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Stereochemistry of Allylic Rearrangements. XIV. Ion-Pair Return Associated with the Solvolysis of *cis*-5-Methyl-2-cyclohexenyl *p*-Nitrobenzoate in Aqueous Acetone[1]

BY HARLAN L. GOERING, JOYCE TAKAHASHI DOI, AND KIRK D. MCMICHAEL

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Solvolysis of *cis*-5-methyl-2-cyclohexenyl *p*-nitrobenzoate (IV) in 80% aqueous acetone is accompanied by ion-pair return which results in racemization of optically active IV (without geometric isomerization) and randomization of the carboxyl oxygen atoms (reactions 2 and 3). The rates of these two transformations in the unsolvolyzed ester are equal, which means that in the ion-pair intermediate (V) the allylic carbon atoms and also the carboxyl oxygen atoms are equivalent. Substrate reformed from an ion-pair system derived from optically pure ether-O^{18} IV has the carboxyl oxygen atoms randomized in each enantiomer. This shows that in V the two carboxylic oxygen atoms are equivalent with respect to each allylic carbon atom. Unlike with systems investigated earlier, an oxygen-18 kinetic isotope effect results in a detectable O^{18} enrichment in the ester during solvolysis.

Introduction

Ion-pair return associated with the solvolysis (alkyl–oxygen cleavage) of symmetrical allylic *p*-nitrobenzoates in aqueous acetone (eq. 1) results in racemization of optically active substrates (eq. 2)[2] and randomization of the carboxyl oxygen atoms of O^{18}-labeled esters (eq. 3).[3-5] In the several systems that have been investigated, all of these transformations are first order and the last two are intramolecular (*i.e.*, the *p*-nitrobenzoyl group remains associated with the same allyl group).

$$ROCOC_6H_4NO_2 \xrightarrow{k_t} ROH + HO_2CC_6H_4NO_2 \quad (1)$$

$$(d \text{ or } l)\text{-}ROCOC_6H_4NO_2 \xrightarrow{k_{rac}} dl\text{-}ROCOC_6H_4NO_2 \quad (2)$$

$$RO^{18}COC_6H_4NO_2 \xrightarrow{k_{eq}} RO^{18}CO^{18}C_6H_4NO_2 \quad (3)$$

In such systems the carbonium ion is symmetrical (the allylic carbon atoms are equivalent), and thus racemization corresponds to randomization of the allylic carbon atoms. If the counter ions in the ion pair are so arranged that the allylic carbon atoms in the cation and the oxygen atoms in the anion are equivalent, racemization and oxygen equilibration are independent measures of total ion pair return. To obtain information about the nature of ion pair intermediates and to determine if oxygen equilibration is a reliable measure of ion pair return, the relative rates of reactions 2 and 3 have been determined for several symmetrical allylic systems. The first-order rate constant for racemization (eq. 2) can be obtained from those for loss of optical activity (k_α) and solvolysis (k_t, eq. 1), *i.e.*, $k_{rac} = k_\alpha - k_t$.[2] Investigations of the *trans*-α,γ-dimethylallyl[3,5] and *trans*-5-methyl-2-cyclohexenyl[4] systems have been reported in earlier papers in this series. This paper describes the results of a similar investigation of ion pair return involved in the solvolysis of *cis*-5-methyl-2-cyclohexenyl *p*-nitrobenzoate (IV) in aqueous acetone.

In the case of α,γ-dimethylallyl *p*-nitrobenzoate, the rates of racemization (eq. 2) and oxygen equilibration (eq. 3) of the unsolvolyzed ester are equal in both 60%[5] and 90%[3] aqueous acetone.[6] This shows that in the ion pair intermediate, the allylic carbon atoms and also the carboxyl oxygen atoms are equivalent. In cases where $k_{eq} = k_{rac}$, information concerning the arrangement of the counter ions in the intermediate can be obtained by determining if, and to what extent, scrambling of carboxyl oxygen atoms occurs in the individual enantiomers as summarized by eq. 4.[3,5] This reaction can be followed using discretely labeled, optically pure ester and determining the distribution of the label in each enantiomer at various times. This amounts to using double labeling—optical activity labels the carbon atoms and an isotope is used to identify the oxygen atoms—and determining to what extent the oxygen and carbon atoms involved in the original carbon–oxygen bond remain associated.

$$\left.\begin{matrix}(+)\text{-}ROCO^{18}C_6H_4NO_2 \\ (-)\text{-}RO^{18}COC_6H_4NO_2\end{matrix}\right\} \xrightarrow{k_s} dl\text{-}RO^{18}CO^{18}C_6H_4NO_2 \quad (4)$$

The rate of reaction 4 relative to that of production of that fraction of the intermediate that returns (measured by k_{rac} and k_{eq}) distinguishes between the two limiting arrangements of the counter ions illustrated by I and II.[7] In each of these, the allylic carbon atoms and the carboxyl oxygen atoms are equivalent, and thus $k_{eq} = k_{rac}$. However, they differ as follows. In I the oxygen atoms and allylic carbon atoms are paired. If there is a tendency for a particular oxygen atom to remain associated with the nearest carbon atom (*i.e.*, the one to which it was bonded), k_s/k_{rac} will be less than unity—if the oxygen atoms bond exclusively with the nearest carbon atom the enantiomers remain discretely labeled, and k_s will be zero. On the other hand, if the oxygen atoms are equivalent with respect to each allylic carbon atom, as in II, the oxygen atoms will be completely scrambled in both

(1) (a) This work was supported by grants from the National Science Foundation (G19244), National Institutes of Health (GM08619), Upjohn Company, and Research Committee of the Graduate School with funds provided by the Wisconsin Alumni Research Foundation.

(2) H. L. Goering, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **21**, 109 (1960).

(3) H. L. Goering and M. M. Pombo, *J. Am. Chem. Soc.*, **82**, 2515 (1960).

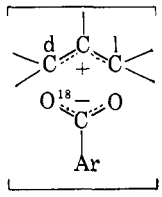
(4) H. L. Goering and J. T. Doi, *ibid.*, **82**, 5850 (1960).

(5) H. L. Goering, M. M. Pombo, and K. D. McMichael, *ibid.*, **85**, 965 (1963).

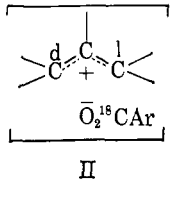
(6) These rates are 34 times faster in 60% acetone than in the less polar 90% acetone; the rate of ionization ($k_t + k_{rac}$) is 280 times faster in the more polar solvent (ref. 5).

(7) As has been pointed out (ref. 2–5), the cation and anion in I are not thought to be coplanar. Rather, presumably the carboxyl oxygen atoms and the allylic carbon atoms form a plane perpendicular to that of the cation.

enantiomers reformed by ion pair return and k_s will equal k_{rac}.[8]



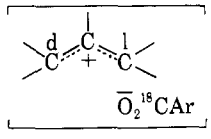
I



II

For solvolysis of *trans*-α,γ-dimethylallyl *p*-nitrobenzoate in 90% acetone at 100° k_s/k_{rac} = 0.34[3]; in 60% acetone at 60° k_s/k_{rac} = 0.42. This means the ions are arranged as in I—the oxygen atoms bond with the nearest carbon atom more rapidly than with the more remote one by factors of 4.9 and 3.8 in 90% and 60% acetone, respectively.

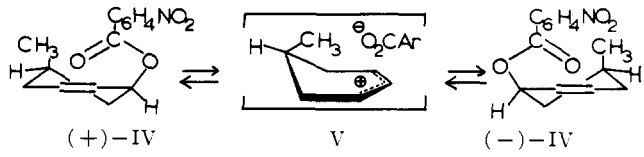
In the case of *trans*-5-methyl-2-cyclohexenyl *p*-nitrobenzoate, the unsolvolyzed ester undergoes oxygen equilibration at a rate about twice that of racemization, *i.e.*, k_{eq}/k_{rac} (and also k_s/k_{rac}) > 1.[4] Moreover, according to all of the usual criteria[9] (*e.g.*, intramolecularity, kinetics, and solvent effects), both tranformations result from ion pair return. This means that although a symmetrical carbonium ion is involved, some oxygen equilibration occurs without randomization of the two allylic carbon atoms. Thus, evidently an unsymmetrical ion pair (III) as well as a symmetrical one (I or II) is involved. It is return from the former that results in the "excess" oxygen equilibration.[10]



III

In the present work we have investigated the relative rates of reactions 1–4 for solvolysis of *cis*-5-methyl-2-cyclohexenyl *p*-nitrobenzoate (IV) in 80% aqueous acetone[11] at 100°. It had been shown earlier[4,12] that under these conditions solvolysis is accompanied by ion pair return, *i.e.*, $k_\alpha > k_t$.

For reasons outlined elsewhere[13] we feel that ionization of cyclohexenyl derivatives proceeds *via* the quasi-axial conformer as shown in the accompanying scheme for the racemization of IV.[14] According to this interpretation, the conformation of the cation and the relative location of the counter ion in the initially formed ion pair are as shown by V.



(+)−IV V (−)−IV

Results

The polarimetric (k_α) and titrimetric (k_t, eq. 1) first-order constants for solvolysis of *cis*-5-methyl-2-cyclohexenyl *p*-nitrobenzoate (IV) in 80% aqueous acetone[11] at 99.72° were determined by methods described earlier.[3-5,12] In each case, reactions were followed to about 80% completion and good first-order behavior was observed. Solvolysis of active IV resulted in complete loss of optical activity, and in the titrimetric experiments infinity titers after ten half-lives were within 1% of theory. Under these conditions k_α = 2.39 ± 0.04 × 10^{-2} hr.$^{-1}$ and k_t = 1.37 ± 0.04 × 10^{-2} hr.$^{-1}$ (these are average values of duplicate experiments). Thus k_{rac} (eq. 2), which corresponds to $k_\alpha - k_t$, is 1.02 ± 0.05 × 10^{-2} hr.$^{-1}$.[15] This value is within experimental error of that obtained earlier[12] (using the same method) and that calculated from the specific rotations of isolated samples of unsolvolyzed ester. A control experiment, that demonstrates solvolysis involves exclusive alkyl–oxygen cleavage under the present conditions, was reported previously.[12]

The rate of equilibration of the carboxyl oxygen atoms of the unsolvolyzed ester (eq. 3) was determined by the method described earlier[4] which involves starting with discretely labeled ester and determining the distribution of the label in the unsolvolyzed ester at appropriate times. In the present case, the ratio of ion pair return to solvolysis is rather low, k_{rac}/k_t = 0.75, and thus the unsolvolyzed ester only can be examined for a limited period. However, oxygen equilibration was followed to 59% completion. Data for this experiment are presented in Table I. This table includes the extent of solvolysis (calculated from k_t) at the time of isolation of the ester. Oxygen-18 contents were determined in triplicate; the average deviation from the mean is included with each value. Determining the distribution of the label in the carboxyl group involves saponification (exclusive acyl–oxygen cleavage)[4] followed by reconversion of the re-

TABLE I

KINETIC DATA FOR OXYGEN-18 EQUILIBRATION ASSOCIATED WITH THE SOLVOLYSIS OF *dl-cis*-5-METHYL-2-CYCLOHEXENYL *p*-NITROBENZOATE, CARBONYL-O^{18} (3.20 ± 0.03 ATOM % EXCESS), IN 80% ACETONE AT 99.72°

Time, hr.	Solvolysis,[a] %	Ether-O^{18} content[b]	Equilibration,[c] %	$10^2 k_{eq}$, hr.$^{-1}$
0	0	0	0	
22.8	27	0.30 ± 0.01	19	0.93
52.0	51	0.65 ± 0.02	41	1.01
92.2[d]	73	0.95 ± 0.02	59	0.98
			Av.	0.97 ± 0.03

[a] Calculated from k_t. [b] O^{18} content of the ether oxygen atom in unsolvolyzed ester. [c] Percentage of unsolvolyzed ester which has equal amounts of O^{18} at both positions, *i.e.*, amount equilibrated. [d] O^{18} content of unsolvolyzed ester was within experimental error of original value.

(8) If the oxygen atoms in I exchange places rapidly relative to reformation of substrate, I and II become equivalent.

(9) S. Winstein, P. E. Klinedinst, Jr., and E. Clippinger, *J. Am. Chem. Soc.*, **83**, 4986 (1961), and previous papers in the series.

(10) It was this observation that led to the discovery that oxygen equilibration is a useful method for measuring the rate of ion pair return (and thus ionization) in systems where return involves exclusive rebonding of the anion with the original carbon atom (ref. 21).

(11) Solvent composition is based on volumes of pure components (25°) prior to mixing.

(12) H. L. Goering and E. F. Silversmith, *J. Am. Chem. Soc.*, **77**, 6249 (1955).

(13) H. L. Goering and R. R. Josephson, *ibid.*, **84**, 2779 (1962).

(14) Absolute configurations of the optical isomers were determined in earlier work [H. L. Goering and E. V. Silversmith, *ibid.*, **77**, 5172 (1955)].

(15) The values reported earlier (ref. 12) for k_α and k_t are about 10% lower than those obtained in the present work. A small difference in solvent composition would result in a discrepancy of this magnitude. In the present work k_{rac} and k_{eq} were determined for the same batch of solvent.

sulting alcohol to the *p*-nitrobenzoate derivative. The latter contains the ether oxygen atom of the unsolvolyzed ester. All of the O^{18} contents in Table I (column 3) are for *p*-nitrobenzoate derivatives.

These data show that oxygen equilibration (eq. 3) as well as racemization (eq. 2) is first order and that within experimental error $k_{eq} = k_{rac}$. This means that in the intermediate, the allylic carbon atoms as well as the carboxyl oxygen atoms are equivalent as in I or II. Thus both k_{rac} and k_{eq} measure total ion pair return.

To determine if the ion pair intermediate corresponds to I (equivalent oxygen atoms associated with different allylic carbon atoms) or II (oxygen atoms equivalent with respect to each carbon atom), the rate of scrambling of the carboxyl oxygen atoms in the enantiomers (eq. 4) was investigated using a method[3,5] that involves starting with optically pure,[16] discretely labeled ester, isolating the unsolvolyzed ester at appropriate times, and determining the distribution of the label in each enantiomer of the partially racemic ester. In the present work optically pure (−)-*cis*-5-methyl-2-cyclohexenyl *p*-nitrobenzoate ((−)-IV, ether-O^{18}) was solvolyzed and the partially racemic unsolvolyzed ester (IV) was isolated and saponified (acyl–oxygen cleavage). The resulting *cis*-5-methyl-2-cyclohexenol was re-resolved as the acid phthalate derivative and the O^{18} contents of both enantiomers were determined. These isomers contain the same ether oxygen atom as the corresponding enantiomer in the unsolvolyzed ester. Since the total O^{18} content of the carboxyl group is known (O^{18} contents are measured for each sample of unsolvolyzed ester), the O^{18} abundance of the carbonyl oxygen atom can be obtained by difference.

Optically pure ether-O^{18} (−)-IV was prepared from optically pure (−)-*cis*-5-methyl-2-cyclohexenol-O^{18}, which in turn was prepared as follows. Optically active *cis*-5-methyl-2-cyclohexenyl acid phthalate, $[\alpha]^{25}D$ −62.2° ($CHCl_3$), was prepared as described earlier[17] and found to be 98 ± 2% optically pure by an isotope dilution method.[4] The acid phthalate was converted to optically pure alcohol (saponification),[17] which was oxidized to 5-methyl-2-cyclohexenone by a method (manganese dioxide) known[14] to preserve optical configuration. The O^{18} label was introduced at this point (without racemization) by acid-catalyzed equilibration of the ketone with O^{18}-enriched water.[13] Reduction of the optically pure O^{18}-labeled ketone with lithium aluminum hydride gave the expected[13,17] mixture of 93% *cis*-5-methyl-2-cyclohexenol and 7% of the *trans* isomer. Recrystallization of the *p*-nitrobenzoate derivative gave optically pure (−)-IV, ether-O^{18} (2.88 atom % excess). That this material was optically pure and discretely labeled was shown by the following experiments. Saponification gave (−)-*cis*-5-methyl-2-cyclohexenol-O^{18} which was converted to the acid phthalate and *p*-nitrobenzoate derivatives. The *p*-nitrobenzoate derivative had the original rotation and O^{18} content (2.91 atom % excess). The acid phthalate was optically pure and contained 2.82 atom % excess O^{18}.[18] This experiment demonstrates that saponification involves exclusive acyl–oxygen cleavage and that the preparation and purification of the *p*-nitrobenzoate derivative does not result in racemization or mixing of the carboxyl oxygen atoms.

In the experiment summarized in Table II a 0.05 molar solution of ether-O^{18} (−)-IV (2.88 atom % excess O^{18}) in 80% acetone[11] was distributed into two ampoules which were placed in a 99.61° thermostat. One ampoule was heated for 42 hr., after which time the remaining ester contained 3.03 atom % excess O^{18}. From k_t and k_{rac} it can be calculated that at this point 44% of the ester is solvolyzed and the remaining ester is 34% racemic (*i.e.*, 17% (+)-isomer; 83% (−)-isomer). The second ampoule was heated for 100 hr. which corresponds to 75% solvolysis and 63% racemization. In this case the O^{18} content of the recovered ester was 3.12 atom % excess. As will be shown below, the enrichment of label in the unsolvolyzed ester (from 2.88% at the outset to 3.12% at 75% solvolysis)[19] results from a kinetic isotope effect. In all cases the samples of recovered ester were found to be configurationally homogeneous (infrared analysis). This confirms earlier reports[4,12] that ion pair return does not result in detectable geometric isomerization. Optical purities of the isolated samples of unsolvolyzed ester were in excellent agreement with the amount of racemization calculated from k_{rac}.

TABLE II

OXYGEN-18 DATA FOR ION-PAIR RETURN DURING SOLVOLYSIS OF (−)-*cis*-5-METHYL-2-CYCLOHEXENYL *p*-NITROBENZOATE, ETHER-O^{18}, IN 80% ACETONE AT 99.61°[a]

Acid phthalate	Optical purity, %[b]	O^{18} content[c] Obsd.[d]	Pure isomer[e]	Corrected[f]
	A. Sample isolated after 42 hr. (3.03 atom % excess O^{18})			
(−)	100	2.71	2.71	1.46
(+)	−6[g]	2.18	1.57	1.57
	B. Sample isolated after 100 hr. (3.12 atom % excess O^{18})			
(−)	94	2.41	2.44	1.63
(+)	17	1.87	1.47	1.47

[a] Original O^{18} content, 2.88 atom % excess. [b] Optical purity of (+)- and (−)-acid phthalate obtained by resolution of alcohol derived from unsolvolyzed ester. [c] All values are atom % excess O^{18}. [d] Observed O^{18} contents of enantiomeric acid phthalates from resolution. [e] Calculated O^{18} contents of optically pure enantiomeric acid phthalates. [f] O^{18} contents of that fraction of enantiomers reformed by ion pair return. [g] This sample contained 53% (−)-isomer and 47% (+)-isomer, *i.e.*, 6% optically pure (−)-isomer.

Each sample of partially racemic unsolvolyzed ester (IV) was converted to the acid phthalate derivative which was resolved and the O^{18} contents were determined for each enantiomer. The optical purities of the (+)- and (−)-acid phthalates obtained from these resolutions and the O^{18} contents of these samples are given in the second and third column of Table II. These data provide two linear equations which can be solved for the O^{18} contents of the pure enantiomers.[3,5] These values are shown in the fourth column. From

(16) Optical purity is required so that the allylic carbon atoms as well as the carboxyl oxygen atoms are discretely labeled.

(17) H. L. Goering and J. P. Blanchard, *J. Am. Chem. Soc.*, **76**, 5405 (1954).

(18) Discrepancies in O^{18} contents of acid phthalate and *p*-nitrobenzoate derivatives of the same labeled alcohol have been noted before (ref. 5). For this reason it is desirable to use the same derivative when comparing relative O^{18} contents.

(19) These values are atom % excess O^{18} determinations for the *p*-nitrobenzoate derivative (see footnote 18).

these, and the total carboxyl O^{18} content of the isolated IV, the distribution of the isotope in each enantiomer can be determined.

The O^{18} contents shown in column 4 of Table II are for the ether oxygen atom of the pure enantiomers at the time of isolation of the unsolvolyzed ester (IV). All of the (+)-isomer has been formed by ion pair return and in this case the observed O^{18} content (column 4) corresponds to that of the ether oxygen atom of (+)-IV formed by ion pair return. The same is not true for the (−)-isomer because racemization is not complete; the recovered ester contained excess (unreacted) (−)-isomer which still has the original labeling. To obtain the ether-O^{18} content of the fraction of (−)-isomer reformed by ion pair return, the value in column 4 must be corrected for contamination by unreacted discretely labeled (−)-III. This is done as illustrated for the sample isolated at 42 hr. (34% racemization). At this point the composition of unsolvolyzed IV is 17% (+)-isomer and 83% (−)-isomer. Only 17/83 of the (−)-isomer has been reformed by ion pair return. The rest, 66/83, is unreacted starting material and still labeled exclusively in the ether position. Thus the ether-O^{18} content of that fraction of (−)-isomer reformed by ion pair return is (83/17)[2.71–3.03 (66/83)]. The ether-O^{18} contents of the enantiomers produced by ion pair return are shown in the last column of Table II. As has been pointed out,[3,5] for cases where $k_{rac} = k_{eq}$, the sums of these values should equal the total O^{18} content of the carboxyl group of the unsolvolyzed ester. It will be noted that for both examples, these sums are in good agreement with the measured O^{18} contents. Thus the data are internally consistent.

It was shown earlier[3,5] how the first-order rate constant for scrambling of carboxyl oxygen atoms in the enantiomers (k_s, eq. 4) can be calculated from the enantiomeric composition of the ester at the time of isolation and the data in Table II. However, in the present case there is no need to do this because the last column in the table shows that within experimental error, the carboxyl oxygen atoms are completely randomized in the individual enantiomers produced by ion pair return. From this it is apparent that $k_s = k_{eq} = k_{rac}$. Thus, all three correspond to the rate of production of that fraction of the intermediate that returns.[20] Or in other words, substrate reformed by ion pair return is not only completely racemic (eq. 2) and oxygen equilibrated (eq. 3), but also the oxygen atoms are completely equilibrated in each enantiomer (eq. 4). This shows that the arrangement of the ions in V correspond to II rather than I, *i.e.*, the carboxyl oxygen atoms are equivalent with respect to each allylic carbon atom.

Unlike with other systems that have been investigated,[5,21] solvolysis of IV, ether-O^{18}, results in detectable enrichment of the label in the unsolvolyzed ester. To investigate this point further, *dl*-IV, ether-O^{18} (4.29 atom % excess O^{18}), was prepared from 5-methyl-2-cyclohexenone by the sequence outlined above for the preparation of optically active O^{18}-labeled IV. This material was solvolyzed under the conditions used in the other kinetic experiments and the O^{18} content of the unsolvolyzed ester was determined for various times up to 92% solvolysis. These data, which are presented in Table III (part B) together with those for the oxygen equilibration studies (part A), clearly confirm that the kinetic isotope effect is sufficient to result in detectable isotopic fractionation. The O^{18} contents in Table III are total % oxygen-18 rather than atom % excess oxygen-18.

TABLE III

DATA FOR ISOTOPIC FRACTIONATION ASSOCIATED WITH SOLVOLYSIS OF *cis*-5-METHYL-2-CYCLOHEXENYL *p*-NITROBENZOATE, ETHER-O^{18}, IN 80% AQUEOUS ACETONE AT 99.61°

Time, hr.[b]	O^{18} content[a] Total[c]	Ether[d]	k_t/k_{O18}[e]
	A. (+)-IV		
0	3.08	3.08	
42	3.23	2.71[f]	1.10 ± 0.03
100	3.32	2.32[f]	1.08 ± 0.01
	B. *dl*-IV		
0	4.49	4.49	
28	4.60	4.08	1.08 ± 0.03
66	4.72	3.65	1.08 ± 0.01
115.1	4.87	3.28	1.07 ± 0.01
187.5	4.96	2.92	1.04 ± 0.02
		Av.	1.08 ± 0.02

[a] Total % O^{18}, *i.e.*, atom % excess plus natural abundance (0.20%). [b] Time at which samples of unsolvolyzed ester were isolated. [c] Per cent O^{18} in isolated ester. [d] Per cent O^{18} in ether position, calculated from eq. 5 and $k_{eq} = 0.96 \times 10^{-2}$ hr.$^{-1}$. [e] Calculated from values in column 3 and eq. 12; uncertainties evaluated from limiting values of R_{ac} and R_{af}. [f] Ether-O^{18} contents calculated from data in Table II in close agreement with these values.

The magnitude of the isotope effect for solvolysis $(k_t/k_{O^{18}})$[22] can be determined from the rate of isotopic fractionation relative to solvolysis.[23] It is apparent that the precision will be rather poor because the uncertainty in the isotopic contents are about 6 to 8% of the total change. An added complication is that the isotope is equilibrated between the two carboxyl positions during solvolysis. Since solvolysis involves alkyl–oxygen cleavage, presumably the labeled ester reacts slower than unlabeled ester only if the oxygen-18 is in the ether position. This means that the apparent isotope effect (reflected by isotopic fractionation) for solvolysis of ether-O^{18} IV will be progressively attenuated as the label is equilibrated between the two positions. It can be seen that isotopic fractionation will be substantially greater for solvolysis of ether-O^{18} IV than for solvolysis of carbonyl-O^{18} IV because the average fraction of the isotope in the ether position during solvolysis is much lower in the latter case. From k_{eq} it can be shown that for solvolysis of ether-labeled IV, the fraction of oxygen-18 in the ether position drops from 100% at the outset to 70% at two half-lives. In the case of carbonyl-labeled IV, the fraction of label at the ether position changes from 0 to 30% during two half-lives. For this period, the average fraction of oxygen-18 in the ether position

(20) The value of k_s calculated by the method outlined in ref. 3 is 0.96 ± 0.06 × 10^{-2} hr.$^{-1}$.

(21) (a) H. L. Goering and J. F. Levy, *J. Am. Chem. Soc.*, **84**, 3853 (1962), and H. L. Goering, R. G. Briody, and J. F. Levy, *ibid.*, **85**, 3039 (1963); (b) H. L. Goering and J. F. Levy, *ibid.*, **86**, 120 (1964).

(22) This ratio is equivalent to k_{O16}/k_{O18}. Since the isotope is present in tracer amounts, the observed titrimetric constant (k_t) is indistinguishable from that of O^{18}-free substrate (k_{O16}).

(23) J. Bigeleisen and M. Wolfsberg, "Advances in Chemical Physics," Vol. 1, I. Prigogine, Ed., Interscience Publishers, Inc., New York, N. Y., 1958, p. 15.

is about five times larger when starting with ether-labeled ester than when starting with carbonyl-labeled ester. This accounts for the absence of detectable fractionation in the oxygen-equilibration experiment summarized in Table I.

To determine the kinetic isotope effect ($k_t/k_{O^{18}}$) from the amount of fractionation at various stages of reaction the usual relationship[23] must be modified to correct for the varying distribution of the isotope between the effective ether position and ineffective carbonyl position. This can be done because the amounts of ether-O^{18} ester (A^*) and carbonyl-O^{18} ester (B) is a known function of time.

$$k_{eq}t = \ln [(A^* + B)/(A^* - B)] \quad (5)$$

The differential equation for disappearance of ether-O^{18} IV (A^*) is

$$-dA^*/dt = k_{O^{18}}(A^*) + {}^1/_2k_{eq}(A^*) - {}^1/_2k_{eq}(B) \quad (6)$$

The corresponding rate law for disappearance of unlabeled ester (A) is

$$-dA/dt = k_t(A) \quad (7)$$

since the isotope is present in small amounts[22] and the conversion of A^* to B is unimportant. The problem now involves simultaneous solution of this set of differential equations.

Equation 6 may be rearranged to give

$$-d \ln A^*/dt = k_{O^{18}} + {}^1/_2k_{eq}(A^* - B)/A^* \quad (8)$$

Rearrangement of 5 to

$$(A^* - B)A^* = 2/(e^{k_{eq}t} + 1) \quad (9)$$

followed by combination of 8 and 9 yields

$$-d \ln A^*/dt = k_{O^{18}} + k_{eq}/(e^{k_{eq}t} + 1) \quad (10)$$

Simultaneous solution of eq. 7 and 10 with the boundary conditions, $A^* = A^*_0$, $B = 0$, and $A = A_0$ at zero time, gives

$$\left(\frac{k_{O^{18}}}{k_t} - 1\right) = \frac{\ln (R_{ao}/R_{af}) + \ln [(e^{-k_{eq}t} + 1)/2]}{\ln (A_0/A)} \quad (11)$$

where R_{ao} is the initial ratio of labeled to unlabeled ester (A_o^*/A_o) and R_{af} is the ratio (A^*/A) at time t. The last term in the numerator in eq. 11 corrects for the redistribution of the isotope during solvolysis. If $k_{eq} = 0$, this term vanishes and the equation reduces to that derived in ref. 23 for uncomplicated isotopic fractionation. For tracer amounts of oxygen-18, $\ln (A_0/A) = k_tt$ because the effect of small amounts of labeled ester (A^*) on the over-all rate of solvolysis is negligible.[22] Thus eq. 11 becomes

$$\left(\frac{k_{O^{18}}}{k_t}\right) - 1 = \frac{\ln (R_{ao}/R_{af}) + \ln [(e^{-k_{eq}t} + 1)/2]}{k_tt} \quad (12)$$

Values of $k_t/k_{O^{18}}$ calculated from this relationship and the data in Table III are included in the table. The observed value (1.08) is about half of the maximum theoretical value (1.19)[23] for the case where the carbon–oxygen stretching vibration is converted completely to translational motion in the transition state. An isotope effect of similar magnitude (1.06) has been observed[24] for a reaction of hydrogen peroxide in which the oxygen–oxygen bond is broken. It appears that this is the first report of an oxygen-18 kinetic isotope effect for a solvolytic reaction involving heterolysis of a carbon–oxygen bond.

Discussion

The data in Table II show that for solvolysis of *cis*-5-methyl-2-cyclohexenyl *p*-nitrobenzoate (IV) $k_s = k_{eq} = k_{rac}$. This indicates, beyond reasonable doubt, that reactions 2–4 are independent measures of total ion pair return. Or to put it another way, in the intermediate (V) the carboxyl oxygen atoms are equivalent with respect to each allylic carbon atom (as in II). Thus reactions 2–4 simply correspond to production of that fraction of intermediate that returns.

This is a very important result in connection with the use of oxygen equilibration (eq. 3) as a measure of ion pair return in systems where the anion returns to the original carbon atom (*e.g.*, benzhydryl[21] and α-phenylethyl[25] systems). In the intermediate derived from IV there is a 50% chance that the anion will rebond with the original carbon atom (k_{rac} measures total return) and the fact that $k_s = k_{rac}$ shows that the carboxyl oxygen atoms are completely randomized even for return to the original carbon atom.

For solvolysis of *trans*-5-methyl-2-cyclohexenyl[4] and *exo*(axial)bicyclo[3.2.1]oct-3-en-2-yl[26] *p*-nitrobenzoates, $k_{eq} > k_{rac}$. In these symmetrical allylic systems there is excess return (with equilibration) to the original carbon atom. Although it cannot be established that ion pair return results in complete equilibration (an independent measure of ion pair return required to do this is lacking) there is no reason to suspect that this is not the case. Thus presumably in these cases, the ions are arranged as in III.

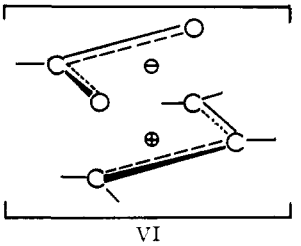
The *trans*-α,γ-dimethylallyl system is the only one that we have investigated in which ion pair return does not result in complete randomization of the oxygen atoms in each enantiomer, *i.e.*, $k_{eq} = k_{rac} > k_s$. This means that return to the original carbon atom (enantiomer) does not result in complete oxygen equilibration—in this case the ions are arranged as in I, and the oxygen atoms bond preferentially with the nearer carbon atom. However, even here there is considerable mixing of oxygen atoms in the enantiomers.

These results show that even in allylic systems, where arrangement I is possible, return to the original carbon atom (enantiomer) results in substantial oxygen equilibration in one case and complete equilibration in three others. This then suggests that for nonallylic systems, where arrangement I is precluded, oxygen equilibration corresponds to total ion pair return[21] (regardless of variety[21b]). In fact, it is interesting to note that for two symmetrical allylic systems[4,26] $k_{eq} > k_{rac}$ which suggests that k_{eq} is a more reliable measure of ion pair return than randomization of carbon atoms in symmetrical carbonium ion systems. This is particularly significant because there are no

(24) A. E. Cahill and H. Taube, *J. Am. Chem. Soc.*, **74**, 2312 (1952).
(25) Unpublished work by R. G. Briody and J. F. Levy.
(26) Unpublished work by R. Anderson.

other methods for measuring total ion pair return in "nonrearranging" systems.

The reason for the different behavior for the *trans*-α,γ-dimethylallyl system (intermediate corresponds to I)[3,5] and the isomeric 5-methyl-2-cyclohexenyl systems (intermediate corresponds to II for *cis* isomer and III for *trans*[4] isomer) is not clear. A possible explanation is that for the oxygen atoms and carbon atoms to be paired as in I requires the parallel *exo* orientation of the ions shown by VI. This orientation corresponds to the favored one for the Cope rearrangement.[27] And in fact, the interconversion of enantiomers without scrambling of oxygen atoms in the enantiomers (*i.e.*, in cases where $k_{rac} = k_{eq} > k_s$) is analogous to the Cope rearrangement. The major difference between the two is a matter of timing of bond rupture and formation. For the Cope rearrangement, bond breaking and bond formation are presumably synchronized, whereas in the allylic ester bond breaking to give an ion pair precedes bond formation (ion pair return) to give rearrangement product.



VI

The parallel *exo* orientation (VI) is possible for the acyclic system but presumably not for the cyclic systems. Evidence has been presented[13] that in cyclohexenyl systems quasi-axial bond breaking (and formation) is stereoelectronically favored over quasi-equatorial bond breaking (and formation)—it has been estimated that the transition state for the former may be favored by as much as 2 to 3 kcal./mole. This means that in the transition state for ionization the partially bonded leaving (or entering) group will be on the same side of the ring as the out-of-plane C-5. Thus, the conformation of the cation with respect to the location of the anion will be that shown in V for the *cis*-5-methyl-2-cyclohexenyl system (IV). This same arrangement is favored for return (microscopic reversibility). If this interpretation is correct it is clear from V that the parallel *exo* arrangement is precluded for cyclohexenyl systems. According to this idea, if arrangement VI is sterically possible, as in the α,γ-dimethyl allyl system, this is the favored arrangement and $k_s \leqq k_{eq} = k_{rac}$. On the other hand, if VI is sterically precluded, $k_s = k_{eq} \geqq k_{rac}$. The reason for the different behavior of the isomeric 5-methyl-2-cyclohexenyl systems ($k_{rac} = k_s$ for the *cis* isomer and $k_{rac} < k_s$ for the *trans* isomer) is not known.

In connection with the isotopic fractionation associated with the solvolysis of IV, it is interesting to note that ether-O^{18} benzhydryl[21] and α,γ-dimethylallyl *p*-nitrobenzoate[5] have been examined with the same care as IV, and no fractionation was detected. The greater isotope effect for IV than for α,γ-dimethylallyl *p*-nitrobenzoate as well as the different behavior of the ion pair systems indicates fundamental differences (*e.g.*, configuration) in the transition states for ionization.

(27) W. von E. Doering and W. R. Roth, *Tetrahedron*, **18**, 67 (1962).

Experimental

Materials.—*dl-cis*-5-Methyl-2-cyclohexenyl *p*-nitrobenzoate (IV), m.p. 93.2–93.9°, for the titrimetric experiments and (−)-IV, $[\alpha]^{25}D$ −94° ($CHCl_3$), for the polarimetric experiments were prepared as described earlier.[17] Carbonyl-O^{18} IV (3.20 atom % excess O^{18}) for the oxygen equilibration experiment (Table I) was prepared in the usual manner from pure *dl-cis*-5-methyl-2-cyclohexenol[17] and *p*-nitrobenzoyl chloride, carbonyl-O^{18}.[3]

Optically pure (−)-*cis*-5-methyl-2-cyclohexenyl *p*-nitrobenzoate, ether-O^{18}, for the oxygen scrambling experiment (Table II) was prepared as follows Thirty-four grams of (−)-*cis*-5-methyl-2-cyclohexenyl acid phthalate, $[\alpha]^{25}D$ −62.2° (*c* 0.8, $CHCl_3$),[17] was saponified by steam distillation of a solution of the acid phthalate in 210 ml. of 2.4 *M* sodium hydroxide. Ether extraction of the distillate gave a solution of (−)-*cis*-5-methyl-2-cyclohexenol (shown to be configurationally homogeneous by gas chromatography). The ethereal solution was stirred with 80 g. of freshly prepared manganese dioxide[28] for 26 hr., after which time another portion (40 g.) of manganese dioxide was added. The progress of the oxidation of (−)-*cis* alcohol to (+)-5-methyl-2-cyclohexenone[14] was followed by gas chromatography. After 48 hr. the reaction was complete and the ether solution was separated from the manganese dioxide (filtration), dried ($MgSO_4$), and treated with 9.5 ml. (0.54 mole) of O^{18}-enriched water (6.45 atom % excess O^{18}) and 0.25 g. of *p*-toluenesulfonic acid. The resulting mixture was stirred for 71 hr., after which the ether layer was separated and dried ($CaSO_4$). The resulting ethereal solution of (+) O^{18}-labeled ketone was reduced[17] with 5 g. of lithium aluminum hydride in 250 ml. of dry ether, and the mixture of (−)-*cis*- and (+)-*trans*-5-methyl-2-cyclohexenols[14] (93% *cis* isomer) was treated with 26 g. of pure *p*-nitrobenzoyl chloride in 75 ml. of dry pyridine.[17] Recrystallization of the resulting *p*-nitrobenzoate derivative three times from petroleum ether (b.p. 90–100°) gave (−)-IV, ether-O^{18}, m.p. 81.7–83.2°, $[\alpha]^{25}D$ −92.5° (*c* 1, $CHCl_3$) (3.78 atom % excess O^{18}). This material was combined with unlabeled (−)-IV, m.p. 84.4–85.3°, $[\alpha]^{25}D$ −96.4° ($CHCl_3$). Two recrystallizations from petroleum ether gave (−)-IV, ether-O^{18}, m.p. 85.1–86°, $[\alpha]^{25}D$ −95.4° ($CHCl_3$) (2.88 atom % excess O^{18}). This material was used in the oxygen scrambling experiment (Table II) and was shown to be of the same optical purity as an acid phthalate derivative with $[\alpha]^{25}D$ −62.2°. The latter corresponds to 98 ± 2% optically pure (see final experiment).

The *dl*-IV, ether-O^{18}, m.p. 92.8–93.7° (4.29 atom % excess O^{18}), used for investigation of isotopic fractionation during solvolysis (Table III) was prepared from *dl*-5-methyl-2-cyclohexenone in the same way.

Kinetic Experiments.—The polarimetric and titrimetric solvolytic rate constants were determined by methods described earlier.[12] In the polarimetric experiments, the change in rotation was over 2.5° and individual measurements were reproducible to well within 0.01°. For the titrimetric experiments, the reaction was followed by titration of 5 ml. of aliquots with 0.0378 *M* aqueous sodium hydroxide to the bromthymol blue end point.

Determination of O^{18} Equilibration and Scrambling.—All O^{18} analyses[3] were determined in triplicate and the average deviation from the mean was less than 1%. Samples used for O^{18} determinations were shown to be pure by their physical properties including infrared spectra. In all cases initial substrate concentration was 0.05 molar.

The rate of O^{16} equilibration (eq. 3) was determined by methods described earlier.[4,5] These data are given in Table I.

Scrambling of carboxyl oxygen atoms in the enantiomers (reaction 4) also was investigated by methods described earlier.[3,5] The data for this experiment are given in Table II.

Isotopic Fractionation during Solvolysis.—In the O^{18} scrambling experiment (Table II) the O^{18} content of the unsolvolyzed ester increased from 3.08% O^{18} at the outset to 3.32% at 75% solvolysis (100 hr.).[29] The following experiment was carried out to confirm the apparent isotopic fraction. A 0.049 *M* solution of *dl*-IV, ether-O^{16} (4.49% O^{18}),[29] was distributed into large heavy-walled ampoules and sealed under nitrogen. The sealed ampoules were placed in a thermostat for the periods indicated in part B of Table III. Samples were isolated, purified, and analyzed for oxygen-18 in the usual manner.[3-5] In all cases, including the point at 92% solvolysis (187.5 hr.)—at this point 85% of the remain-

(28) S. Ball, T. W. Goodwin, and R. A. Morton, *Biochem. J.*, **42**, 516 (1948).

(29) For this experiment all O^{18} contents are total % O^{18}, *i.e.*, atom % excess O^{18} plus natural abundance (0.20%).

ing ester has been reformed by ion pair return—the samples were configurationally homogeneous. Oxygen-18 contents for various times are shown in the second column of Table III[29] and values of the isotope effect ($k_t/k_{O^{18}}$), calculated from these data (eq. 12), are given in the last column.

Determination of Optical Purity of (−)-*cis*-5-Methyl-2-cyclohexenyl Acid Phthalate.—*dl-cis*-5-Methyl-2-cyclohexenyl acid phthalate 7-C^{14}, was prepared from pure *cis* alcohol and phthalic anhydride, 7-C^{14} (Tracerlab, Inc.). After purification by recrystallization, this material gave a correct carbon and hydrogen analysis, melted at 75.3–77°, and had 93,750 ± 900 d.p.m.[30]

A mixture of 0.8837 g. of (−)-acid phthalate, $[\alpha]^{25}D$ −61.8° ($CHCl_3$), lit.[17] −62.2°, and 0.4444 g. of radioactive *dl*-acid phthalate was dissolved in acetone and re-resolved as the cinchonidine salt in the usual manner.[12,17] The resulting (−)-acid phthalate, 7-C^{14}, had $[\alpha]^{25}D$ −60.00° ($CHCl_3$), 20,890 ± 200 d.p.m.[30] From these data it can be shown that optically pure acid phthalate has $[\alpha]^{25}D$ 63.4 ± 1.5°. Thus (−)-acid phthalate, $[\alpha]^{25}D$ −62.2° ($CHCl_3$), as well as the corresponding (−)-IV, ether-O^{18}, $[\alpha]^{25}D$ −95.4° ($CHCl_3$), are 98 ± 2% optically pure.

(30) This value is per millimole of compound and has been corrected for background and efficiency of counting. These measurements were made as described earlier (ref. 4).

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE UNIVERSITY, EAST LANSING, MICH.]

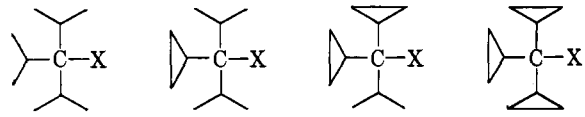
The Solvolysis of Tricyclopropylcarbinyl Benzoate[1]

BY HAROLD HART AND PAUL A. LAW

RECEIVED JANUARY 8, 1964

Tricyclopropylcarbinyl benzoate was found to solvolyze 10^3 times faster than dicyclopropylisopropylcarbinyl benzoate in 95% aqueous dioxane at 25°. The sole products were tricyclopropylcarbinol and benzoic acid; in methanol, the product was tricyclopropylcarbinyl methyl ether. Tricyclopropylcarbinyl derivatives solvolyze more than 10^7 times faster than triisopropylcarbinyl compounds, and probably appreciably faster than triphenylcarbinyl compounds, indicating that all three cyclopropyl groups are remarkably effective in delocalizing the charge in the tricyclopropylcarbonium ion.

It is well known that a cyclopropyl group is uncommonly efficient at delocalizing a positive charge generated on an adjacent carbon atom, though the mechanism is still a subject of debate and experiment.[2] In an earlier paper[3] it was shown that two cyclopropyl groups are nearly twice as effective as one at stabilizing an adjacent positive charge. The relative solvolysis rates of I, II, and III (X = *p*-nitrobenzoate, PNB) in 80%



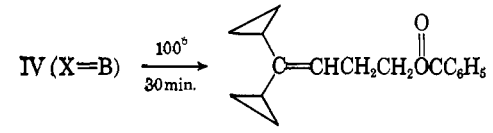
I II III IV

aqueous dioxane at 60° were 1:246:23,500. Unfortunately, efforts to extend the study to include a third cyclopropyl group were thwarted then by our inability to synthesize tricyclopropylcarbinyl *p*-nitrobenzoate (IV, X = PNB).[4]

We have now synthesized tricyclopropylcarbinyl benzoate (IV, X = benzoate, B) and found that it solvolyzes with alkyl–oxygen fission.[5] To relate it to the previous[3] series, III (X = B) was also prepared and solvolyzed.

Results and Discussion

Preparation and Stability of the Esters.—Tricyclopropylcarbinyl benzoate (IX, X = B) was prepared in nearly quantitative yield by reaction of benzoyl chloride with the potassium salt of tricyclopropylcarbinol in pentane.[6] Attempts to distil or chromatograph the ester caused its decomposition or rearrangement. Elemental analysis was not possible (or indeed, in view of the facile thermal rearrangement, meaningful) but the ester gave a satisfactory saponification equivalent, and the infrared and n.m.r. spectra, as well as the solvolysis products, clearly substantiate the assigned structure. Particularly, the n.m.r. spectrum of freshly prepared ester showed no vinyl protons, but twelve cyclopropane methylene, three methine, and five aromatic protons. Ester which was kept at room temperature for a few hours, however, soon developed several new n.m.r. bands; the rearrangement to 4,4-dicyclopropylbut-3-en-1-yl benzoate (V) was complete in 30 min. at 100°. The structure of V follows from its



V

elemental analysis, infrared, and n.m.r. spectra (the latter included a triplet at 4.95 τ, one vinyl proton, a triplet at 5.8 τ, two ether protons, and a quartet centered at 7.47 τ, two allylic protons, all with J = 8.0 c.p.s., in addition to other expected bands). This rearrangement probably involves the formation of a tricyclopropylcarbonium benzoate ion pair, but the extent to which the two oxygens become equivalent during the process is not yet known. In kinetic experiments on the solvolysis of IV (X = B), either freshly prepared samples free of V were used, or the amount of V present (determined by titration) was corrected for. Independent experiments showed that V solvolyzed at a negligible

(1) We are grateful to the Petroleum Research Fund of the American Chemical Society and to the National Science Foundation for grants which contributed to the financial support of this research.

(2) For leading references, see *Annual Reports*, 208 (1962); also, R. Breslow in P. de Mayo, "Molecular Rearrangements," Interscience Publishers, Inc., New York, N. Y., 1963, pp. 259–273.

(3) H. Hart and J. M. Sandri, *J. Am. Chem. Soc.*, **81**, 320 (1959).

(4) This is perhaps understandable, when one considers the rates at which these esters hydrolyze. The half-life of III (X = PNB) in 80% aqueous dioxane at 25° is 8.67 min.; extrapolation of the data reported in the present paper to IV (X = PNB), if it could be prepared, predicts a half-life of 0.5 sec. under similar conditions.

(5) For a preliminary account of these results, see H. Hart and P. A. Law, *J. Am. Chem. Soc.*, **84**, 2462 (1962).

(6) This procedure and many variants thereof were entirely ineffective in attempts to prepare the *p*-nitrobenzoate. The crude product from such attempts showed no nitro absorption in the infrared, so presumably reactions of the nitro group with strong base gave side reactions which prevented synthesis of the desired ester.