and cyclohexene were purified by preparative GLC on an Aerograph Autoprep 700 using a 3 m × 6 mm column of the same packing.

The isotopic purity of the cyclohexanone was verified by mass spectroscopy on an EAI Model MS 12. Deuterium substitution in the products was measured by integration of the ^1H NMR signals vs. those of an internal standard using a Perkin-Elmer R12B spectrometer. Evaluation of this method using known amounts of a very pure nondeuterated sample indicated an error range of 1–3% depending upon the concentrations.

Cyclohexanone-*2,2,6,6-d*$_4$ (I). This compound was produced according to the method discussed by Hammond and Warkentin.[11] After three exchanges with D_2O and triethylamine a product 98.5% D (94% d_4 and 6% d_3) was obtained.

Cyclohexanol-*2,2,6,6-d*$_4$ (II). A solution of 30 g (0.3 mol) of I in anhydrous ether was added dropwise to a suspension of 15 g (0.04 mol) of $LiAlH_4$ in 300 ml of anhydrous ether. The reaction mixture was refluxed overnight, cooled, and hydrolyzed with 10% HCl, then extracted with ether. The ethereal solution was neutralized with $NaHCO_3$, washed with water, dried with anhydrous Na_2SO_4, and then distilled, yield 21 g (0.21 mol), 70% of II.

Cyclohexyl Tosylate-*2,2,6,6-d*$_4$ (III). Toluenesulfonyl chloride (19 g, 0.1 mol) was added to a stirred solution of 8 g (0.08 mol) of II in 80 ml of anhydrous pyridine maintained in an ice bath. Stirring was continued for 2 h, after which the reaction mixture was let stand for 18 h at room temperature. The mixture was then recooled in an ice bath after which 350 g of ice was slowly added. The precipitate was filtered, washed with cold water, and dried. Recrystallization from petroleum ether gave 16 g (0.06 mol) of III (85% yield, mp 43.5 °C).

Acetolysis.[12] III (8 g, 0.03 mol) was added to 80 ml of anhydrous acetic acid containing 5.2 g (0.053 mol) of anhydrous potassium acetate (acetolysis in the presence of base) and 0.56 g (0.0053 mol) of $LiClO_4$ (acetolysis in the presence of $LiClO_4$). The mixture was stirred for 7 days at 50 °C in a thermostated reactor fitted with a reflux condensor. At the end of the reaction period, the mixture was cooled in an ice–water bath, neutralized to pH 8 with chilled 30% KOH, and then extracted with ether. The collected ether layers were washed with water, dried, then analyzed by GLC to determine S/E. The ether was then distilled taking care to keep the liquid temperature below 45 °C. Cyclohexene and cyclohexyl acetate were separated from the unreacted tosylate by vacuum distillation and trapped with liquid nitrogen. These products were then separated and purified by preparative GLC. The unreacted tosylate was recrystallized from petroleum ether.

^{1}H NMR Analysis of Solvolysis Products. The extent of deuteration was determined using the following internal standard: trichloroethylene (for the acetate); the phenyl protons of the tosyl group (for the tosylate); chloroform (for cyclohexene); bromobenzene (for total deuterium interpretation). The relative amounts of deuteration in the various positions of cyclohexyl acetate were determined by integration of simplified spectra obtained upon the addition of a shift reagent, $Eu(DPM)_3$. Each value in Table I represents an average of two or three experiments, each of which was integrated ten times.

The error in the integration was of the order of 1% of the proton signal in the most favorable cases (those where total proton content was measured) and 2–3% in the less favorable cases (where proton content per position was measured). These errors, when translated into deuterium content, are approximately the following: (a) total D in cyclohexene, ±0.06 D; (b) total D in cyclohexyl tosylate or acetate, ±0.10 D; (c) D per position in cyclohexyl acetate, ±0.02 D; (d) D per position in cyclohexene, ±0.03 D. The small deuterium content in position 3 of cyclohexene formed in the presence of $LiClO_4$ was specifically confirmed by 270-MHz spectra.

Registry No.—I, 1006-03-7; II, 21273-03-0; III, 98-59-9; toluenesulfonyl chloride, 967-93-1; potassium acetate, 127-08-2; $LiClO_4$, 7791-03-9.

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Structure and Reactivity in the Reduction of Cycloalkenes and Cycloalkadienes by Diimide[1]

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The reduction of alkenes by diimide is believed to consist of a single step in which the diimide, formed in situ, transfers a pair of hydrogen atoms to the olefinic center by a synchronous suprafacial process via a transition state of negligible ionic character.[2–5] The relative rates of diimide reductions of nearly 40 cyclic, exocyclic, and acyclic alkenes have been determined by Garbisch, Schildcrout, Patterson, and Sprecher.[6] They concluded that the major factors that contribute to the differences in reactivity are torsional strain, bond angle bending strain, and the α-alkyl substituent effect and, in support, cited the good agreement between the calculated and observed values for the relative rates. Bird, Franzus, and Surridge[7] concluded that the relative rate of reduction of the nonconjugated dienes (nonbornadienes) is a function of the degree of substitution of the double bond attacked. In our previous paper[8] we proposed that Garbisch's general approach (for estimating the contribution of torsional strain and bond angle strain to the relative reactivities of alkenes) can be extended to conjugated dienes by an appropriate estimate of the conjugation energy which diminishes as the geometry of the conjugated system departs from planarity.[8,9]

To provide additional information on the effect of ring size upon the reactivity of cycloalkadienes, we have determined the relative rate constants for the sequential reduction of some conjugated and nonconjugated cycloalkadienes to the derived cycloalkenes and cycloalkanes, and through a series of competitive reactions, the relative rates of reduction of cycloalkenes and cycloalkadienes of different ring size ($C_5 \rightarrow C_{12}$). The reductions were carried out at 25 °C with diimide which was generated from the decomposition of azodicarboxylic acid produced by the slow addition of a methanol solution of acetic acid to potassium azodicarboxylate in methanol.[7,8]

Results and Discussion

The competitive reductions of cycloalkenes by diimide generated from the decarboxylation of azodicarboxylic acid at 25 °C yielded relative rate constants whose values are compared in Table I to those calculated and found experimentally by Garbisch et al.[6] Each constant represents the average obtained from six to ten samples of the reaction mixtures which were removed at arbitrary intervals of time in each experiment. Some cross checks were done to verify the relative rates obtained indirectly. Since our experiments were done at 25 °C, rather than 80 °C, the relative rates were found to be larger than those reported by Garbisch et al.[6] but the general trend in the observed relative reactivities of the alkenes is in good agreement. Cyclopentene, cycloheptene, and *cis*-cyclooctene are considerably more reactive than cyclohexene and, according to Garbisch et al., *cis*-cyclononene and *cis*-cyclododecene are only slightly more reactive.[6] Bicyclo[2.2.1]heptene and *trans*-cyclooctene are by far the most reactive of the alkenes, a fact that is attributed to the unusually large bond angle bending and torsional strains (estimated to be 23.6 and 17.8 kcal/mole, respectively),[10] which are relieved in part upon reaching the transition state. The highly strained *trans*-cyclooctene is 22 000 times more reactive than cyclohexene at 25 °C.

For the 12-member ring, the cis isomer, which possesses a very low strain energy,[6] was found to react 1.4 times as fast as cyclohexene while Garbisch reports a relative rate of 0.6 (calculated 1.5).[6] However, the trans isomer was found to react eight times as fast, a fact attributed again to the relief of torsional strain as well as to the absence of the vicinal methylene–methylene interactions which are present in the cis isomer.

With respect to ring size, the trend found for the cycloalkadienes, however, was opposite to that of the cycloalkenes (Table II). The most reactive compound was 1,3-cyclohexadiene while cyclopentadiene, 1,3-cycloheptadiene, and 1,3-cyclooctadiene were reduced more slowly. Indeed the conjugated 1,3-cyclohexadiene was reported by Siegel, Forman, Fisher, and Johnson[8] to be more reactive than the corresponding nonconjugated diene as well as cyclohexene, when the rates are adjusted for the reactivity per double bond. They suggested that the expected rate-diminishing effect of conjugation in this instance is small because of the nonplanarity of the conjugated system which is due to internal torsional and bond angle strains.[8,9] The lower reactivity of other cyclic dienes relative to 1,3-cyclohexadiene arises because the decreased torsional strains in those dienes not only permits a more effective conjugative interaction in the diene (rate diminishing) but also results in a smaller driving force from the release of torsional strain at the transition state.

Ring size (Table II) influences the relative reactivity toward diimide of nonconjugated dienes in a manner which indicates the importance of the release of torsional strain as a driving force. Thus 1,5-cyclooctadiene, which has been estimated to have a torsional strain energy of 13.3 kcal/mol,[10] was found to react five times as fast as 1,3-cyclooctadiene while the unconjugated 1,4-cyclohexadiene, whose torsional strain appears to be relatively small,[9] has a lower reactivity than the corresponding conjugated diene, 1,3-cyclohexadiene.

The determination of the relative reactivity of a particular cyclic diene and the resulting monoene was obtained directly as before (Table III).[8] While for 1,3- and 1,4-cyclohexadiene, the reactivity (per double bond) of the diene is greater or equal to that of the monoene, the other cycloalkadienes examined are less restrictive per double bond than the corresponding monoene. This fact suggests again that although conjugation is important in tending to lower the reactivity of the alkenyl double bond, torsional strain (as in 1,3-cyclohexadiene) may