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Deuterium Isotope Effects in the Solvolysis of Benzal Chlorides. 5. Salt Effects and Solvent Isotope Effects

V. P. Vitullo* and F. P. Wilgis

Contribution from the Laboratory for Chemical Dynamics, Department of Chemistry, University of Maryland Baltimore County, Baltimore, Maryland 21228.

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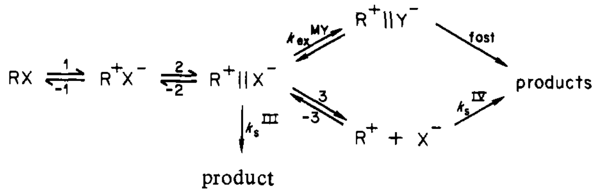
Abstract: Rates and solvent isotope effects have been determined for the solvolysis of *p*-methoxybenzal chloride (**1**) and diphenyldichloromethane (**2**) in 75% (v/v) dioxane–25% H_2O and 85% (v/v) dioxane–15% H_2O in the presence of various salts. Both **1** and **2** have solvolysis rates which follow the Winstein equation for the "special" salt effect, i.e., $k_{obsd} = k^0_{ext}(1 + b_s[\text{salt}])$. For both **1** and **2**, k^0_{ext}/k^0_{obsd} is identical for the two different salts $LiClO_4$ and Bu_4NClO_4 in 85% dioxane. For dissociation of intimate ion pair rate limiting in 85% dioxane for **1** and **2**, the solvent isotope effect is ~1.3. Rate-limiting capture of ion-pair intermediates in 75% and 85% dioxane furnish solvent isotope effects of ~1.5. It is suggested that these differences are due predominantly to the presence or absence of some covalent bonding to water in these transition states.

In previous papers in this series,[1,2] we have shown how changes in the α-deuterium isotope effect (α-D) provide basic information regarding the mechanisms of solvolysis of benzal chlorides. Thus, a maximum α-D effect for benzal chlorides (1.20) results if the rate-limiting step involves (a) conversion of an intimate ion pair to a solvent-separated one or (b) ion-pair exchange of solvent-separated ion pairs. On the other hand, rate-limiting collapse of solvent-separated ion pair furnishes a much reduced α-D effect (1.12). These results are in substantial accord with Shiner's[3] mechanistic analysis of α-D effects.

Shiner and we have used Winstein's scheme[4-6] extensively for solvolysis reactions. This is summarized as Scheme I.

Scheme I. Winstein Solvolysis Scheme



Results

Rates of hydrolysis of *p*-methoxybenzal chloride (**1**) and diphenyldichloromethane (**2**) in various dioxane–H_2O compositions are given in Table I. Hydrolysis rates of **1** and **2** increase with increasing solvent polarity. Furthermore, the solvolysis rates for **1** and **2** are very similar. The response of the solvolysis rate to increasing solvent polarity (Grunwald–Winstein *Y* value) is very large and nearly identical for **1** and **2** with $m = 1.32 \pm 0.04$ and $m = 1.30 \pm 0.02$, respectively.

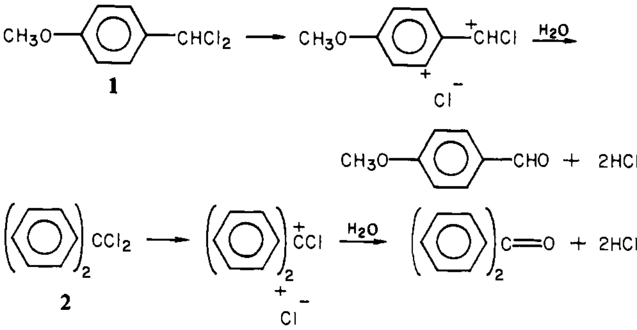
Table I. Rates of Hydrolysis of *p*-Methoxybenzal Chloride (**1**) and Diphenyldichloromethane (**2**) in Dioxane–Water (v/v) Mixtures at 25 °C

substrate	$10^5 k_{obsd}$, s^{-1} [a]	vol % dioxane–water
1	2110 ± 100	65
2	1400 ± 20	65
1	652 ± 18	70
2	467 ± 5	70
1	154 ± 6	75
2	135 ± 4	75
1	34.2 ± 0.2	80
2	31.0 ± 0.6	80
1	8.96 ± 0.18	85
2	6.15 ± 0.14	85
1	1.38 ± 0.05	90
2	1.03 ± 0.01	90

[a] *m* value based on Grunwald–Winstein equation; $\log k_{obsd} = mY$. $m = 1.32 \pm 0.04$ for **1**; $m = 1.30 \pm 0.02$ for **2**.

Reasonable mechanisms consistent with these and other data are given in Scheme II.

Scheme II. Solvolysis Mechanisms for Benzal Chlorides



Perchlorate salts at low concentration increase the rate of hydrolysis of **1**. We have seen earlier[1,2] that these rate increases are paralleled by an *increase* in the α-D isotope effect as the concentration of perchlorate salt is increased. In this paper we wish to examine the effect on the rate of the change $H_2O \rightarrow D_2O$ for the aqueous component of the solvent in dioxane–H_2O mixtures. The results of these investigations for 85% dioxane–15% H_2O (v/v) are given in Table II for $LiClO_4$ and Bu_4NClO_4. Here, the solvent isotope effect (SIE) for **1** *decreases* as the concentration of $LiClO_4$ increases (Table II). In greater than 0.05 M $LiClO_4$, the SIE is reduced from 1.45 to 1.298 ± 0.015.

A similar situation obtaines for Bu_4NClO_4 in this solvent. In greater than 0.25 M Bu_4NClO_4, the SIE is reduced to 1.324 ± 0.006.

The hydrolysis of dichlorodiphenylmethane in 85% dioxane also undergoes a perchlorate-induced rate increase most probably by a similar mechanism once again (Table III). The SIE *decreases* from 1.45 ± 0.01 to 1.30 in >0.25 M Bu_4NClO_4. The Winstein special-salt-effect parameters obtained from plots of k_{obsd} vs. [salt] for the data in Table III are summarized in Table IV.

As with **1**,[2] **2** shows very little common-ion rate depression in 85% dioxane. The rates, along with several SIE's, are given in Table V. It is interesting to note that in the absence of all salt the SIE is 1.45 while it is substantially unchanged (1.48) in the presence of 0.15 M LiCl.

By contrast, common-ion rate depression is substantial in 75% dioxane–25% H_2O (v/v) for **1** and **2**. Our results for this solvent for **1** and **2** are recorded in Table IV. These results for this solvent suggest that the SIE is also little changed in the presence of

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Table II. Rates of Hydrolysis of *p*-Methoxybenzal Chloride in 85% Dioxane-15% H_2O (v/v) at 25 °C. Special Salt Effect and Solvent Isotope Effect with Perchlorate Salts

$[MClO_4]$, M	$10^5 k_{obsd}$, s^{-1}	k_{H_2O}/k_{D_2O}
0.00	8.96 ± 0.18	1.45 (1)
0.010^a	21.0 ± 0.2	1.35 (1)
0.010^b	10.3 ± 0.2	1.393 (5)
0.025^b	14.5 ± 0.1	1.383 (4)
0.050^a	69.7 ± 1.6	1.314 (6)
0.100^a	130 ± 1	1.294 (8)
0.100^b	28.3 ± 0.5	1.363 (4)
0.150^a	185 ± 0.6	1.285 (7)
0.250^b	51.0 ± 1.0	1.319 (5)
0.500^b	57.7 ± 0.6	1.328 (7)

[a] $LiClO_4$. [b] Bu_4NClO_4.

Table III. Rates of Hydrolysis of Dichlorodiphenylmethane in 85% Dioxane-15% H_2O (v/v) at 25 °C. Special Salt Effect and Solvent Isotope Effects with Perchlorate Salts

$[MClO_4]$, M	$10^5 k_{obsd}$, s^{-1}	k_{H_2O}/k_{D_2O}
0.00	6.15 ± 0.14	1.45 (1)
0.01^a	16.0 ± 0.2	1.368 (7)
0.01^b	8.65 ± 0.03	1.407 (5)
0.025^b	11.9 ± 0.5	1.405 (4)
0.030^a	31.1 ± 0.1	
0.050^a	42.9 ± 0.03	1.35 (1)
0.050^b	15.8 ± 0.1	1.372 (8)
0.075^a	56.8 ± 0.2	
0.100^a	71.2 ± 1.0	1.303 (2)
0.100^b	22.1 ± 0.5	1.359 (8)
0.130^a	85.5 ± 0.8	
0.150^a	94.5 ± 1.1	1.30 (1)
0.250^b	32.4 ± 0.5	1.33 (1)
0.400^b	38.8 ± 0.6	1.303 (3)
0.500^b	40.3 ± 0.5	1.302 (9)

[a] $LiClO_4$. [b] Bu_4NClO_4.

Table IV. Special Salt Effect Parameters for Diphenyldichloromethane in 85% (v/v) Dioxane-Water at 25 °C

salt	$[salt]_{1/2}$	b_s	$10^5 k_{ext}^0$, s^{-1}	k_{ext}^0/k_0
$LiClO_4$	9×10^{-3}	19.0	24.6	4.0
Bu_4NClO_4	45×10^{-3}	1.32	24.6	4.0

common-ion salt. If anything, the SIE may increase slightly with common salt.

Discussion

In the preceding paper[2] we demonstrated that in the presence of "special" salts a change in rate-limiting step occurs which produces a change in the α-deuterium (α-D) isotope effect. Thus, addition of $LiClO_4$ or Bu_4NClO_4 to 85% dioxane-15% H_2O increases the solvolysis rate of **1** and, importantly, increases the α-D effect from 1.12 to 1.20, a maximum α-D effect for benzal chlorides. According to Scheme I, this change in α-D effect corresponds to a change in rate-limiting step from k_s^{III} to k_2. The identity of k^0_{ext} for the two salts $LiClO_4$ and Bu_4NClO_4 in 85% dioxane attest to this conclusion.

The α-D effect and the rate change only slightly in 85% dioxane with added common ion. However, addition of common-ion salt to 85% dioxane containing perchlorate salts results in substantial reductions in both the rate and α-D effect.

In the more polar solvent (75% dioxane-25% of H_2O (v/v)), the changes in rate and α-D effect for incremental addition of perchlorates are more consistent with ion pair exchange rate limiting since k^0_{ext} values are different for Bu_4NClO_4 and $LiClO_4$. In this solvent, chloride ion depresses the rate substantially and reduces the α-D effect. Here, in the presence of chloride ion, k_s^{III} is rate limiting.

For these systems the rate-limiting step can be changed from a "nonnucleophilic" conversion of an ion pair (k_2 or k_3) to nucleophilic capture of an ion-pair intermediate. The role of solvent (nucleophile) for these two processes should be quite different. differences in the SIE should reflect these differences.[7-11]

Table V. Rates of Hydrolysis of *p*-Methoxybenzal Chloride (1) and Diphenyldichloromethane (2) in Aqueous Dioxane. Solvent Isotope Effects with Added Common Ion

[LiCl], M	$10^4 k_{obsd}$, s^{-1}	k_{H_2O}/k_{D_2O}
0.00^a	15.8 ± 0.1	1.45 (2)
0.00^b	0.896 ± 0.018	1.45 (1)
0.00^c	0.615 ± 0.014	1.45 (1)
0.010^a	9.24 ± 0.20	1.509 (6)
0.020^a	4.88 ± 0.02	1.509 (8)
0.400^a	3.54 ± 0.18	1.501 (7)
0.075^c	0.583 ± 0.003	
0.150^c	0.531 ± 0.004	1.48 (2)
0.150^d	1.09 ± 0.03	1.44 (1)
0.016^c	8.63 ± 0.04	
0.050^c	7.54 ± 0.16	
0.100^c	6.07 ± 0.03	
0.150^c	5.29 ± 0.03	
0.400^c	3.54 ± 0.18	

[a] *p*-Methoxybenzal chloride, 75% dioxane-25% H_2O (v/v). [b] *p*-Methoxybenzal chloride, 85% dioxane-15% H_2O (v/v). [c] Diphenyldichloromethane, 85% dioxane-15% H_2O (v/v). [d] Diphenyldichloromethane, 85% dioxane-15% H_2O (v/v), 0.05 M $LiClO_4$ added (induced common-ion depression).

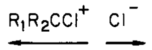

Figure 1. Transition state for k_2 rate limiting.

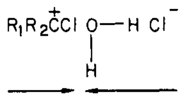

Figure 2. Transition state for k_5^{III} rate limiting.

Several years ago Kresge[12] and Gold[13] introduced the technique of isotopic fractionation factors for the study of reaction mechanisms.[12,13] This has been reviewed and expanded by Schowen.[8] Thus,

$$k_{D_2O}/k_{H_2O} = \prod_{\pi}^{i} \phi_i^{\ddagger} / \prod_{\pi}^{j} \phi_j^{R} \tag{1}$$

where the solvent isotope effect is expressed as a ratio of fractionation factors for the exchangeable *i*-hydrogenic sites in the transition state to the fractionation factors for the exchangeable *j*-hydrogenic sites of the reactants.

For our purposes, the fractionation factor for the solvating water molecules of Cl^- is 0.72[14,15] In addition, we take the fractionation factor for the solvating water molecules of univalent cations as 1.00.[16] Likewise, we assume unit fractionation factor for nonelectrolytes which have no exchangeable hydrogens.[16]

An analysis of our data will also require the fractionation factor for OL^+ (L = H, D). Since an accurate estimate for the fractionation factor for OL^+ is now available[17,18] (0.69), we will use this for all OL^+ sites.

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In 85% dioxane we suggest that interconversion of ion pairs is rate limiting (k_2, Scheme I) in the presence of perchlorate ion. Thus, we might formulate the transition state for this process as Figure 1.

However, in the absence of perchlorate salts or in the presence of common-ion salts, we imagine the rate-limiting step to involve capture of solvent-separated ion pair (k_s^{III}, Scheme I). This is shown schematically in Figure 2.

Assuming that the fractionation factor for chloride ion is $(0.72)^{1/4} = 0.921$ per fully developed lone pair, we estimate $\phi^{\ddagger}_1$ for k_2 rate limiting as in eq 2. Here, X represents the degree

$$\phi_1^{\ddagger} = 0.921^3 0.921^X \tag{2}$$

of separation of chloride ion from the carbonium ion in the transition state.

Assuming ϕ^R is unity and the transition state resembles[19] the tight ion pair ($X = 0$), we have

$$k_{H_2O}/k_{D_2O} = 1/0.921^3 = 1.28 \tag{3}$$

The agreement between our estimate and the experimental results is gratifying on the one hand and somewhat surprising on the other. For example, this fractionation factor refers to a wholly aqueous solvent although the experimental results refer to 85% dioxane–15% H_2O. The similarity of the SIE for **1** and **2** suggest that the SIE has its origin primarily in changes of the chloride ion fractionation factor between ground and transition state.

For the transition state resembling nucleophilic capture of the solvent-separated ion pair, we estimate the transition-state fractionation factor from eq 4 where X is the amount of oxygen–carbon bond making in the transition state.

$$\phi_2^{\ddagger} = \phi_{Cl^-}{}^4 \phi_{OL^+}{}^{2X} = 0.921^4 \phi_{OL^+}{}^{2X} \tag{4}$$

The average SIE for **1** and **2** in 75% and 85% dioxane–water in the presence and absence of chloride ion salts is 1.47 ± 0.03. Assuming this "exploded"[20] transition state is ion-pair like, we have

$$k_{H_2O}/k_{D_2O} = (1/0.921^4)1/0.69^{2X} \tag{5}$$

$$k_{H_2O}/k_{D_2O} = 1/0.921^4 = 1.39 \tag{6}$$

Treating X as an adjustable parameter furnishes a substantially identical transition state involving very little carbon–oxygen bond making, i.e., $X \approx 0.1$.

Experimental Section

1 was made available from a previous investigation.[2] **2** was made available from Aldrich Chemical Co. and distilled prior to use.

Reaction rates were obtained by monitoring the appearance of *p*-methoxy benzaldehyde (275 nm) or benzophenone (250 nm) for **1** and **2**, respectively, in the thermostated cell compartment of a Gilford Model 2400 spectrophotometer. The rate constant was obtained by a nonlinear least-squares regression analysis of the absorbance–time data. The standard deviation of each individual rate constant was <0.5%. The standard deviation of the isotope effect is based on two–five runs which involved two (one) H_2O runs and one (two) D_2O runs determined concurrently and is listed following the isotope effect in the tables, i.e., 1.302 (9) = 1.302 ± 0.009.

Reaction rates were initiated by adding 1–2 μL of a dioxane solution of **1** or **2** to a solution of a given salt in 75% or 85% dioxane–H_2O (D_2O) made by adding 25 (15) mL of H_2O (D_2O) to 75 (85) mL of purified dioxane.

All salts were the highest purity commercially available samples.

Acknowledgment. We thank the National Institues of Health for support of this work (Grant No. GM-21933).

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Total Synthesis of Isopavine and Intermediates for the Preparation of Substituted Amitriptyline Analogues: Facile Routes to Substituted Dibenzocyclooctatrienes and Dibenzocycloheptatrienes

Michael E. Jung*[1] and Steven J. Miller

Contribution from the Department of Chemistry, University of California, Los Angeles, California 90024. *Received August 4, 1980*

Abstract: We report the total synthesis of isopavine (**1**) and a key intermediate for the synthesis of analogues of antidepressant agents such as amitriptyline in only four steps, each in excellent overall yields. The double ortho Friedel–Crafts alkylation of homoveratraldehyde (**11**), promoted by trimethylsilyl iodide, afforded an excellent yield of the dibenzocyclooctadienyl ether **12**. This cyclic ether, although stable to acid, could be readily opened with *n*-butyllithium to produce the dibenzocyclooctatrienol **13**. From this alcohol (available from **11** in 92% yield), either of the synthetic targets could be prepared in two steps in nearly 60% yield. Several rearrangements of dibenzocyclooctatrienyl systems to substituted methyldibenzocycloheptatrienyl systems are reported in high yields. The mechanisms of these processes are discussed in detail. In addition, a novel oxidative cleavage of the *exo*-methylenedibenzocycloheptatriene (**23**) is described and its likely mechanism discussed. Finally, several approaches for the total synthesis of the pavine alkaloids are also presented which indicate the peculiarities of the chemistry of these dibenzocycloalkadiene and -triene systems.

Recently in a study of the addition reactions of trimethylsilyl iodide[2] with aldehydes, we reported a new method for the simple preparation of dibenzocyclooctadienes in good yields.[3] This involved a double ortho Friedel–Crafts alkylation of phenylacetaldehyde promoted by trimethylsilyl iodide. Since a large number of natural alkaloids possess a dibenzocyclooctadiene or dibenzocycloheptadiene ring system, e.g., isopavine (**1**),[4] thalisopavine (**2**),[5] pavine (**3**),[4] and argemonine (**4**),[6] we thought this

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(1) Camille and Henry Dreyfus Teacher-Scholar, 1978–1983. Fellow of the Alfred P. Sloan Foundation, 1979–1981.

(2) For the preparation of this reagent for use in chlorinated hydrocarbon solvents, see: Jung, M. E.; Lyster, M. A. *Org. Synth.* **1979**, *59*, 35 and references therein.

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