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SECONDARY TRITIUM ISOTOPE EFFECTS, A USEFUL MECHANISTIC PROBE FOR THE STUDY OF ACETOXYL PARTICIPATION AND TRANSFER

Saul Wolfe*
Department of Chemistry, Queen's University, Kingston, Ontario, Canada K7L 3N6
and
Peter G.C. Campbell*
Institut national de la recherche scientifique (INRS-EAU), Université du Québec,
Case postale 7500, Sainte-Foy, Québec, Canada G1V 4C7

Summary: Tritium labelling on the acetoxyl methyl group has been used to probe the mode of incorporation of acetate into cinnamyl acetate in the solvolyses of cinnamyl chloride and cinnamylmercuric acetate, and in the allylic oxidation of allylbenzene with mercuric acetate.

The formation of the acetoxonium ion 1 from 2 is expected to proceed at different rates for X = ^1H and X = ^3H (1). However, the direction and magnitude of the isotope effect are difficult to predict because, in a transition state with partial development of cationic character at the carbonyl carbon, the different inductive effects of ^1H and ^3H should lead to rate enhancement by tritium, whereas the different hyperconjugative effects should result in rate retardation by tritium (1). We have now determined that $k_H/k_T < 1$ for the solvolysis of 2, labelled with tritium in the methyl group. *Trans*-2-acetoxycyclohexyl tosylate (specific activity 651.4 ± 1.5 DPM/mg (2)) was dissolved in preheated (100°) anhydrous acetic acid to form a 0.1 M solution, which was maintained at 100° for 19.0 min, corresponding (3) to 19.5% of reaction, and then cooled rapidly to -78°. The recovered tosylate was recrystallized to a constant specific activity of 647.8 ± 1.4 DPM/mg. The 0.56% decrease in the tritium content corresponds (4) to $k_H/k_T = 0.976 \pm 0.018$.

This small, but observable, isotope effect constituted the experimental precedent for a proposed examination of secondary tritium isotope effects as a novel and subtle mechanistic probe in some solvolytic and oxidative processes in which acetoxyl group participation or migration may occur. The reactions of particular interest in the present work are summarized by eq [1] - [3], and are performed in anhydrous acetic acid solvent. Reaction [1] proceeds at room temperature to give a 37:63 mixture of 4 and 5 (5), a finding reproduced in the present work. At 75°, reactions [2] and [3] also lead to *ca* 40:60 mixtures of 4 and 5 in the product of kinetic control (6), and it has been proposed (6, 7) that allylic oxidation of allylbenzene by mercuric acetate in anhydrous acetic acid proceeds via a rate-determining formation of the allylorganomercurial 6, followed by a product-determining solvolysis of the latter compound. This proposal is consistent with kinetic studies of both the oxidation of allylbenzene and the solvolysis of 6. Whether the solvolyses of 3 and 6 involve the same intermediate(s) is not known, although the work of Rappoport *et al.* (6, 7) suggests that they do not. We were particularly interested in the behavior of 6 under the conditions of the oxidation of allylbenzene; reaction [2] was, therefore, performed in the presence of allylbenzene and mercuric acetate.

[1] $$\underset{3}{\text{Ph-CH=CH-CH}_2\text{Cl}} + \text{AgOAc} \longrightarrow \underset{4}{\text{PhCH(OAc)-CH=CH}_2} + \underset{5}{\text{Ph-CH=CH-CH}_2\text{OAc}}$$

[2] $$\underset{6}{\text{Ph-CH=CH-CH}_2\text{HgOAc}} \longrightarrow \underset{-}{4} + \underset{-}{5}$$

[3] $$\text{Ph-CH}_2\text{-CH=CH}_2 + \text{Hg(OAc)}_2 \longrightarrow \underset{-}{4} + \underset{-}{5}$$

Initial experiments revealed that complete equilibration of acetate between silver acetate and acetic acid required heating at 100° for at least 30 h; for reactions [2] and [3], equilibration of acetate among all of the components of the medium (8) was complete in < 8 h at room temperature, and there was no significant formation of 4 and 5 under these conditions. The exploratory experiments also revealed that 5 or mixtures of 4 and 5 could be isolated from reactions [1]-[3] in 70-100% yield, depending on the nature, temperature and time of reaction, by dilution with water, extraction with petroleum ether, and chromatography on silica gel. The composition of mixtures was established most readily by infrared analysis, using peaks at 697 cm^{-1} for 4 and 687 cm^{-1} for 5. It was also established that mixtures of 4 and 5 could be microdistilled under reduced pressure without a change in the ratio of the two compounds. However, this mode of purification was found to be unsatisfactory for the accurate determination of the small isotope effects eventually observed, and a crystalline derivative was sought. Extensive experimentation led to the following procedure: the chromatographically homogeneous, distilled product was brominated with pyrrolidone hydrotribromide (9) in purified chloroform (10, 11), and the *erythro*-dibromide 7, m.p. 90.5 - 91.0°, was isolated by chromatography on silica gel, followed by repeated crystallization from absolute ether.

All radioactivity measurements were performed on solutions having the same composition, so that quenching was similar in all counting vials, and "starting material" and "product" differed only in the location of the label. In each case a non-radioactive control containing all components was also prepared and counted. The results of these experiments are presented in the Table both as percentage differences between "starting material" and "product", and as apparent k_H/k_T values; in each case the observed isotope effect is the composite of the possible isotope effects associated with the individual stages between reactants and products. We conclude that $k_H/k_T = 1$ in reaction [1], for the conversion $3 \rightarrow 4 + 5$, and also for the isomerization of $4 \rightarrow 5$ in acetic acid. In reaction [2], $k_H/k_T < 1$ for the overall conversion $6 \rightarrow 5$ in a mixture also containing allylbenzene and mercuric acetate; in reaction [3], $k_H/k_T > 1$ for the overall conversion of allylbenzene to 5.

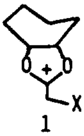
Isotope fractionation in reaction [1] will depend on the fate of the initially formed ion pair, 8: (a) if this ion pair collapses rapidly, without appreciable exchange with solvent, the isotopic composition of the product will reflect that of the original AgOAc. According to the relative basicities of $^{-}$OAc and $^{-}$OAc* (1), we anticipate that the silver acetate would be slightly depleted in tritium relative to the bulk medium; a slight decrease in radioactivity in the product would result, as is observed; (b) on the other hand, if the transformation of the initially formed intimate ion pair to a solvent-separated ion pair occurs much more rapidly than does its collapse (or if the initially formed entity is a solvent-separated ion pair), then one must consider the exchange of $^{-}$OAc and $^{-}$OAc* with the solvent sheath and the relative rates of collapse of $[R^{+}\ldots{}^{-}OAc]$ and $[R^{+}\ldots{}^{-}OAc^{*}]$, where R^{+} = cinnamyl. The two effects would tend to cancel each other and again we anticipate an overall isotope effect close to zero. The observed $k_H/k_T \sim 1.0$ is consistent with either (a) or (b) above.

Possible mechanisms for the solvolysis of 6 (i.e. reaction [2]) include both the formation of an ion pair 8, and the intramolecular reaction shown in 9 and 10. By analogy with the results obtained for reaction [1], a value of $k_H/k_T \sim 1.0$ is expected if solvolysis of 6 also

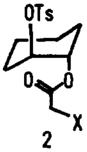
TABLE. Percent Difference in Radioactivity Between Starting Materials and Product for Reactions [1] - [3][a]

Reaction	Starting Materials (mmoles)		Temperature (deg C)	Time (hr)	Percent Difference[f]	Apparent[g] k_H/k_T
[1]	AgOAc*	(8.2818)[b]	25	12	1.56 ± 1.68%	1.016
	HOAc*	(393.69)	100[c]	24	1.05 ± 1.16%	1.011
	3	(7.8254)				
[2]	$Hg(OAc^*)_2$	(7.5514)[d]	125	3	-(5.25 ± 0.89%)	0.950
	allylbenzene	(7.9326)				
	6*	(6.1142				
	HOAc*	(2162.1)				
[3]	$Hg(OAc^*)_2$	(15.280)[d]	125	40[e]	2.32 ± 0.36%	1.024
	allylbenzene	(15.648)				
	HOAc*	(332.02)				
	$Hg(OAc^*)_2$	(63.527)[d]	125	1.5[e]	6.76 ± 1.81%	1.073
	allylbenzene	(63.468)				
	HOAc*	(1637.4)				

[a] See text for definitions of "starting materials" and "product" in the radioactive assays. [b] The acetic acid and silver acetate were equilibrated and counted prior to addition of 3. [c] These conditions lead to complete isomerization of 4 to 5. [d] Acetate was allowed to equilibrate among the "starting materials" prior to heating at the reaction temperature. [e] Cinnamyl acetate undergoes 69.0% exchange of the acetoxyl group with acetic acid solvent after 24 h at 125° in the presence of mercuric acetate. Therefore, prolonged reaction times lower the observed isotope effect. [f] Percent difference calculated as (starting materials) - (products); a negative difference (i.e. reaction [2]) indicates that radioactivity was higher in the products. [g] Apparent isotope effect is the composite of various possible isotope effects associated with the individual stages between reactants and products.



1



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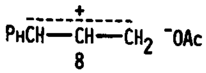
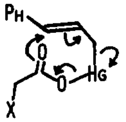


$$\overset{+}{PhCH\text{---}CH\text{---}CH_2}\ {}^{-}OAc$$

8

$Ph\text{-}CHBrCHBr\text{-}CH_2OAc$

7



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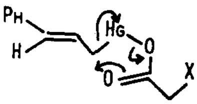

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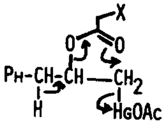

11

12

13

involves the formation of an ion pair. As for the SN_i' and SN_i reactions depicted in 9 and 10, isotope fractionation will be observed provided that the acetate moiety of 6 is in rapid equilibrium with the acetic acid medium and $k_H/k_T \neq 1.0$ for the intramolecular acetate transfer. By analogy with the isotope effect observed in the solvolysis of 2, $k_H/k_T < 1$ is anticipated, and is observed. It should be noted that 6 was prepared from unlabelled acetate, stirred at room temperature in the radioactive medium for 50 min, and then solvolyzed. If equilibration of 6 with the medium had been incomplete, a *lower* radioactivity would have been found in the product. That the opposite result is obtained supports the hypothesis that exchange of 6 with the medium was complete, and that isotope fractionation in reaction [2] occurs during an intramolecular acetate transfer step. It thus appears that the solvolyses of 3 and 6 in acetic acid proceed via different intermediates, as suggested by Rappoport *et al.* (6, 7).

Based on the above analysis, if the allylic oxidation of allylbenzene were to proceed in two steps, via 6, as suggested in the literature (6, 7), the overall isotope effect would be determined in the product-determining step, i.e. the solvolysis of the allylic mercuric acetate, and $k_H/k_T < 1$ would be anticipated, as in reaction [2]. In fact, the opposite result is obtained. The alternative mechanism depicted in 11, which leads specifically to 5 by an intramolecular acetate transfer from an acetoxymercuric acetate adduct (8), has been proposed by some workers (12). This mechanism should also be characterized by $k_H/k_T < 1$, and is thus incompatible with the present experiments. Rappoport *et al.* (6, 7) also rule out this mechanism, for other reasons.

A route from allylbenzene to 4 and 5 which is consistent with these isotope effects would involve the loss of [HHgOAc] from a mercurinium ion (8) to form an intimate ion pair (12 or 13) directly. Since the acetate counterion of the mercurinium ion is in equilibrium with the bulk medium (8), and the equilibrium $HOAc + {}^{-}OAc^* \rightleftarrows HOAc^* + {}^{-}OAc$ lies slightly to the right (1), the ratio 12/13 should be slightly less than the ratio of HOAc*/HOAc in the bulk medium. If ion pairs 12 and 13 collapse to product without appreciable exchange of the acetate moiety with the medium, 4 and 5 will be depleted in tritium relative to the medium, as is observed (13).

REFERENCES AND NOTES

1) E.A. Halevi, *Progr. Phys. Org. Chem.*, 1, 109 (1963); E.R. Thornton, *Ann. Rev. Phys. Chem.*, 17, 349 (1966); P. Laszlo and Z. Welvart, *Bull. Soc. Chim. France*, 2142 (1966).
2) All radioactivity measurements were performed on a Nuclear Chicago Series 720 Liquid Scintillation Counter. Counting efficiencies were determined by the channel ratio method, using chloroform quench correction standards. The scintillator solution was prepared by dissolving POP (1 g) and dimethyl-POPOP (0.1 g) in toluene (1 litre). Standard errors are based on eight to twelve accurately weighed samples, each of which was counted twenty times.
3) S. Winstein, C. Hanson, and E. Grunwald, *J. Am. Chem. Soc.*, 70, 812 (1948).
4) L. Melander and W.H. Saunders, Jr., Reaction Rates of Isotopic Molecules, Wiley-Interscience, New York, 1980, page 98.
5) J. Meisenheimer and J. Link, *Justus Liebigs Ann. Chem.*, 479, 211 (1930).
6) Z. Rappoport, L.K. Dyall, S. Winstein, and W.G. Young, *Tetrahedron Lett.*, 3483 (1970).
7) Z. Rappoport, S. Winstein, and W.G. Young, *J. Am. Chem. Soc.*, 94, 2320 (1972).
8) S. Wolfe, P.G.C. Campbell, and G.E. Palmer, *Tetrahedron Lett.*, 4203 (1966).
9) S. Wolfe and D.V.C. Awang, *Can. J. Chem.*, 47, 706 (1969).
10) A. Heslinga, *Rec. trav. chim.*, 78, 473 (1959).
11) Bromination of cinnamyl acetate is complicated by 1,3-acetoxyl group participation, which leads to bromohydrins (*cf* Gy. Schneider, I. Vincze, and A. Vass, *Acta Chim. Scient. Hung.*, 99, 51 (1979)). Under the conditions used here, the yield of 7 is reproducibly 82-84%.
12) A. Kergomard, *Ann. Chim.*, 8, 153 (1953); G.E. Palmer, PhD thesis, Queen's University, 1967.
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