On the Solvolysis of 2-Cyclohexenyl 3,5-Dinitrobenzoate and *p*-Nitrobenzoate in Aqueous Acetone. Introduction of Acyl-Oxygen Cleavage by Basic Buffer Systems[1]

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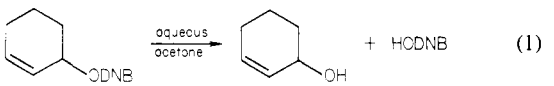
Abstract: Solvolysis of α- and γ-deuterium-labeled 2-cyclohexenyl 3,5-dinitrobenzoate (**1**-ODNB) and *p*-nitrobenzoate (**1**-OPNB) in 60% aqueous acetone containing diisopropylethylamine (to protect initially formed product from subsequent acid-catalyzed allylic rearrangement) results in only partial randomization of the α- and γ-carbon atoms. With 3 equiv of amine, >50% excess preservation of allylic structure is observed. Solvolysis of ether-^{18}O-labeled esters shows that this results from acyl-oxygen hydrolysis caused by the basic amine used to buffer the solution. Various amines have been investigated to find buffers sufficiently basic to protect initially formed solvolysis product but not basic enough to superimpose acyl-oxygen hydrolysis on the ionic solvolytic reaction. In the presence of such buffers, solvolysis of the allylic esters gives a slight excess (~6%) of solvent capture at the γ position. This shows that some product is derived from an unsymmetrical intermediate, presumably an ion-pair intermediate, in which solvent capture at the γ position is favored.

Conflicting reports in the literature have prompted us to investigate the symmetry properties of product-forming intermediates in S_N1 solvolytic reactions of 2-cyclohexenyl *p*-nitrobenzoate (**1**-OPNB) and 3,5-dinitrobenzoate (**1**-ODNB) in aqueous acetone (eq 1). Product studies in such systems are complicated by the



1-ODNB 1-OH (1)

instability of the products in the presence of the acid produced by solvolysis. To avoid subsequent acid-catalyzed rearrangement of the initial product, which randomizes the allylic positions, the solution must be buffered. Even so, the product should be exposed to reaction conditions for a minimum period and this requires knowing the rate of product formation. In this work we have investigated various buffer systems and have found three (*N*-methylmorpholine, 2,6-lutidine, and *N*-cyclohexylmorpholine) which are sufficiently basic to protect the initial product for up to 5 solvolytic half-lives (97% reaction) without introducing base-promoted side reactions (e.g., acyl-oxygen hydrolysis). Thus conditions have been developed for examining the initial product derived from ionic solvolysis of α-D- and γ-D-**1**-OPNB and the corresponding 3,5-dinitrobenzoates.

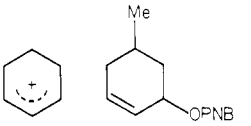
An additional complication is that in such symmetrical allylic systems, ion-pair return results in randomization of allylic positions of the substrate prior to generation of capturable intermediates. However, methods have been developed for measuring the amount of ion-pair return,[3-5] and from this the amount of product derived from substrate that has not undergone ion-pair return can be determined.[6] Moreover, from earlier work[5] the magnitude of ion-pair return to solvolysis ratios is predictable for cyclohexenyl systems and suitable conditions can be selected accordingly.

In earlier work[3,4] we concluded that in cyclohexenyl systems, the symmetrical allylic cation (**2**) is the major, if not exclusive, product-forming intermediate. This conclusion was based on indirect evidence that the initial product derived from solvolysis of optically active *trans*-[3a] and *cis*-5-methyl-2-cyclohexenyl *p*-nitrobenzoate (**3**-OPNB)[3b] in aqueous acetone is completely racemic.[7]

Table I. Titrimetric First-Order Rate Constants (k_t) for Solvolysis of 2-Cyclohexenyl 3,5-Dinitrobenzoate (1-ODNB) and 2-Cyclohexenyl *p*-Nitrobenzoate (1-OPNB) in Aqueous Acetone

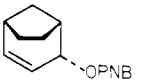
ester	concn, M	% acetone solvent[a]	temp, °C	10^4k_t, min^{-1} [b]
1-ODNB	0.050	90	110.00	8.55 ± 0.02
1-OPNB	0.051	80	109.70	6.37 ± 0.12
1-ODNB	0.050	80	94.54	12.97 ± 0.08
1-OPNB	0.019	60	75.21	2.62 ± 0.07
1-OPNB	0.017	60	94.85	20.3 ± 0.5
1-ODNB	0.0049	60	75.21	18.8 ± 0.8
1-ODNB	0.0052	60	94.85	152 ± 8

[a] Composition of aqueous acetone based on volumes of pure components at 25 °C prior to mixing. [b] The indicated uncertainty is the standard deviation from the mean of four to ten values for each experiment.



2 3-OPNB

More recently, products resulting from solvolysis of optically active *exo*-bicyclo[3.2.1]oct-3-en-2-yl *p*-nitrobenzoate (*exo*-**4**-OPNB) in 80% acetone were carefully examined and found to be racemic.[5] Control experiments showed that as little as 1% retention of optical configuration would have been detected.



exo-4-OPNB

Our results and conclusions were in sharp contrast to a report that solvolysis of 2-cyclohexenyl 3,5-dinitrobenzoate (**1**-ODNB) in 60% aqueous acetone buffered with a fourfold excess of diisopropylethylamine gives 2-cyclohexenol (**1**-OH) with 44% excess

(1) Presented in part at the 2nd Chemical Congress of the North American Continent, Las Vegas, NV, August 1980.
(2) National Science Foundation Fellow, 1977–1980.
(3) (a) Goering, H. L.; Silversmith, E. F. *J. Am. Chem. Soc.* **1955**, *77*, 6249. (b) Goering, H. L.; Doi, J. T.; McMichael, K. D. *Ibid.* **1964**, *86*, 1951.
(4) Goering, H. L. *Rec. Chem. Prog.* **1960**, *21*, 109.
(5) Goering, H. L.; Anderson, R. P. *J. Am. Chem. Soc.* **1978**, *100*, 6469.
(6) The fraction of product derived from substrate that has not undergone ion-pair return (F) is the ratio of the rate constants for solvolysis (k_t) and total ionization (k_i), i.e., $F = k_t/k_i$. See: Winstein, S.; Trifan, D. *J. Am. Chem. Soc.* **1952**, *74*, 1154 for derivation of this relationship.
(7) These experiments were designed for investigation of ion-pair return phenomena rather than the symmetry properties of product-forming intermediates and solutions were not buffered. However, the cleanly first-order complete loss of optical activity indicated that the initial product is racemic **3**-OH derived from the symmetrical 5-methylcyclohexenyl ion.

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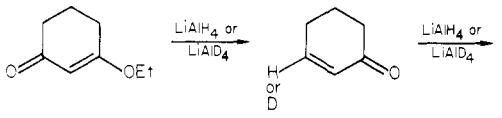
retention of allylic structure and optical configuration.[8] Similar results were observed with the 2-cycloheptenyl ester and the 2-cyclooctenyl ester gave essentially complete retention of allylic structure and optical configuration. In this work we have found that the results reported[8] for **1**-ODNB are reproducible in detail. However, the excess retention of allylic structure and optical configuration does not result from capture of unsymmetrical allylic intermediates, but instead results from acyl-oxygen hydrolysis which is superimposed on the S_N1 solvolytic reaction. We now find that under optimum conditions (i.e., initially formed **1**-OH stable and no acyl-oxygen hydrolysis) solvolysis of **1**-ODNB or **1**-OPNB in aqueous acetone gives a slight excess (~6%) of solvent capture at the γ position and excess (~14%) inversion of optical configuration instead of excess retention of allylic structure and optical configuration.

Results and Discussion

The necessary rate constants (k_t) for product studies for solvolysis of **1**-OPNB and **1**-ODNB in aqueous acetone are presented in Table I. These constants were determined by methods described earlier.[9] Reactions were followed to 75% completion and clean first-order behavior was observed in all cases. Infinity titers were 2–5% low because of contamination with unreactive cyclohexyl esters which result from conjugate addition during preparation of **1**-OH. The rate constant for solvolysis of **1**-ODNB in 60% aqueous acetone at 75 °C is ~40% smaller than the value cited previously.[8]

The preparation of 2-cyclohexenol (**1**-OH) involves two lithium aluminum hydride ($LiAlH_4$) reductions.[10] As illustrated by eq 2, the use of lithium aluminum deuteride ($LiAlD_4$) in the appropriate step incorporates deuterium into either the α or γ position.[11]



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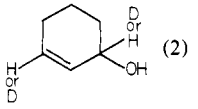


(2)

1-OH

Solvolysis of 0.05 M α-D- and γ-D-**1**-ODNB at 75 °C in 60% aqueous acetone containing 0.155 M diisopropylethylamine gives **1**-OH with 62% and 52% excess retention of allylic structure.[12] Similarly, solvolysis of α-D- and γ-D-**1**-OPNB under these conditions gives 50% and 42% excess retention of allylic structure. In these experiments the product was isolated after 10 solvolytic half-lives and α,γ deuterium distributions were determined by 15.36 MHz deuterium mangetic resonance (^2H NMR). Control experiments showed that the initial products are stable and that excess retention of allylic configuration can be determined with an accuracy of ±3% by ^2H NMR.

These experiments confirm the earlier report[8] that under these conditions there is considerable retention of allylic configuration for solvolysis of **1**-ODNB. Moreover, the results are similar for solvolysis of **1**-OPNB. However, the excess retention of allylic configuration results from acyl-oxygen hydrolysis superimposed on the S_N1 solvolysis.

The involvement of acyl-oxygen cleavage was established with ether-^{18}O-labeled deuterated esters. The doubly labeled esters were obtained by equilibration[13] of the enone (**5**) with oxygen-18 enriched water prior to reduction with $LiAlH_4$ or $LiAlD_4$. Acyl-oxygen hydrolysis of the ether-^{18}O-deuterated esters gives unrearranged **1**-^{18}OH whereas ionic solvolysis gives **1**-OH without excess ^{18}O.

Table II. Product Studies for Solvolysis of 0.050 M α- and γ-D-[*ether*-^{18}O]-2-Cyclohexenyl 3,5-Dinitrobenzoates (1-ODNB)[a] and *p*-Nitrobenzoates (1-OPNB)[b] in 60% Aqueous Acetone Containing 0.10 M Diisopropylethylamine

ester	% excess retention[c]	% acyl oxygen cleavage[d]
α-D-1-ODNB	48	48.2 ± 0.9
γ-D-1-ODNB	49	51.8 ± 0.7
α-D-1-OPNB	23	22.8 ± 0.6
γ-D-1-OPNB	22	23.4 ± 0.5

[a] Product alcohol isolated after 6 solvolysis half-lives for 1-ODNB at 75.2 °C. [b] Product alcohol isolated after 6 solvolysis half-lives for 1-OPNB at 95.0 °C. [c] Excess retention of allylic structure. Experimental uncertainty is ±3%. [d] Percent excess ^{18}O in product (1-OH). Average and standard deviation of three or four analyses.

In these experiments α- and γ-D-[*ether*-^{18}O]-**1**-OPNB and **1**-ODNB were solvolyzed for 6 half-lives in 60% acetone buffered with diisopropylethylamine. Results of these studies are presented in Table II. The excess retention of allylic structure was determined directly by the deuterium distribution[12] and the amount of acyl-oxygen hydrolysis was determined directly from the amount of ^{18}O retained. Oxygen-18 contents were determined by a modified Schütze–Unterzaucher method.[14] Control experiments showed that there is no loss of ^{18}O from the product during solvolysis or work up. Total ^{18}O contents of the esters remained constant. Thus there is no detectable enrichment due to either a solvolytic[3b] or hydrolytic[15] isotope effect.

The data in Table II show that the amount of retained ^{18}O (acyl-oxygen cleavage) corresponds to the excess retention of allylic structure.[12] From this it is clear that the excess retention of structure results from acyl-oxygen hydrolysis superimposed on the ionic solvolytic reaction. It is now apparent that the reported[8] complete preservation of allylic structure and optical configuration for solvolysis of 2-cyclooctenyl 3,5-dinitrobenzoate under these conditions also results from acyl-oxygen rather than alkyl-oxygen cleavage. Extrapolation of the constants in Table I for solvolysis of **1**-ODNB in 60% acetone to 120 °C gives a value 80 times larger than that reported[8] for the 2-cyclooctenyl ester. These constants (k_t) are for solvolysis in the absence of a buffer and thus correspond to the rate of ionic solvolysis. The rate of acyl-oxygen hydrolysis induced by the buffer would be expected to be similar for both esters. Thus the ratio of acyl-oxygen cleavage to ionic solvolysis is presumably ~80 times larger for the 2-cyclooctenyl ester and this results in essentially complete preservation of allylic structure and optical configuration.

Ion-pair return associated with solvolysis of the esters randomizes the carbonyl oxygen atoms[5,16] as well as the allylic positions[3,4] in the unsolvolyzed ester and thus obscures part of the acyl-oxygen cleavage. The importance of ion-pair return for solvolysis of **1**-OPNB under conditions for the experiments in Table II was investigated by determining the amounts of carboxyl oxygen equilibration (eq 3) and randomization of allylic positions in the unsolvolyzed ester (eq 4).

For solvolysis of 0.05 M ether-^{18}O-labeled **1**-OPNB at 95 °C in 60% acetone containing 0.1 M diisopropylethylamine, k_{eq} (eq 3) is $(4.7 \pm 0.4) \times 10^{-4}$ min^{-1}. The fraction of product derived from substrate prior to oxygen equilibration is approximated by $k_s/(k_{eq} + k_s)$ where k_s is the rate constant for product formation.[6] The reason this is an approximation is that k_s is a composite of ionic solvolysis and acyl-oxygen hydrolysis and the latter is not first order. Moreover, k_s cannot be determined directly because

(8) Wiberg, K. B.; Nakahira, T. *Tetrahedron Lett.* **1974**, 1773 and 1769.
(9) Goering, H. L.; Silversmith, E. F. *J. Am. Chem. Soc.* **1955**, *77*, 1129.
(10) Gannon, W. F.; House, H. O. "Organic Synthesis"; Wiley: New York, 1973; Collect. Vol. V, pp 294 and 539.
(11) Goering, H. L.; Singleton, V. D. *J. Am. Chem. Soc.* **1976**, *98*, 7854.
(12) The excess retention of allylic structure is the difference in percents of total deuterium in the original and other allylic positions.
(13) Goering, H. L.; Josephson, R. R. *J. Am. Chem. Soc.* **1962**, *84*, 2779.
(14) Taylor, J. W.; Chen, I.-J. *Anal. Chem.* **1970**, *42*, 224. Goering, H. L.; Vlazny, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 1801.
(15) Sawyer, C. B.; Kirsch, J. F. *J. Am. Chem. Soc.* **1973**, *95*, 7375.
(16) Goering, H. L.; Pombo, M. M. *J. Am. Chem. Soc.* **1960**, *82*, 2515.

Table III. Product Studies for Solvolysis of α- and γ-D-2-Cyclohexenyl 3,5-Dinitrobenzoates (1-ODNB) and *p*-*p*-Nitrobenzoates (1-OPNB) in 60% Aqueous Acetone Containing Various Amines at 75.2 °C

ester (concn, M)	amine (concn, M)	% excess retention[a]
α-D-1-ODNB (0.051)	2,6-lutidine (0.070)	−4[b]
γ-D-1-ODNB (0.051)	2,6-lutidine (0.070)	−6[b]
α-D-1-ODNB (0.033)	*N*-methylmorpholine (0.100)	−5
γ-D-1-ODNB (0.033)	*N*-methylmorpholine (0.100)	−5
α-D-1-ODNB (0.033)	allyldimethylamine (0.100)	22
γ-D-1-ODNB (0.033)	allyldimethylamine (0.100)	21
α-D-1-ODNB (0.051)	diisopropylethylamine (0.155)	62
γ-D-1-ODNB (0.051)	diisopropylethylamine (0.155)	54
α-D-1-ODNB (0.033)	triethylamine (0.100)	74
γ-D-1-ODNB (0.033)	triethylamine (0.100)	72
α-D-1-OPNB (0.050)	2,6-lutidine (0.070)	−6[c]
γ-D-1-OPNB (0.050)	2,6-lutidine (0.070)	−4[c]
α-D-1-OPNB (0.033)	*N*-methylmorpholine (0.100)	−6
γ-D-1-OPNB (0.033)	*N*-methylmorpholine (0.100)	−9
α-D-1-OPNB (0.033)	allyldimethylamine (0.100)	12
α-D-1-OPNB (0.050)	diisopropylethylamine (0.077)	50
γ-D-1-OPNB (0.050)	diisopropylethylamine (0.077)	42
α-D-1-OPNB (0.033)	triethylamine (0.100)	64
γ-D-1-OPNB (0.033)	triethylamine (0.100)	57

[a] Determined from the percent deuterium in the original position minus that in the other allylic position. Experimental uncertainty is ±3%. [b] Added α-D-1-OH 6% randomized under these conditions. [c] Added α-D-1-OH 20% randomized under these conditions.

the reaction cannot be followed in the buffered solution. The data in Table II show that for these conditions the ratio of acyl-oxygen cleavage to ionic solvolysis is ~23/77. From this we conclude that the best estimate for k_s is $(1 + 23/77)k_t$. This leads to a value of ~85% for the amount of product derived from ester that has not undergone prior oxygen equilibration.

$$\text{1-}^{18}\text{OCOAr} \xrightarrow{k_{eq}} \text{1-}^{18}\text{OC}^{18}\text{OAr} \quad (3)$$

$$\alpha\text{-D-1-ODNB} \xrightarrow{k_{rand.}} \alpha,\gamma\text{-D-1-ODNB} \quad (4)$$

The rate of randomization of allylic positions in the unsolvolyzed ester (eq 4) that results from ion-pair return was determined by isolation of the unreacted ester and determination of the deuterium distribution. For solvolysis of α-D-**1**-ODNB in 60% acetone at 75.2 °C, $k_{rand.}$ (eq 4) is $(3.3 \pm 1) \times 10^{-4}$ min^{-1} which is about one sixth as large as k_t. This also leads to a value of ~15% for the amount of product derived from ester that has undergone ion-pair return prior to reaction. In the presence of diisopropylethylamine, acyl-oxygen hydrolysis is superimposed on ionic solvolysis and the amount of product derived from prerandomized ester is decreased. In any case, it appears that the amount of acyl-oxygen cleavage obscured by ion-pair return is small and that the data in Table II provide good measures of amounts of product resulting from acyl-oxygen cleavage.

It is noteworthy that the results in Table II show that acyl-oxygen cleavage/ionic solvolysis ratios are remarkably similar for **1**-OPNB and **1**-ODNB even though there is a sevenfold difference in ionic solvolytic reactivity. This shows that substituent effects are very similar for the two competing processes.

In earlier product studies we found that for solvolysis of tertiary *p*-nitrobenzoates in aqueous acetone, 2,6-lutidine is an effective buffer and does not introduce acyl-oxygen hydrolysis.[17] The absence of any acyl-oxygen hydrolysis with 2,6-lutidine in a system[17b] only slightly more reactive than the cyclohexenyl system[18] suggested that the reason for the competing acyl-oxygen hydrolysis in the present case is that the buffer (diisopropylethylamine) is too basic.

Results for solvolysis of α- and γ-D-**1**-ODNB and **1**-OPNB in the presence of the various amines are presented in Table III. The order of decreasing basicity (and apparent pK_a's in 60% acetone)[19] for these amines is as follows: diisopropylethylamine (10.0) ≃ triethylamine (9.7) > allyldimethylamine (8.3) > *N*-methylmorpholine (7.0) > 2,6-lutidine (5.6). In these experiments products were isolated after 10 solvolytic half-lives. For each amine, product stability was checked by solvolyzing unlabeled ester in solvent containing α- or γ-D-**1**-OH. Except as noted in footnotes, these control experiments showed that the product is stable under the reaction conditions.

These results show that the amount of acyl-oxygen cleavage (excess retention of allylic structure) parallels amine basicity. The negative amounts of excess retention of allylic structure observed with the less basic amines, 2,6-lutidine and *N*-methylmorpholine, mean that in these cases there is excess allylic rearrangement. Or put another way, there is excess solvent capture at the γ position. The amount of acyl-oxygen hydrolysis is consistently somewhat larger for the α-deuterated esters than for the corresponding γ-deuterated ester. Evidently this results from a secondary isotope effect. The α deuterium impedes the S_N1 solvolytic reaction but has no effect on acyl-oxygen hydrolysis.

Acyl-oxygen hydrolysis of cyclohexyl 3,5-dinitrobenzoate in 60% acetone containing basic amines was also investigated. In this saturated system acyl-oxygen cleavage is cleanly isolated from S_N1 solvolysis—in the absence of a basic amine no detectable solvolysis occurs in a time corresponding to 10 solvolytic half-lives for **1**-ODNB. However, rates of acyl-oxygen hydrolysis would be expected to be similar for the allylic and nonallylic systems.

Rates of acyl-oxygen hydrolysis of the saturated ester in 60% acetone in the presence of allyldimethylamine, triethylamine, diisopropylethylamine, and quinuclidine were determined as follows. Solutions of 0.05 M 1-D-cyclohexyl 3,5-dinitrobenzoate and 0.02 M 2-D-cyclohexanol (internal standard) in 60% acetone buffered with 0.055 M amine and 0.005 M 3,5-dinitrobenzoic acid (to adjust basicity to the buffer region) were heated to 75.2 °C. The reactions were followed by determining the ratio of 1-D-cyclohexanol (produced by hydrolysis) to 2-D-cyclohexanol (internal standard) by ^{2}H NMR. The α-deuterated ester was obtained from the corresponding alcohol which was pepared by $LiAlD_4$ reduction of cyclohexanone and 2-D-cyclohexanol was obtained by $LiAlD_4$ reduction of cyclohexene oxide.[20] Under these conditions acyl-oxygen hydrolysis proceeds at the expected rate. For example, with the diisopropylethylamine buffer there is 20% reaction after a period required for 22% S_N1 solvolysis of **1**-ODNB and the saturated ester undergoes 51% acyl-oxygen hydrolysis during the period required for 75% ionic solvolysis of **1**-ODNB. Doubling the buffer concentration (0.11 M diisopropylethylamine and 0.01 M 3,5-dinitrobenzoic acid) increases the rate of acyl-oxygen hydrolysis of the saturated ester. Under these conditions, a period required for 22% ionic solvolysis of **1**-ODNB results in 32% hydrolysis of the saturated ester. These experiments clearly show that under the conditions of the experiments in Table II, rates of acyl-oxygen cleavage of the saturated and unsaturated ester are comparable to rates of S_N1 solvolysis of the allylic ester.

The rates of hydrolysis of cyclohexyl 3,5-dinitrobenzoate under conditions described above are second order, first order in ester and first order in free (excess) amine. These second-order constants, which show considerable scatter but no trends, are in the same order as the pK_a's for the four basic amines used as buffers. The fact that the rate is proportional to amine concentration at constant pH leads us to conclude that acyl-oxygen cleavage results from general base catalysis. This indicates that less basic buffers are required to minimize or eliminate competing acyl-oxygen hydrolysis for solvolysis of **1**-OPNB and **1**-ODNB and that steric requirements of the amine are of secondary importance.[21]

(17) (a) Goering, H. L.; Humski, K. *J. Am. Chem. Soc.* **1968**, *90*, 6213. (b) Goering, H. L.; Chang, C.-S.; Clevenger, J. V. *Ibid.* **1974**, *96*, 7602. (c) Goering, H. L.; Chang, C.-S. *Ibid.* **1976**, *98*, 1547. Goering, H. L.; Chang, C.-S.; Masilamani, D. *Ibid.* **1978**, *100*, 2506. Goering, H. L.; Humski, K. *J. Org. Chem.* **1975**, *40*, 920.

(18) The higher the ionic solvolytic reactivity, the easier it is to isolate ionic solvolysis from competing acyl–oxygen hydrolysis.

(19) Apparent pK_a's in 60% acetone determined from titration curves and are apparent pH values at the half-equivalency point.

(20) Finley, K. T.; Saunder, W. H. *J. Am. Chem. Soc.* **1967**, *89*, 898.

However, the buffer must be sufficiently basic to prevent acid-catalyzed transformations of the initial products.

2,6-Lutidine, *N*-methylmorpholine, and *N*-cyclohexylmorpholine were shown to be satisfactory buffers for solvolysis of the 2-cyclohexenyl esters in 60% and 80% acetone as follows. A 0.05 M solution of **1**-ODNB was solvolyzed in 60% acetone containing 0.075 M amine (0.150 M in the case of lutidine), 0.05 M α-D-cyclohexyl 3,5-dinitrobenzoate, 0.02 M 2-D-cyclohexanol, and 0.05 M γ-D-**1**-OH and products were examined by ^{2}H NMR at times corresponding to 4, 10, and 20 solvolytic half-lives. The deuterated cyclohexyl ester was present to check for acyl-oxygen hydrolysis which would result in the appearance of 1-D-cyclohexanol; 2-D-cyclohexanol was present as an internal standard. The γ-D-**1**-OH was present to check product stability.

With these three buffer systems, competitive acyl-oxygen hydrolysis and acid-catalyzed transformations of the initial produce are insignificant. Only 2,6-lutidine fails to eliminate isomerization of the added γ-D-**1**-OH completely. In this case 6% randomization of the deuterated 2-cyclohexenol was observed at 10 half-lives and 10% was observed at 20 half-lives. *N*-Methylmorpholine is the only amine that gave detectable acyl-oxygen hydrolysis of the added α-D-cyclohexyl 3,5-dinitrobenzoate. And here, only 2% reaction is observed at 10 half-lives and 3% is observed at 20 half-lives.

Similar experiments in 80% aqueous acetone showed the effect of longer contact time due to slower rates of solvolysis. In this solvent, with 2,6-lutidine, 5% of the added γ-D-**1**-OH was randomized at 4 half-lives. With *N*-methylmorpholine and *N*-cyclohexylmorpholine there is essentially no rearrangement at 4 half-lives but small amounts (8% and 4%) are observed at 10 half-lives. With *N*-cyclohexylmorpholine 5% acyl-oxygen hydrolysis is observed after 20 half-lives for solvolysis of **1**-ODNB. From this it can be seen that acyl-oxygen hydrolysis is insignificant during a period required for formation of 99% of the product (7 half-lives).

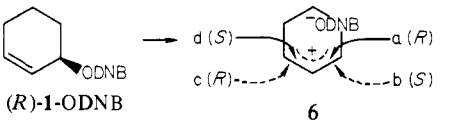
The present experiments suggest that optimum conditions for product studies for solvolysis of allylic 3,5-dinitrobenzoates involve buffering the solution with 1.5 equiv of *N*-cyclohexylmorpholine and isolating products not later than 6 or 7 half-lives. Under these conditions the initial products are stable and the S_N1 process is cleanly isolated from acyl-oxygen hydrolysis.

These conditions also apply for solvolysis of allylic *p*-nitrobenzoates. In this case reaction periods are about seven times larger because of the reduced solvolytic reactivity. However, acyl-oxygen hydrolysis is slower by a similar amount. Although the products are exposed to the reaction conditions for a longer period, there is only slightly more rearrangement because the acid produced by solvolysis is weaker.

The most striking observation in the present work is that the product resulting from S_N1 solvolysis of **1**-ODNB and **1**-OPNB is not completely randomized but instead there is excess solvent capture at the γ position. Thus, although the unperturbed cation (**2**) is symmetrical, significant amounts of product are derived from an unsymmetrical intermediate. We presume that this intermediate is an unsymmetrical ion-pair intermediate (**6**).

In other work we observed that in the *trans*-5-methyl-2-cyclohexenyl (*trans*-**3**-OPNB)[22] and the *endo*-bicyclo[3.2.1]oct-3-en-2-yl systems (*endo*-**4**-OPNB)[5] unsymmetrical ion-pair intermediates are involved in ion-pair return that accompanies solvolysis in aqueous acetone. This was established by showing that in these systems, ion-pair return results in a larger rate of oxygen equilibration (eq 3) than randomization of allylic positions (eq 4). Thus an unsymmetrical ion-pair intermediate returns to oxygen equilibrated but unrearranged ester. However, until now there was no indication that such species were product-forming intermediates.

Products resulting from solvolysis of optically active **1**-ODNB were also examined. For this experiment the ester was prepared from active 2-cyclohexenol (**1**-OH)[23] containing 10% α-D-**1**-OH. The ester was solvolyzed at 75.2 °C in 60% acetone containing 1.5 equiv of *N*-cyclohexylmorpholine and product was isolated at 6 half-lives. Experiments described above show that under these conditions there is no acyl-oxygen cleavage and products are stable. The purified product showed 5% excess rearrangement of deuterium (i.e., excess γ capture) and 14.4 ± 0.8% excess inversion of optical configuration.



(5)

As illustrated by the curved arrows in **6**, solvent capture at the α carbon with retention of configuration a and anti-γ capture c result in retention of the original optical configuration (*R* in the example shown by eq 5). Capture at the α position with inversion b or syn-γ capture d leads to the inverted configuration (*S*). Evidently α capture with retention a is partially blocked by the counterion so capture occurs preferentially at the other sites (b, c, and d). This accounts for both excess allylic rearrangement (c + d > a + b) and inversion of optical configuration (b + d > a + c). Since the (b + d)/(a + c) ratio is larger than the (c + d)/(a + b) ratio it follows that b > c and d > a.

Experimental Section

General Methods. Deuterium magnetic resonance (^{2}H NMR) spectra were determined in hexafluorobenzene with a Varian XL-100 instrument equipped with Gyro Observe and a deuterium probe; $CDCl_3$ was used as an internal standard. Fourier transform NMR was used with a 65-μs pulse width, 4.0-s acquisition time, and 100 transients. Satisfactory spectral data were obtained for all compounds. Mass spectra were obtained with an AEI-MS-902 high-resolution mass spectrometer. Melting points and boiling points are uncorrected.

Materials. 2-Cyclohexenol[10](1-OH) and α- and γ-D-1-OH,[11] bp 62–63 °C (10 torr) [lit.[23] bp 78–79 °C (28 torr)], were prepared as described earlier.

2-Cyclohexenyl *p*-nitrobenzoate (1-OPNB), mp 77–78 °C (hexane), was prepared by reaction of **1**-OH with *p*-nitrobenzoyl chloride in dry pyridine. IR ($CHCl_3$) 3110 (w), 3030 (m), 2950 (m), 2865 (w), 2835 (w), 1720 (s), 1650 (w), 1610 (m), 1530 (s), 1350 (s), 1280 cm^{-1} (s); NMR ($CDCl_3$) δ 1.7–2.2 (m, 6 H), 5.6 (m, 1 H), 5.9 (m, 1 H), 6.1 (m, 1 H), 8.28 (s, 4 H); mass spectrum *m/e* (relative intensity) 247 (M^+, 6), 151 (24), 150 (77), 149 (9), 104 (12), 97 (10), 81 (64), 80 (86), 79 (100), 77 (14), 69 (20), 57 (47), 56 (30); exact mass calcd for $C_{13}H_{13}NO_3$ 247.0841, found 247.0844. Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.60. Found: C, 63.28; H, 5.74; N, 5.60.

2-Cyclohexenyl 3,5-dinitrobenzoate (1-ODNB), mp 121–122 °C (heptane) (lit.[23] mp 123–124 °C) was prepared from **1**-OH and 3,5-dinitrobenzoyl chloride.

Oxygen-18-labeled 1-OH was obtained by equilibrating[13] 2-cyclohexenone with ^{18}O-enriched water (1.6 atom % ^{18}O excess) followed by $LiAlH_4$ reduction. The resulting alcohol contained 0.96 atom % ^{18}O excess.

Optically active 1-OH, $[\alpha]^{24}_D$ 7.54° (*c* 5.2, $CHCl_3$), was prepared by asymmetic oxidation of cyclohexene with *tert*-butyl hydroperoxide and the cupric salt of di-*O*-acetyltartaric acid half-methyl ester as reported earlier.[23] It was mixed with 10% α-D-**1**-OH and converted to 3,5-dinitrobenzoate (**1**-ODNB), mp 120.5–121 °C, $[\alpha]^{24}_D$ 9.40° (*c* 7.9, $CHCl_3$).

1-D-Cyclohexanol, bp 154 °C (lit.[20] bp 159 °C), was prepared by reducing cyclohexanone with $LiAlD_4$ and converted to the 3,5-dinitrobenzoate, mp 112.5–113 °C (heptane) (lit.[24] mp 111–112 °C), in the usual manner. **2-D-Cyclohexanol,** bp 158 °C (lit.[20] bp 159–160 °C), resulted from the $LiAlD_4$ reduction of cyclohexene oxide.[20]

Quinuclidine (Aldrich) was used without further purification. 2,6-Lutidine, *N*-methylmorpholine, triethylamine, and diisopropylethylamine were obtained from commercial sources and purified by drying over KOH followed by fractional distillation from BaO. Allyldimethylamine, bp 58 °C (lit.[25] bp 61 °C), was obtained from the reaction of dimethylamine with allyl bromide in dry ether. *N*-Cyclohexylmorpholine, bp 104 °C (9.7 torr) [lit.[26] bp 119 °C (11 torr)] was prepared by reduction of *N*-cyclo-

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hexenylmorpholine hydrochloride[27] with $LiAlH_4$ at −78 °C.

Reagent grade acetone was purified by fractional distillation after being treated with $CaSO_4$ and $KMnO_4$ for 1 week. Conductivity water was obtained from a Millipore Super Q filtration system. The resistance of this water was at least 18 MΩ. Aqueous solvent compositions are based on volumes of pure liquids prior to mixing at ambient termperature.

Basicity of Amines. The titration curves for the neutralization of 0.1 M amine in aqueous acetone with 0.6 N 3,5-dinitrobenzoic acid in aqueous acetone were recorded with a Radiometer automatic titration apparatus. End points were set equal to the inflection point of the curve. The apparent pK_a is given by the apparent pH at the half-equivalency point.

Kinetic Experiments. A. Solvolysis of *p*-Nitrobenzoate and 3,5-Dinitrobenzoate Esters in Aqueous Acetone. Titrimetric rate constants (k_t) were determined by methods described earlier.[9] Reactions were followed to 75% completion by titration of 5-mL aliquots with 0.10 M sodium hydroxide with a Radiometer automatic titration apparatus. Acetone solutions of **1**-ODNB turn dark purple during titration obscuring a visual end point. This is presumable due to formation of a Meisenheimer complex.[28,29] Experimental infinity titers were taken at 10 half-lives and are essentially unchanged at 20 half-lives. Data for the titrimetric experiments are summarized in Table I.

B. Hydrolysis of Cyclohexyl 3,5-Dinitrobenzoate in the Presence of Basic Amines. A typical experiment was performed as follows. Ampules containing 10 mL of a solution of 0.05 M α-D-cyclohexyl 3,5-dinitrobenzoate, 0.055 M diisopropylethylamine, 0.005 M 3,5-dinitrobenzoic acid, and 0.02 M 2-D-cyclohexanol (internal standard) in 60% acetone were placed in a 72.5 °C thermostated bath.[29] A zero-point ampule was removed after thermal equilibration, then ampules were removed after 2, 6, and 12 h. Each ampule was worked up by saturating the reaction mixture with NaCl, extracting with pentane, and washing the combined organic layers successively with brine, saturated $NaHCO_3$, and brine. After drying ($MgSO_4$) and removing the solvent by distillation, product alcohol was vacuum transferred from unreacted ester. The ratio of 1-D-cyclohexanol (δ 3.36) to 2-D-cyclohexanol (δ 1.71) was obtained with ^2H NMR. An infinity value for the ratio was obtained by heating the above mixture of deuterated ester and internal standard with 0.10 M free amine for 6 days. By using this infinity value and the ratios at each point, concentrations of unreacted ester were calculated. The concentration of free amine at each point is the same as ester, so rate constants (k_2) were calculated using a simplified second-order rate law. Values obtained were: 2.46 L mol^{-1} h^{-1} (at 2.17 h), 2.06 (at 6.55 h), and 1.85 (at 11.95 h), which gives an average $k_2 = 2.1 \pm 0.3$ L mol^{-1} h^{-1}. The downward drift observed here was not seen in all cases but the scatter is typical.

Product Studies. A. Solvolysis of α- and γ-D-1-ODNB and 1-OPNB in Aqueous Acetone in the Presence of Amines. In a typical experiment 249 mg (1.0 mmol) of α-D-**1**-OPNB was weighed into a nitrogen-flushed ampule and 30 mL of 0.100 M triethylamine in 60% acetone was added.[29] The ampule was sealed leaving 20% headspace and placed in a 75.2 °C thermostat for 18 days and 8 h (10 half-lives). Product alcohol was isolated as for the saturated alcohol described earlier. The concentrated solution was used directly for ^2H NMR analysis. Proton-decoupled spectra give signals at δ 5.50 (γ-D-**1**-OH) and δ 3.80 (α-D-**1**-OH). Peak areas were determined by electronic integration. Application to samples of known composition demonstrated that this method has an uncertainty of ±3%. Results are presented in the text.

Product stability was checked by examining the deuterium label in α-D-**1**-OH which was present during solvolysis of unlabeled ester. Except as noted in Table III, the alcohol remained discretely labeled.

For examination of the prerandomization of allylic positions due to internal return, solutions of 735 mg (2.5 mmol) of α-D-**1**-ODNB in 50 mL of 60% aqueous acetone were sealed in ampules and placed in a 75.2 °C thermostat. They were removed and chilled after 6.25 h (1 half-life) and 12.4 h (2 half-lives). Unreacted ester was isolated by saturating the reaction mixture with NaCl, extracting with ether, washing the combined organic layers with saturated $NaHCO_3$ and brine, drying ($MgSO_4$), and removing the solvent. The resulting solid was dried in vacuo (0.4 torr, 100 °C) for 20 h to remove product alcohol **1**-OH. the ester was reduced with excess $LiAlH_4$ in dry THF and the resulting alcohol (**1**-OH) isolated by preparative GC (5 ft × 0.25 in. 5% carbowax 20 M on Chromosorb G). ^2H NMR showed 7% scrambling of label (i.e., 3.4% γ-D-**1**-OH) at 1 half-life and 32% at 2 half-lives. This gives a first-order rate constant ($k_{rand.}$) of (3.3 ± 1) × 10^{-4} min^{-1}.

B. Solvolysis of α- and γ-D-[*ether*-^{18}O]-1-ODNB and 1-OPNB in Aqueous Acetone in the Presence of Amines. These experiments were carried out in a manner similar to those described above for deuterium-labeled esters except on a three times larger scale in order to obtain sufficient alcohol for ^{18}O analysis. After concentration of the product extract, the alcohol was purified by preparative GC (10 ft × $^3/_8$ in. 20% UCON-LB-550-X on Chromosorb W). Analytical capillary GC (61 ft LAC-2R-446) of isolated alcohol showed >99% purity.

Deuterium distributions were determined as before and ^{18}O contents were determined by a modified Schütze–Unterzaucher method.[14] Four to five carbon dioxide samples were obtained for each organic sample and the mass spectral data (using a Nuclide RMS-6-60) from the last three samples was used to determine the atom % ^{18}O excess. Results are presented in Table II.

Oxygen equilibration experiments were conducted by using methods described earlier.[16] The purified **1**-OH resulting from reduction of **1**-OPNB with $LiAlH_4$ was analyzed directly for oxygen-18 contents. Control experiments demonstrated that the total oxygen-18 content of the ester remains constant during the reaction.

C. Solvolysis of Optically Active 1-ODNB in 60% Acetone. To ampules containing 731 mg (2.5 mmol) of optically active **1**-ODNB was added 50 mL of 0.075 M *N*-cyclohexylmorpholine in 60% acetone. The ampules were sealed and placed in a 75.2 °C thermostat for 6 solvolytic half-lives. Product alcohol was isolated and purified as described for the ^{18}O-labeled alcohols. The rotation of the isolated alcohol was $[\alpha]^{24}_{365}$ −3.37° (*c* 3.2, $CHCl_3$). Comparison with alcohol obtained from reduction of the starting ester with $LiAlH_4$, $[\alpha]^{24}_{365}$ 23.5° (*c* 0.6, $CHCl_3$), shows that the product alcohol has 14% inversion of optical configuration.

D. Examination of Product Stability and Acyl-Oxygen Hydrolysis for Weakly Basic Amines. A typical experiment was performed as follows: To ampules containing 148 mg (0.5 mmol) of α-D-cyclohexyl 3,5-dinitrobenzoate and 146 mg (0.5 mmol) of unlabeled **1**-ODNB was added 10 mL of 60% aqueous acetone which contained 0.02 M 2-D-cyclohexanol, 0.05 M γ-D-**1**-OH, and 0.075 M *N*-methylmorpholine. The ampules were sealed and placed in a 75.2 °C thermostat. Ampules were removed after thermal equilibration and then at 4, 10, and 20 solvolytic half-lives. Each ampule was worked up as described previously followed by vacuum transfer of the product alcohols from unreacted esters. Deuterium NMR was used to detect rearrangement of γ-D-**1**-OH, δ 5.50, to α-D-**1**-OH, δ 3.80 (product stability), and determine the amount, if any, of 1-D-cyclohexanol, δ 3.36 (acyl-oxygen hydrolysis), relative to 2-D-cyclohexanol (δ 1.71) (internal standard). All signals were fully resolved in the proton-decoupled spectrum.

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Registry No. **1**-OH, 822-67-3; (*R*)-(+)**1**-OH, 3413-44-3; (*S*)-(−)**1**-OH, 6426-26-2; **1**-OPNB, 38313-01-8; **1**-ODNB, 80642-11-1; (*R*)-(+)-**1**-ODNB, 80695-65-4; α-D-**1**-OPNB, 80642-12-2; α-D-**1**-ODNB, 80642-13-3; γ-D-**1**-ODNB, 80642-14-4; γ-D-**1**-OPNB, 80642-15-5; allyldimethylamine, 2155-94-4; *N*-cyclohexylmorpholine, 6425-41-8; 2,6-lutidine, 108-48-5; *N*-methylmorpholine, 109-02-4; diisopropylethylamine, 7087-68-5; triethylamine, 121-44-8.

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