Solvolyses of Polycyclic Cyclobutyl Toluenesulfonate Derivatives

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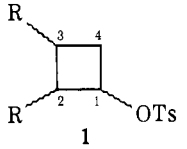
Abstract: A number of isomeric 3-tosyloxytricylo[4.2.1.$0^{2,5}$]non-7-enes and their corresponding saturated analogues have been prepared and solvolyzed. The chemical behavior of these ROTs esters is of particular interest because the influence of the remote double bond on the developing cation can be tested. In the case of the inside esters (i.e., inside, *endo*- and *exo*-**1**-OTs), the highly strained 2,5 bond opens in a disrotatory fashion to generate cyclopropylcarbinyl-type rearrangement products. Consistently, the stereochemistry of the actual cyclopropylcarbinyl products mirrors that of the starting material. In the case of the unsaturated esters inside, *endo*- and *exo*-**1**-OTs, the presence of the remote double bonds results in only an inductive rate retardation relative to the corresponding saturated derivatives. The epimeric outside, *endo*- and *exo*-**1**-OTs and the corresponding saturated derivatives solvolyze very slowly with little evidence of 2,5-bond opening. The outside, *endo*-**2**-OTs is the only case where the remote double bond produces relative rate enhancement. The extensive skeletal reorganization in the solvolysis of the rearranged tosylate **6** again illustrates the importance of orbital alignment in the ground state for participation in the course of a solvolysis reaction.

Introduction

The solvolysis of cyclobutyl toluenesulfonate esters proceeds with anchimeric assistance and ionization is accompanied by a disrotatory ring opening to produce a cyclopropylcarbinyl cation.[1] This ring-opening process appears to proceed with the σ bond opening in a direction opposite to the leaving group in a manner so as to ensure maximum overlap with the developing p orbital. In this respect, the solvolytic behavior of the cyclobutyl compounds parallels that of cyclopropyl derivatives.[2] In the cyclobutyl series (e.g., I), the solvolytic reactions are sensitive to conformation and to the nature of the substituents on the ring at positions 2 and 3. Owing to the specificity of the overall ionization process, the steric interaction of these groups can be very important and large reactivity differences are observed between cyclobutyl esters with cis or trans substituents.[3] As might be expected, the reactivity of cyclobutyl derivatives is also enhanced as the strain of the participating bond increases. For example, in a series of cis-fused bicyclo[*n*.2.0]-alkyl esters II, the epimeric (exo/endo) rate ratios vary by eight orders of magnitude as the rigidity of the peripheral ring changes.[4]



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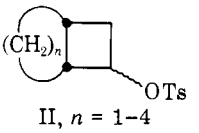


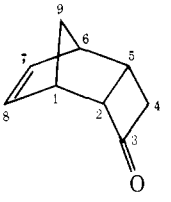
II, n = 1–4

It is of interest to test the kinetic influence of a rigidly held double bond proximate to the σ bond which participates in the ionization process. A bicyclo[2.2.1]hept-5-enyl substituent which has a cyclobutane ring cis fused in positions 2 and 3 provides such a structural unit and is of interest since homo interactions are known to be important in unsaturated bicyclo[2.2.1]heptyl cations.[5] For example, the 5-bicyclo[2.2.1]-hept-2-enyl cation is fully delocalized while the uncharged counterpart norbornadiene shows little evidence of π–π interaction.[6] The incorporation of a rigid peripheral bicyclic substituent also removes any conformational ambiguities, since the attending cyclobutane ring is restricted to near planarity and at the same time creates a highly strained σ bond (i.e., 2,5) to promote regioselectivity in the ring opening.

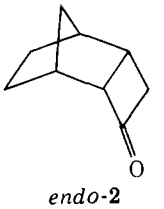
For this reason, we have prepared and now discuss the solvolytic behavior of the epimeric tosylate derivatives derived from the reduction of the polycyclic cyclobutanones, *exo*- and *endo*-**1** and -**2**.[7,8] It was anticipated that the exo or endo nature of these materials might be relevant to the question of remote π interaction in the developing cations, since the disrotatory opening of the strained 2,5 bond in the *exo*-**1**-OTs would result in the buildup of electron density on the bottom side of the bicyclic molecule in the same spatial region as the remote π bond, while comparable ring opening of *endo*-**1**-OTs would place the increased electron density exo, away from the double bond. At the same time, from a synthetic point of view, disrotatory opening would result in the stereospecific generation of cyclopropylcarbinyl derivatives where the three-membered ring retains the original orientation of the starting material thus providing a synthesis of derivatives useful for subsequent studies of homoconjugation which are difficult to prepare by more conventional routes.

Discussion

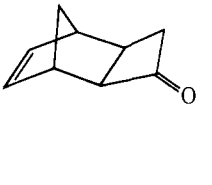
The compounds used in this study were prepared from the synthetically available ketones, *exo*-**1**, *exo*-**2**, *endo*-**1**, and *endo*-**2**.[7] In every case, the reduction of these ketones with



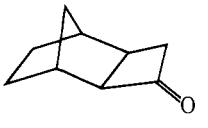
endo-1



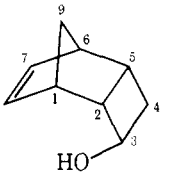
endo-2



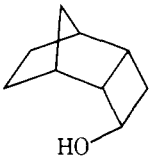
exo-1



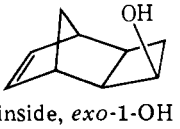
exo-2



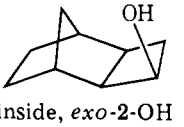
inside, *endo*-1-OH



inside, *endo*-2-OH



inside, *exo*-1-OH



inside, *exo*-2-OH

$NaBH_4$–ethanol produced predominantly the kinetically controlled inside alcohols. Under these conditions, only a few percent of the thermodynamically more stable outside epimer was produced as determined by NMR. On the other hand, the

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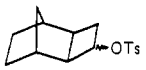
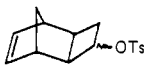
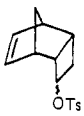
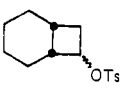
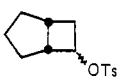
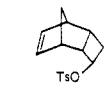
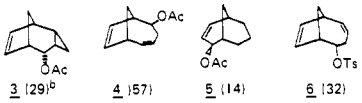
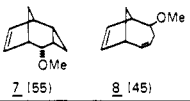
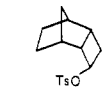
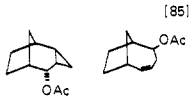
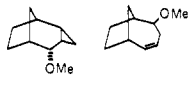
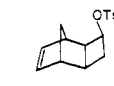
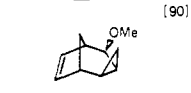
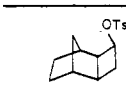
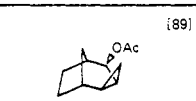
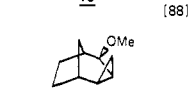
Table I. Summary of Rate Constants Measured in Acetic Acid

	10^5 k, sec^{-1}	
	Inside (25°)	Outside (120°)
	2.51	3.55 ± 0.07
	0.08[a]	2.2[c]
	33.5	1.7 ± 0.1
	1.40	18[d]
	1.27 (30°)[b] 18.3 (50°)[b]	121 (50°)
	120 (50°)[b]	0.26 (50°)[b]
	0.2	

[a] Estimated values obtained by extrapolation from higher temperatures[12]; [b] Reference 1.; [c] Initial k, k values drift down during the run; [d] Initial k, k values drift up during the run.

Table II

Solvent	Products [85][a]	[90][a]
 inside, endo-1-OTs	HOAc, 22°	 3 (29)[b] 4 (57) 5 (14) 6 (32)
	MeOH, 65°	 7 (55) 8 (45)
 inside, endo-2-OTs	HOAc, 25°	[85]  9 (72) 10 (28)
	MeOH, 65°	[86]  11 (83) 12 (17)
 inside, exo-1-OTs	HOAc, 66°	[90]  13
	MeOH, 65°	[90]  14
 inside, exo-2-OTs	HOAc, 25°	[89]  15
	MeOH, 65°	[88]  16

[a] Combined Yield of all Products of Solvent Capture; [b] Relative Yields

reduction of corresponding cyclobutanones under equilibrating conditions (i.e., aluminum isopropoxide–2-propanol)[9] invariably generated a mixture of the epimeric alcohols with the outside epimer predominating to the extent of 85–95%. The saturated alcohols, inside, *exo*-OH, and inside, *endo*-OH, were alternatively produced by catalytic hydrogenation (PtO_2, pentane, 1 atm) of the corresponding unsaturated alcohols.

In this report, we use the terms exo and endo to designate the geometry of the fused cyclobutyl ring relative to the bicyclic substituent and inside/outside to describe the epimeric nature of the carbinol. Clearly, inside OH refers to the situation where the OH group is cis to the peripheral bicyclic structure. In those cases where the carbinol mixtures generated by reduction contained a significant amount of the minor epimer, purification was effected by TLC on silica gel.

For the most part, the NMR spectra of the corresponding carbinol derivatives were not particularly informative, since the aliphatic signals were complex and clustered between δ1 and 3. However, the chemical shift and splitting pattern of the methine proton α to the OH group were distinctly different and characteristic for both the inside and outside epimers. The absorption for the inside alcohols varied from δ 4.3 to 4.1, and the band shape was that of a distorted quartet. The corresponding adsorption for the outside epimers appeared upfield in every case at δ 3.4–4.1 and appeared as a complex multiplet of distinctly different shape than that of the inside epimers. As anticipated, the methine signal of the outside, *endo*-**1**-OH was most shifted owing to the internal shielding by the double bond.[10]

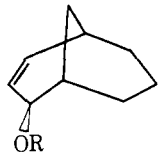
The carbinols were converted into the corresponding alkyl toluenesulfonate esters in the usual manner.[11] Owing to the increased steric hinderance, the inside, *endo*-**2**-OH esterified very slowly under the standard conditions and was more conveniently prepared by catalytic hydrogenation of the inside, *endo*-**1**-OTs in ethyl acetate (PtO_2, 1 atm, 0.5 h). Material prepared in this fashion was identical with that generated via direct esterification of the alcohol. Some of the tosylates were oils at room temperature while others were low-melting solids (see Experimental Section). As expected, the NMR signal for the α-methine proton of the tosylates was shifted downfield (δ 0.5–0.8) from the corresponding alcohol but maintained the same general peak shape.

The rates of acetolysis of the various alkyl toluenesulfonate esters were measured by titration of the produced *p*-toluenesulfonic acid in the usual manner.[11] With the exception of a few cases, the reactions showed good first-order kinetics and proceeded to completion. The kinetic results are shown in comparison with appropriate model compounds in Table I. Inspection of Table I provides two obvious general impressions. First of all, there is a very large reactivity difference between the epimeric ester. Adjusting for the differences in temperature provides an approximate reactivity ratio of 10^4, which is attributed primarily to the low reactivity of the outside epimers. This conclusion is reached by comparison of the present series with the corresponding bicyclo[4.2.0]octyl and bicyclo[3.2.0]heptyl derivatives. Secondly, the presence of the double bond in the inside-ROTs series reduces the solvolytic reactivity by a factor of ~30, which is consistent with an inductive retardation. This decrease in the solvolytic rate seems to be *independent* of the geometry of the cyclobutane ring in the starting material. Further inspection of Table I shows that

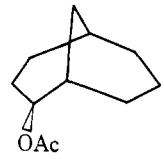
the *endo*, outside-**1**-OTs is the only case where the presence of the double bond favorably influences the reactivity of the compound. For example, the solvolytic k for this ester is ca. 10 times greater than that of the saturated analogue.

The product analyses from the solvolyses of the inside-OTs derivatives in both acetic acid and methanol (buffered with NaOAc) are shown in Table II. With exception of the *endo*, inside-**1**-OTs, which will be discussed separately, the basic structure of the products was the same in either solvent, although the site of solvent capture varied somewhat. As expected, the NMR spectra of the acetates and their corresponding methyl ethers were quite similar with the exception of the methine proton α to the functionality which was downfield in the acetates relative to the analogous methyl ethers. The spectral similarity of both derivatives thus allowed the observation of features which were obscured either by the OAc or the OMe resonances. All structural assignments rest firmly on analytical and spectral data. Dimide reductions of the ethers **7** and **14** produced the saturated derivatives **11** and **16**, respectively, whose spectral data were compared with those of Kirmse and co-workers.[13] In every case, the homoallylic and cyclopropylcarbinyl derivatives were separated by careful column chromatography on $AgNO_3$-silica gel (see Experimental Section) prior to characterization.

The acetolysis of the inside, *endo*-**1**-OTs at 25 °C proved relatively complex and a mixture of three acetates was obtained in the ratio of 1:2:0.5. The major products were identified as the expected cyclopropylcarbinyl and homoallylic acetates **3** and **4**, respectively. In each case predominantly one epimer was generated. The third acetate derivative was clearly extensively rearranged and had the following NMR spectrum: δ (CCl_4) 6.0–5.4 (m, 4 H), 4.77 (br, J = 5 Hz, 1 H), 2.45 m, 2 H), 2.22–1.42 (m, 9 H). Decoupling experiments showed that the acetate methine proton was coupled to one of the vinyl protons. Catalytic hydrogenation (PtO_2, pentane, 1 atm) resulted in the uptake of 2 mol of hydrogen to produce *exo*-2-acetoxybicyclo[3.3.1]nonane (**18**). This material was prepared independently for comparison from the known exo alcohol **17a**[14] by acetylation and subsequent hydrogenation. On the basis of these data, the structure of the rearranged acetate was assigned as **5**. The position of the double bonds was clearly indicated by analysis of the NMR spectrum in the presence of Eu(fod)$_3$. In the case of the cyclopropylcarbinyl derivative **3** the stereochemical assignment was obvious from the NMR spectra. The methine proton α to acetate appeared as a triplet (actually a doublet of doublets, J = 7 Hz) at δ 4.95. The strong coupling to the bridgehead proton is indicative of an exo orientation. Further confirmation was derived from the fact that reduction of the methyl ether **7**, which showed the same methine splitting pattern, with dimide yielded **11** which was identified by spectral comparison with an authentic sample from another source.[13] The assignment of the configuration of the acetate group in **4** is considerably more difficult owing to the basic conformational flexibility of the bicyclo[4.2.1]nonadiene ring. If one makes the reasonable assumption that C_3 would prefer to be flipped downward to avoid the unfavorable interaction with the syn hydrogen on C_9, it follows routinely from NMR analysis in the presence of Eu(fod)$_3$ that the configuration of the acetate group is as shown (i.e., quasi-equatorial). This is based on the large coupling of H_a to H_b (J = 11 Hz) characteristic of diaxial coupling,[15] as well as an analysis of the change in chemical shifts with concentration of Eu(fod)$_3$. In this respect, the vinyl proton at C_8 was shifted almost twice as far downfield as the corresponding syn proton on C_9. The spectral similarity of the structurally related derivative **8** led accordingly to the same tentative configurational assignment.[16]



17a, R = H
b, R = Ac



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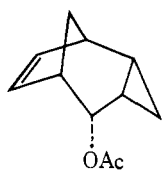
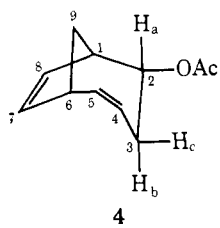


3



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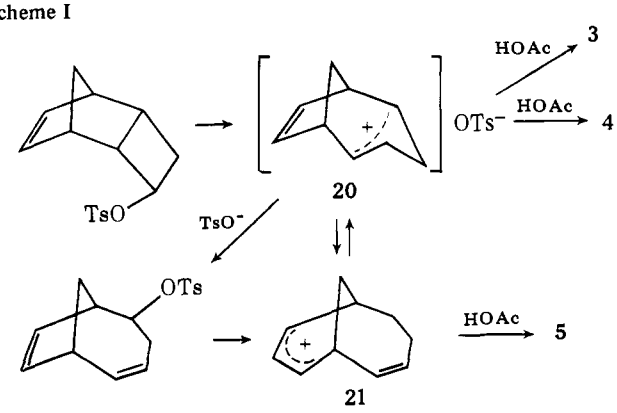
19

In addition, ~32% of a crystalline, rearranged alkyl tosylate was isolated from the crude solvolysis mixture. The material was subsequently identified as **6** by the close similarity of its NMR spectrum to that of the acetate derivative **4**. Further structural confirmation was obtained from the cleavage of **4** by methyllithium to the alcohol **19** and subsequent esterification with *p*-toluenesulfonyl chloride. The alkyl tosylate generated in this manner was identical in every respect with that isolated from the solvolysis of the inside,*endo*-1-tosylate. The solvolytic k for the tosylate **6** in buffered acetic acid (75 °C) was 9×10^{-5} s^{-1}, which is ~70 times smaller than that of the original inside,*endo*-**1**-OTs. This low rate suggests that the solvolysis of **6** contributes relatively little to the products formed during the solvolysis of the inside,*endo*-**1**-OTs at 25 °C. Surprisingly, when **6** was solvolyzed at 75 °C, the rearranged acetate **5** was the major product (86%). The minor products in this reaction were acetates **3** and **4** (14% combined yield) which were produced in the same relative ratio as in the solvolysis of the *endo*, inside-**1**-OTs. This result was somewhat unexpected, since **6** could have ionized directly to the same cationic intermediate as the inside,*endo*-**1**-OTs and reacted accordingly. This rearrangement is, however, consistent with the assignment of a pseudoequatorial configuration to the tosylate group **6**, since inspection of molecular models shows an almost perfect antiperiplanar arrangement between the leaving group and the corresponding 1,9 bond which must migrate to ultimately produce **5**.[17] A mechanistic postulate which rationalizes the overall solvolytic behavior is shown in Scheme I. Consistent with the suggestion of two cationic intermediates is the observation that the solvolysis of inside,*endo*-**1**-OTs in a more nucleophilic solvent such as methanol generates only **7** and **8** and produces none of the rearranged methyl ether corresponding to **4**. Thus, while a comparison of the solvolytic k's implies that the double bond of the inside,*endo*-**1**-OTs is not involved in the ionization step, it must certainly have some effect on the fully formed cation, since it is now sufficiently long lived to permit the occurrence of a

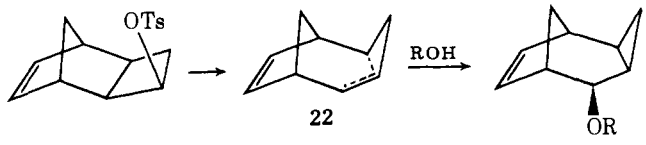
Scheme I



subsequent rearrangement to produce the allyl cation plus internal return with OTs, in competition with solvent capture.

The product analysis from the saturated derivative inside,*endo*-**2**-OTs was considerably simpler, since only the expected acetates **9** and **10** were produced in the relative ratio of 2.6/1.[18] A similar result was obtained in methanol and again the cyclopropylcarbinyl derivative predominated (**11**/**12**, 4.9). As in the unsaturated case, the products seemed to be generated predominantly as single epimers. In this respect, the spectral data of **11** were identical with those obtained by the dimide reduction of **7** and also to those described for **11** prepared in a different fashion.[13]

In contrast, a single product was obtained from the solvolyses of the corresponding exo isomers (i.e., *exo*-**1**-OTs and *exo*-**2**-OTs). In both cases, the only products of solvent capture were the corresponding cyclopropylcarbinyl derivatives (see Table II). The same types of products were again formed in methanol and in both solvents they were generated as predominantly a single isomer (i.e., solvent was captured syn to the cyclopropane group). The saturated derivatives **15** and **16** were generated by dimide reduction of **13** and **14**, respectively,

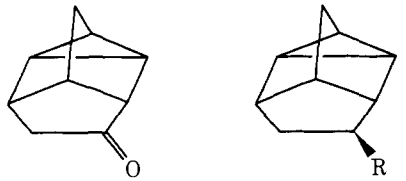


22

13, R = Ac
14, R = Me

and the spectral data of **16** were compared with those of a known sample.[13] Interruption of the solvolysis of either the inside,*exo*-**1**-OTs or inside,*exo*-**2**-OTs after approximately 1 half-life and isolation of the tosylate derivative revealed that no rearrangement had occurred. The specific cleavage of the strained 2,5 bond and the stereospecific formation of products containing the cyclopropane moiety exclusively in the exo position are consistent with an assisted ionization process where the 2,5 bond undergoes a disrotatory ring opening to generate the corresponding cyclopropylcarbinyl cation as illustrated below for the inside,*exo*-**1**-OTs derivative. This description is also consistent with the large rate differences observed for the inside and outside epimers of the exo series (see Table I). In this respect, while the double bond of the inside,*exo*-**1**-OTs does not appear to directly intervene in the ionization process, the decreased solvolytic rate relative to the saturated epimer is consistent with inductive retardation.

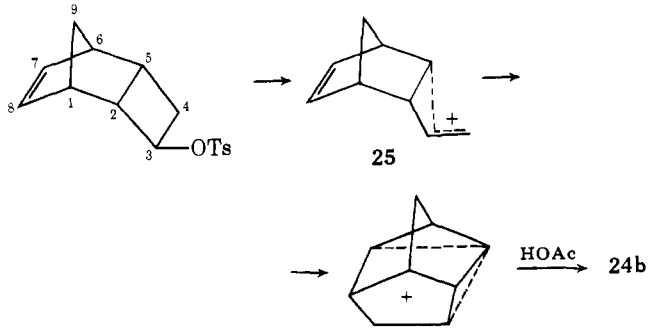
As described, the solvolyses of the outside epimers (*endo*- and *exo*-**1** and -**2**) are slow in comparison with the corresponding inside epimers in a fashion consistent with the suggested disrotatory assisted ionization process. The *endo*,-outside-**1**-OTs is unusual, since it represents the only case where the presence of the double bond favorably influences the reactivity relative to its saturated isomer (Table I). In this respect the solvolytic k for this ester is ca. 10 times greater than the rate constant for the saturated derivative. Analysis of the products of solvent capture from ionization of *endo*,outside-**1**-OTs showed a single acetate as the major product (>86%). This material was subsequently identified by its spectral and analytical data as the rearranged acetate **24b**. Again this material was produced predominantly (>95%) as a single epimer. The same acetate could be prepared by reduction of **23**[19] with aluminum isopropoxide and subsequent acetylation of the major epimer. The spectral and GLC data for the acetate prepared by both routes were identical.



23

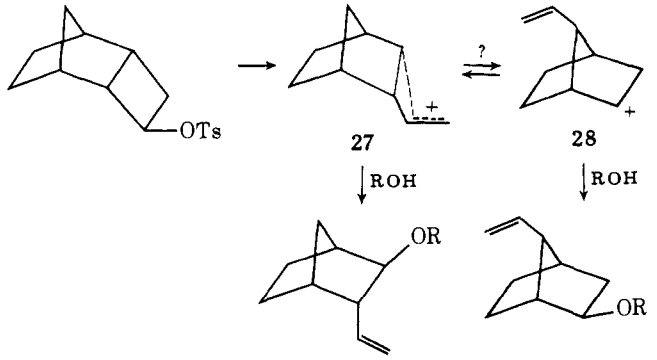
24a, R = OH
b, R = OAc

The solvolytic reaction of outside,*endo*-**1**-OTs was again remarkably specific in that virtually none (<5%) of the products expected from cleavage of the 2,5 bond could be detected. This is rationalized on the basis that disrotatory assisted ionization involving cleavage of the 2,5 bond with concomitant backside displacement of the leaving group would necessarily result in the formation of a strained trans-fused cyclopropylcarbinyl system. However, no such problem is created by the cleavage of the 4,5 bond which produces a cation capable of ultimately generating the observed product via internal electronic reorganization as shown below.[20] Similar cationic cyclizations have been reported previously as a synthetic route to related tetracyclic systems.[21]



The availability of substituted derivatives of the outside,*endo*-**1**-OTs coupled with the high yield and specificity of the solvolytic rearrangement suggests potential utility in the synthesis of a number of interesting tetracyclic sesquiterpenes, e.g., cyclosativene and longicyclene.[22]

The corresponding saturated derivative outside,*endo*-**2**-OTs exhibits a similar proclivity for cleavage of the 4,5 bond relative to the more highly strained 2,5 bond. Accordingly, the solvolysis of this tosylate derivative in acetic acid produced a mixture of alkyl acetates in ~85% yield. GLC and NMR analysis demonstrated that <8% of the products expected from 2,5-bond cleavage (i.e., **3** and **4**) could be detected in the mixture. To facilitate separation and analysis of the product mixture, the crude acetate mixture was cleaved with methylmagnesium bromide, and the resulting alcohols subsequently methylated with sodium hydride–methyl iodide. The major products were isolated by GLC and identified as **29b** and **30b** formed in a ratio of 1:2.7. The spectral and chromatographic data of these ethers were identical with those of samples prepared independently by photolysis of the tosylhydrazone sodium salt of *endo*-**1** in methanol.[23] The formation of the rearranged acetates **29a** and **30a** is readily rationalized in terms of initial cleavage of the 4,5 bond of outside,*endo*-**2**-OTs as shown below.[24]



29a, R = Ac
b, R = Me

30a, R = Ac
b, R = Me

The analysis of the products from the solvolysis of the exo derivatives (outside,*exo*-**1** and **2**-OTs) proved much more difficult. In each case a complex and inseparable mixture of acetates was produced. For example, the unsaturated case (outside,*exo*-**1**-OTs) solvolyzed to a mixture of at least four acetates. The only product from this mixture which could be isolated and positively identified was the corresponding inside,*exo*-**1**-OAc, which suggests that under the vigorous conditions employed S_N2-type processes may be occurring.[25] An added complication was the observation that one potential product from the solvolysis, **3**, was not stable under the vigorous reaction conditions. In a similar fashion, the acetolysis of outside,*exo*-**2**-OTs produces a complex mixture consisting of at least six products. In light of the complexities these reactions were not furthered investigated.

Conclusion

The solvolyses of *exo*- and *endo*-3-tosyloxytricyclo[4.2.1.$0^{2,5}$]nonane derivatives appear to proceed via disrotatory opening of the cyclobutane ring during ionization. This is confirmed by kinetic measurements showing large rate differences between the inside and outside epimers as well as stereospecific product formation. For the inside epimers where disrotation can lead to backside displacement of the leaving group by the developing orbital, the highly strained 2,5 bond is selected for cleavage. In these cases, the direction of rotation is further demonstrated by the retention of stereochemistry of the original cyclobutane ring (i.e., either exo or endo) in the cyclopropylcarbinyl-type products. This provides a stereospecific synthesis of a number of derivatives which are otherwise relatively inaccessible. The presence of a potential interacting double bond in the inside,*exo*- and *endo*-**1**-tosylate seems to have little effect on the ionization step other than inductive deactivation. The only example where the presence of the internal double bond favorably influences the solvolytic rate was in the case of the outside,*endo*-**1**-OTs, whose decomposition was accelerated by approximately a factor of 10 over the corresponding saturated derivative.

Experimental Section[26]

General Procedure for Reduction of Cyclobutanones. The desired cyclobutanones were all prepared as previously described.[7] The inside cyclobutanol derivatives were prepared from the corresponding cyclobutanone derivatives by treatment with sodium borohydride in ethanol. The crude carbinol product was recovered in the usual manner and was generally pure enough for subsequent transformations.

The outside cyclobutanol derivatives were prepared by treatment of the cyclobutanone derivatives with freshly prepared aluminum isopropoxide. The crude carbinols were recovered in 80–90% yield. The more stable epimer was present to the extent of 85–90%.

Preparation of Tosylate Derivatives of the Cyclobutanols. In each case the alcohols were esterified with *p*-toluenesulfonyl chloride (recrystallized from hexane) in pyridine at low temperature (−10 °C) in the usual manner.[11] A number of the alkyl tosylates, particularly those of the outside epimers, would not crystallize even though spectral and chromatographic criteria indicated that they were pure. These were subsequently used in the kinetic and preparative runs without further purification.

Solvolytic Rate and Preparative Experiments. Solvolytic rate measurements were performed in acetic acid using the sealed ampule technique described elsewhere.[11] The solutions for product analyses were prepared in anhydrous solvent containing a twofold molar excess of sodium acetate. The solutions were heated for 10 reaction half-lives and then worked up in the usual manner.

Acetolysis of inside,*endo*-1-OTs at 22 °C for 55 h yielded a mixture of acetates as well as a rearranged tosylate ester. The acetates were vacuum transferred (0.01 mm, 40 °C) and the rearranged tosylate **6** left behind (32%) was recrystallized from pentane. The yield of acetates was 85% based on solvolyzed tosylate. The acetates **3**, **4**, and **5** were separated by careful column chromatography on 20% $AgNO_3$–silica gel (50 g/g) by eluting with 2% ether–pentane.

Pure **5** (20 mg) was dissolved in 5 mL of pentane containing 50 mg of PtO_2 and hydrogenated (1 atm, 25 °C). The catalyst was filtered and the pentane distilled to yield 21 mg of acetate **18.**

Preparation of *exo*-2-Acetoxybicyclo[3.3.1]non-3-ene (17b). A mixture of 57 mg (0.4 mmol) of *exo*-2-hydroxybicyclo[3.3.1]non-3-ene[14] in 0.7 mL of pyridine was treated with 0.2 mL of acetic anhydride at 25 °C for 2 h. The reaction mixture was diluted with water and extracted with ether. The ether was washed with 10% salt solution, dried over $MgSO_4$, and distilled to yield 113 mg (95%) of the allylic acetate **17b.** This material was hydrogenated over PtO_2 in pentane to yield the saturated exo acetate **18** in quantitative yield. The spectral data and chromatographic behavior of this material were identical with those of previously prepared material.

Alternative Preparation of the Alkyl Tosylate 6. Into a flask under nitrogen were placed 235 mg (1.32 mmol) of purified acetate **4**, 10 mL of ether, and 9 mL of 1.65 M methyllithium. The reaction mixture was stirred for 3 h (0 °C) and quenched with 20% NH_4Cl. The ether extracts were washed with water, dried over $MgSO_4$, and evaporated to yield 168 mg of the alcohol **19.** Treatment of the alcohol **19** with *p*-toluenesulfonyl chloride in pyridine yielded 269 mg (75%) of the tosylate **6** whose spectral and chromatographic properties were identical with those of previously isolated material from the solvolysis of the inside,*endo*-**1**-OTs.

Acetolysis of **6** at 75 °C for 24 h yielded an acetate mixture (90%) composed of 86% of **5** and 14% of a 2:1 mixture of **4** and **3** as determined by a combination of NMR and GLC analysis (6 ft × ⅛ in. 10% UCW 98 on 60/80 Chromosorb W, *T* 120 °C, *f* 60 mL/min).

Methanolysis of inside,*endo*-1-OTs at 65 °C for 7 h yielded the methyl ethers **7** and **8** in a relative ratio of 1.2/1 (90%). The ethers were separated by column chromatography on 20% $AgNO_3$–silica gel using pentane as the eluent.

Acetolysis of inside,*endo*-2-OTs, freshly prepared, was performed at 25 °C for 17 h. NMR examination of the crude mixture showed a small amount (ca. 10%) of an unidentified rearranged tosylate ester. The acetates were collectively separated by chromatography on neutral alumina (activity II, 25 g/g) by eluting with 10% ether–pentane (85% based on consumed tosylate). NMR analysis of the acetate fraction showed it to be a mixture (72/28) of **9** and **10.** Again separation of **9** and **10** was effected on 20% $AgNO_3$–silica gel using 2% ether–pentane.

Methanolysis of inside,*endo*-**2**-OTs was performed at 65 °C for 3 h. The methyl ethers **11** and **12** were isolated as a 83/17 mixture (85%) and were separated by chromatography on 20% $AgNO_3$–silica gel using pentane.

Alternate Preparation of 11 by Reduction of 7. The ether **7** (75 mg, 0.5 mmol) was reduced by diimide generated by the oxidation of hydrazine as described by Corey and co-workers.[25] The spectral and chromatographic properties of the ether **11** (58 mg, 77%) produced in this manner were identical with those of the major product of the methanolysis of the inside,*endo*-**2**-OTs.

Acetolysis of inside,*exo*-**1**-OTs was performed at 66 °C for 26 h. Shortpath distillation yielded the acetate **13** in 90% yield.

Methanolysis of the inside,*exo*-**1**-OTs for 32 h at 65 °C provided the cyclopropylcarbinyl methyl ether **14** as the only detectable product (90%).

Acetolysis of the inside,*exo*-2-OTs for 65 h at 25 °C produced the acetate **15** as the predominant volatile product (90%).

Methanolysis of the inside,*exo*-**2**-OTs at 65 °C for 7 h yielded the methyl ether **16** as the sole product, produced in 89% yield. The same material was generated by diimide reduction of the unsaturated ether as described above.

Acetolysis of outside,*endo*-**1**-OTs at 110 °C for 55 h yielded an acetate fraction in 85% yield. The major product (87%) was purified by GLC (6 ft × ¼ in. 10% SE-30 on 60/80 Chromosorb W, *T* 120 °C, *f* 60 mL/min) and identified as the rearranged acetate **24b.**

Alternate Preparation of 24b. The known ketone **23**[19] was reduced on a 2-mmol scale in the usual manner with aluminum isopropoxide to yield an epimeric alcohol mixture which contained ~85% of **24a.** The major epimer was purified by TLC (silica gel, 50/50 ether–pentane) and esterified with acetic anhydride (1 mL) and pyridine (0.33 mL) for 18 h (25 °C). The reaction mixture was diluted with water and extracted with ether. Distillation of the ester gave a quantitative yield of the desired exo acetate **24b.** The material had the same spectral and GLC properties as that previously prepared.

Acetolysis of the outside,*endo*-**2**-OTs at 115 °C for 75 h yielded 54 mg of acetate product. GLC analysis of the mixture (6 ft × ⅛ in. 10% Carbowax 20M on 60/80 Chromosorb P, *T* 145 °C, *f* 60 mL/

min) showed two major low boilers (89%). By coinjection it was determined that the acetates which result from cleavage of the 2,5 bond (i.e., **9** and **10**) comprised <8% of the mixture. The crude acetate mixture was dissolved in 5 mL of ether and treated with 2 mL of methylmagnesium bromide (3 M) at 0 °C for 2 h. The reaction mixture was quenched with 20% NH_4Cl and extracted with ether. The crude alcohol mixture thus obtained was directly methylated in 5 mL of THF using 25 m (0.6 mmol) of NaH and 0.4 mL of CH_3I. The ether mixture was purified by GLC (6 ft × 1/4 in. 20% triscyanoethoxypropane on 60/80 Chromosorb P) and identified as **29b** and **30b** (1/2.8) by their spectral data and comparison with a sample prepared by a different route.[23]

Acetolysis of the outside,*exo*-**1**-OTs was performed at 120 °C for 240 h. Workup and GLC analysis (6 ft × 1/8 in. 10% Carbowax 20M in 60/80 Chromosorb P, *T* 151 °C, *f* 30 mL/min) showed a complex mixture of at least four poorly resolved major peaks. The only component which could be isolated from the mixture was identified by comparison with a known sample as the inside, *exo*-**1**-OAc. Owing to the complexity of the mixture the reaction was not further investigated.

Acetolysis of the outside,*exo*-**2**-OTs was performed at 125 °C for 60 h. GLC analysis (10% Carbowax 20M, 145 °C, *f* 30 mL/min) showed at least six major products, all poorly resolved. The mixture was not further characterized.

Supplementary Material Available: All the spectral data and mass spectroscopic molecular weights (7 pages). Ordering information is given on any current masthead page.

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(25) An authentic sample of the inside,*exo*-1-OAc was prepared for comparison by reduction of *exo*-1 with sodium borohydride and subsequent acetylation.
(26) All melting points are uncorrected. NMR spectra were recorded on a Varian HA-100 instrument with Me_4Si as an internal standard. Infrared spectra were run on a Beckman 521 grating instrument. The low-resolution mass spectra were recorded on a Perkin-Elmer Hitachi RMS-4 machine. The analytical and preparative gas chromatography were run on a Hewlett-Packard 5750 instrument.
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Tracer Studies of Carboxylic Acids. 7. Oxygen-18 Exchange of Propionic Acid with Solvent Water and with Surfactant Solubilized Water in Benzene

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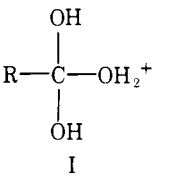
Abstract: Oxygen atom exchange between propionic acid/propionate ion and solubilized $H_2{}^{18}O$ has been measured in micellar solutions of dodecylammonium propionate in benzene and in aqueous solutions of ammonium propionate. The size of the solubilized water pool affects the rate of exchange of carboxylate oxygen atoms in the presence of mineral acid but not in its absence.

The exchange of the oxygen atoms of carboxylic acids and carboxylate ions with solvent water has been extensively studied using an oxygen-18 label.[1-5] In the mass spectrometric studies[1-4] it was assumed that exchange went through formation of a tetrahedral intermediate, I–III, which decomposed rapidly to give the exchange products.



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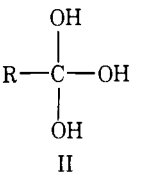

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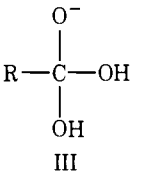

III

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