Mechanisms of Elimination Reactions. 29. Deuterium Kinetic Isotope Effects in Eliminations from Amine Oxides. The Consequences of Nonlinear Proton Transfer[1]

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Abstract: 2-Phenylethyldimethylamine and 2-phenylpropyldimethylamine oxides and their β-deuterated analogues have been prepared and k_H/k_D values determined for their elimination reactions in binary mixtures of dimethyl sulfoxide with water, *tert*-butyl alcohol, and tetrahydrofuran. The k_H/k_D values (at 59.8 °C, except for 52.3 °C in the mixtures with tetrahydrofuran) were all low, 2–3 in most cases, and showed little or no variation with change in solvent composition. There were, however, changes in transition state structure to a less carbanion-like β carbon as dimethyl sulfoxide was diluted by the cosolvent. This conclusion derives from ratios of rates for 2-phenylpropyl- vs. 2-phenylethyldimethylamine oxides. The low isotope effects and their slight change with transition-state structure confirm theoretical predictions for nonlinear proton transfers.

The interpretation of deuterium kinetic isotope effects in hydrogen transfer reactions has for some time been based upon a picture developed by Melander[3] and Westheimer.[4] According to this picture, a k_H/k_D maximum near 7 at room temperature was to be expected when the hydrogen atom in the transition state was half transferred; i.e., when the stretching force constants were equal for the bonds between the hydrogen and the donor atom and the hydrogen and the acceptor atom. Smaller isotope effects were expected when the hydrogen was either less or more than half transferred in the transition state. These ideas have been particularly useful in deducing transition-state structures in elimination reactions.[5]

Unfortunately, an unsymmetrically located proton in the transition state is not the only possible source of small isotope effects. We have predicted on the basis of calculations that coupling of heavy-atom motions with the proton-transfer motion can reduce the magnitudes of deuterium kinetic isotope effects,[6,7] and very recently experimental evidence for this phenomenon has been obtained.[8] Nonlinear hydrogen transfers are also expected to occur with low isotope effects.[7,9] Transition states with nonlinear proton transfer have been proposed for syn eliminations[10-13] and E2C reactions,[14-15] and k_H/k_D values no larger than 2–3 are usually found in these reactions.

In neither syn eliminations nor E2C reactions is a transition state with nonlinear proton transfer *demanded* by the evidence, so that the low isotope effects do not serve as unequivocal confirmation of the calculations.[7,9] Consequently, we set out to study a system in which there was strong evidence for a cyclic transition state which could not accommodate a linear proton transfer without prohibitive strain. Amine oxide pyrolysis is a stereospecifically syn elimination[18,19] believed to occur via the five-membered cyclic transition state **1**, in which

1
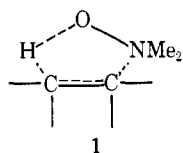
a C—H—O angle not far from 120° is expected. The reaction is more closely analogous to E2 reactions than are most pyrolytic eliminations, since it can be made to occur readily in solution at moderate temperatures (<100 °C).[19,20] In fact, it can be considered as involving the attack of an alkoxide-like base on the β hydrogen, just as in an E2 reaction.

Results

The substrates chosen for the isotope-effect studies were the oxides of 2-phenylethyldimethylamine (**2**) and 2-phenylpropyldimethylamine (**3**). The E2 reactions of similar systems

2   **3**
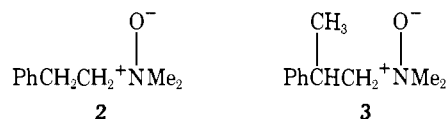
have been extensively studied,[5] and the reactions can be followed conveniently by observing the UV absorptions of the product olefins.

The deuterated amine oxides, **2-2,2-d_2** and **3-2-d_1**, were prepared by sequences of reactions that mainly followed literature procedures. The tertiary amine, 2-phenylethyl-2,2-d_2-dimethylamine, had been previously prepared[21] and was oxidized with hydrogen peroxide[22] to give **2-2,2-d_2**. The preparation of the amine involved hydrolysis and decarboxylation of the sodium salt of diethyl phenylmalonate,[23] followed by lithium aluminum hydride reduction of the resulting ethyl phenylacetate-α,α-d_2 to 2-phenylethanol-2,2-d_2, conversion to the tosylate, and treatment of the tosylate with dimethylamine.[21]

The synthesis of **3-2-d_1** was accomplished by a sequence of reactions closely similar to that described above for **2-2,2-d_2**.[21-23] The initial step, hydrolysis and decarboxylation of methylphenylmalonic ester (**4**) in sodium deuteroxide and deuterium oxide, gave <10% of the desired product **5**, the major product being **6**. Refluxing **6** with deuterium chloride

4   **5**   **6**
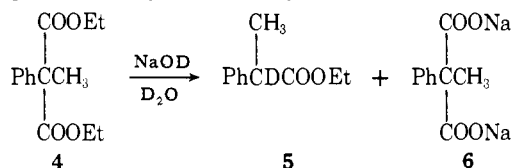
in deuterium oxide, however, converted it smoothly in 91% yield to 2-phenylpropanoic-2-d acid of high isotopic purity. The acid and the ester **5** were equally satisfactory as starting materials for the remainder of the sequence.

The amines oxides used in the kinetic studies contained 1.2–1.6 mol of water per mol of amine oxide, since the anhydrous form is unstable.[19] The spectrophotometrically determined rate constants are listed in Table I. The isotope effects are listed in Table II, some of them using rate constants extrapolated from different temperatures. Substituent effects, expressed as ratios of rates for **3** to **2**, are given in Table I. Many of the reactions were studied over a 15–20 °C temper-

Table I. Rate Constants for the Elimination Reactions of Amine Oxides in Mixed Solvents Containing Dimethyl Sulfoxide

Cosolvent, %[a]	Temp, °C[b]	$k \times 10^5$ s^{-1}, for[c]		k_H/k_D	k_X/k_H
		H	D		
2-Phenylethyldimethylamine Oxide					
None	40.0	6.52 ± 0.04	1.95 ± 0.05		
None	52.3	29.5 ± 0.4	9.57 ± 0.18		
None	59.8	71.6 ± 0.6	24.9 ± 0.7	2.87	
H$_2$O, 10	59.8	13.0 ± 0.4	4.48 ± 0.04	2.91	
H$_2$O, 20	59.8	4.44 ± 0.05	1.65 ± 0.01	2.68	
H$_2$O, 20	70.1	17.4 ± 0.5	5.85 ± 0.01		
H$_2$O, 20	78.8	44.5 ± 0.4	17.8 ± 0.2		
H$_2$O, 30	59.8	1.81[d]	0.66[d]	2.74	
H$_2$O, 30	70.8	7.13 ± 0.20	2.63 ± 0.06		
H$_2$O, 30	78.8	19.2 ± 0.7	7.60 ± 0.22		
H$_2$O, 30	84.6	35.6 ± 0.0	13.5 ± 0.0		
t-BuOH, 20	52.8	6.08 ± 0.05	1.98 ± 0.02		
t-BuOH, 20	59.8	15.9 ± 0.1	5.34 ± 0.01	2.98	
t-BuOH, 20	70.1	54.5 ± 0.8	18.2 ± 0.2		
t-BuOH, 40	59.8	5.08 ± 0.03	1.64 ± 0.02	3.09	
t-BuOH, 40	70.1	19.6 ± 0.1	6.74 ± 0.02		
t-BuOH, 40	79.0	54.2 ± 0.6	18.0 ± 0.1		
t-BuOH, 60	59.8	1.63[d]	0.56[d]	2.91	
t-BuOH, 60	70.5	6.39 ± 0.02	2.30 ± 0.04		
t-BuOH, 60	77.8	16.3 ± 0.1	6.03 ± 0.01		
t-BuOH, 60	84.5	34.2 ± 0.5	13.0 ± 0.2		
THF, 30	40.0	10.0 ± 0.2			
THF, 70	40.0	12.5 ± 0.3			
2-Phenylpropyldimethylamine Oxide					
None	39.9	2.45 ± 0.03	0.98 ± 0.02		0.38
None	52.3	11.2 ± 0.4	4.36 ± 0.10	2.38	
None	59.8	26.5 ± 0.4	11.4 ± 0.4	2.32	0.37
H$_2$O, 10	59.8	6.98 ± 0.10	3.07 ± 0.04	2.27	0.54
H$_2$O, 20	59.8	2.63[d]	1.17[d]	2.25	0.77
H$_2$O, 20	65.9	5.45 ± 0.04	2.40 ± 0.04		
H$_2$O, 20	73.5	13.1 ± 0.3	5.75 ± 0.13		
H$_2$O, 20	83.0	36.8 ± 1.0	15.9 ± 0.3		
H$_2$O, 30	59.8	1.11[d]	0.47[d]	2.36	0.61
H$_2$O, 30	71.2	4.40 ± 0.20	1.98 ± 0.07		
H$_2$O, 30	79.3	11.3 ± 0.6	5.31 ± 0.16		
H$_2$O, 30	86.4	24.2 ± 1.4	11.7 ± 0.5		
t-BuOH, 20	59.8	9.16 ± 0.05	3.19 ± 0.01	2.87	0.58
t-BuOH, 40	59.8	3.15 ± 0.07	1.06 ± 0.05	2.98	0.62
THF, 20	52.3	20.3 ± 0.3	6.00 ± 0.23	3.38	
THF, 30	40.0	4.35 ± 0.11			0.44
THF, 40	52.3	24.8 ± 0.3	7.97 ± 0.10	3.11	
THF, 60	52.3	37.4 ± 1.2	11.9 ± 0.1	3.15	
THF, 70	40.0	6.78 ± 0.01			0.54
THF, 100	52.3	90.0 ± 1.4	29.6 ± 0.5	3.04	

a Solvent compositions are in mole percent (100 × mole fraction). "None" indicates that the solvent is pure Me$_2$SO, and the percentages refer to the other solvent. THF stands for tetrahydrofuran. *b* ±0.05 °C. *c* Each value is the average of two runs, with standard deviation. *d* Extrapolated from data at other temperatures.

ature range, both to permit extrapolations where needed and to derive the activation parameters listed in Table II.

Discussion

In an effort to avoid the possibility that small isotope effects might result from an unsymmetrically located proton in the transition state rather than nonlinear proton transfer, we made extensive variations in the solvent–base systems used. Our rationale was that changing the hydrogen-bonding ability of the solvent should change the effective basicity of the oxide oxygen just as in the case of hydroxide or alkoxide solutions.[24,25] Changes in the basicity of hydroxide ion in water caused by the addition of dimethyl sulfoxide have been shown to lead to first a rise and then a fall in k_H/k_D values with 2-phenylethyldimethylsulfonium and -trimethylammonium ions.[5,26] These clear maxima in k_H/k_D are most reasonably interpreted as arising from variation in the extent of proton transfer in the transition states.[3,4] We also determined substituent effects (β-methyl vs. β-hydrogen) in the amine oxide

elimination. Changes in the substituent effects with changes in solvent would serve as evidence that the carbanion character at the β carbon and the extent of proton transfer were varying, whether or not there were any changes in k_H/k_D.

The rates in Table I decrease sharply as the dimethyl sulfoxide is diluted with water, and somewhat less when *tert*-butyl alcohol is the diluent. This phenomenon is quite consistent with a decrease in basicity of the oxide oxygen through increased hydrogen bonding, as postulated above. Sahyun and Cram, however, argue that the similar decrease in rate which they observed in aqueous dimethyl sulfoxide results from a decrease in equilibrium concentration of a reactive anhydrous form of the amine oxide, and a concomitant increase in concentration of an unreactive hydrogen-bonded form.[19] This simple picture fails to account for the significant changes in substituent effects (last column of Table I) with solvent composition. As the dimethyl sulfoxide is diluted with cosolvent, a monotonic increase in the k_{Me}/k_H ratio occurs (the one exception, the reaction in 30% water–70% dimethyl sulfoxide, involves extrapolation of

Table II. Activation Parameters for the Elimination Reactions of Amine Oxides in Mixed Solvents Containing Dimethyl Sulfoxide[a]

Cosolvent, %[b]	Isotope	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, cal/mol °C
2-Phenylethyldimethylamine Oxide			
None	H	24.3 ± 0.2	-0.12 ± 0.57
None	D	25.9 ± 0.4	2.41 ± 1.10
H_2O, 20	H	27.6 ± 1.2	4.41 ± 3.48
H_2O, 20	D	28.4 ± 0.8	4.68 ± 2.32
H_2O, 30	H	27.9 ± 0.9	3.39 ± 2.48
H_2O, 30	D	28.5 ± 2.0	3.16 ± 5.61
t-BuOH, 20	H	27.4 ± 0.7	6.16 ± 2.05
t-BuOH, 20	D	27.7 ± 1.0	4.84 ± 2.94
t-BuOH, 40	H	28.1 ± 0.7	5.89 ± 1.93
t-BuOH, 40	D	28.4 ± 1.3	4.81 ± 3.87
t-BuOH, 60	H	28.5 ± 0.9	4.83 ± 2.61
t-BuOH, 60	D	29.4 ± 0.9	5.58 ± 2.52
2-Phenylpropyldimethylamine Oxide			
None	H	24.1 ± 0.1	-2.65 ± 0.08
None	D	24.7 ± 0.8	-2.56 ± 2.61
H_2O, 20	H	26.1 ± 0.1	-1.31 ± 0.23
H_2O, 20	D	25.8 ± 0.2	-3.71 ± 0.48
H_2O, 30	H	26.9 ± 0.3	-0.60 ± 0.87
H_2O, 30	D	28.1 ± 0.4	1.20 ± 1.10

[a] Determined from a least-squares fit of the data to a log k vs. $1/T$ plot. [b] See footnote [a], Table I.

both rates from data at other temperatures). Evidently there are changes in the number and/or strength of hydrogen bonds to the amine oxide oxygen in the transition state, resulting in a steady variation with solvent composition of the extent of proton transfer in the transition state.

Addition of tetrahydrofuran to dimethyl sulfoxide produces an increase in rate. Here both solvents are aprotic, and the rate increase probably arises from the lower dielectric constant of tetrahydrofuran, which destabilizes the polar reactant relative to the less polar transition state.[19] The change in transition-state structure, as shown by data in Table I, is the same as with the hydroxylic cosolvents, though less marked. The fact that cosolvents both more and less polar then dimethyl sulfoxide produce the same changes in substituent effects makes it evident that the change is not a simple response to the dielectric constant of the solvent.

The isotope effects in Table I are all rather small, running approximately half of the maximum value (ca. 6) predicted by the Melander–Westheimer model[3,4] for a linear proton transfer at the temperature of measurement. The values are about as expected, however, for a nonlinear transition state with a C—H—O angle near 120°.[7,9]

No significant trends in isotope effects are found in the dimethyl sulfoxide–water mixtures for either substrate, but the substituent effects in Table I show a clear decrease in carbanion character as water is added. It is probable that this decrease signifies a decreasing extent of proton transfer in the transition state, although it could also result at least partly from increasing C–N cleavage. The lack of change in k_H/k_D is not necessarily in conflict with this interpretation, for the k_H/k_D maximum in a nonlinear proton transfer is expected to be rather broad and ill defined.[7]

A decrease in the extent of proton transfer with decreasing basicity (increased hydrogen bonding, see above) of the attacking base is contrary to predictions from the Hammond postulate[27] or a parallel Thornton-rule effect.[28,29] This pattern might thus be an example of the perpendicular Thornton-rule effect.[29] It might also result from some effect other than the change in basicity of the oxide oxygen, but what kind of effect this could be is not at all obvious.

The k_H/k_D values for **2** in dimethyl sulfoxide-*tert*-butyl

alcohol mixtures likewise show little change with solvent composition, though a shallow maximum near 40% *tert*-butyl alcohol may exist. The results with **3** in the same media show a significant change only from pure dimethyl sulfoxide to 20% *tert*-butyl alcohol. A similar large jump from pure dimethyl sulfoxide to 20% tetrahydrofuran is observed. Further addition of tetrahydrofuran produces a slow decrease. It is possible that the value in 20% tetrahydrofuran represents a true Melander–Westheimer maximum, though one cannot be entirely confident that it does.

The activation parameters in Table II are not sufficiently precise to permit detailed interpretation. It does seem that activation enthalpies are distinctly lower in pure dimethyl sulfoxide than in any of the mixtures with hydroxylic cosolvents. The further increase in $\Delta H^{\ddagger}$ with increasing dilution by the cosolvent is small, however. The differences in activation parameters between the hydrogen and deuterium species are too inconsistent to give clear evidence on the possible importance of tunneling.[30] Values for A_H/A_D vary randomly from 0.3 to 3.3, averaging near 1.3. In combination with the small isotope effects, this observation argues against any significant tunnel corrections.

Taken as a whole, our results clearly confirm the prediction[7,9] that nonlinear proton transfers should be accompanied by small kinetic hydrogen isotope effects. The apparent readiness with which the amine oxide pyrolysis adopts a markedly nonlinear transition state indicates that such transition states must be considered possible for proton-transfer reactions whenever some energetic advantage could come either from avoidance of strain, as in the present case, or from simultaneous interaction of the base with the β proton and some other center in the molecule, as in syn eliminations[10–13] or E2C reactions.[14,15]

Experimental Section[31]

Diethyl methylphenylmalonate was obtained by addition of 190 g of diethyl phenylmalonate to 19 g of sodium in 400 mL of absolute ethanol, followed by the bubbling in of 80 g of methyl bromide over 4 h. Removal of sodium bromide by filtration, followed by distillation, yielded a product shown by NMR to be contaminated with 13% of unreacted starting material. Treatment with excess sodium hydride in dry ether, followed by filtration and distillation, gave 114 g of diethyl methylphenylmalonate, bp 109–110 °C (2 mm).

Reaction of Diethyl Methylphenylmalonate with Sodium Deuteroxide in Deuterium Oxide. A mixture of 100 g of diethyl methylphenylmalonate and 50 mL of 10% sodium deuteroxide in deuterium oxide was refluxed for 8 h in a nitrogen atmosphere. The organic layer was separated, the aqueous layer was extracted twice with ether, and the combined organic layer and extracts were dried over magnesium sulfate. Fractionation yielded 5.5 g (8%) of ethyl 2-phenylpropionate-*2-d₁*, bp 69–70 °C (1.5 mm), >98% d_1 by NMR. From the aqueous layer was recovered 45 g of sodium methylphenylmalonate, which was converted to the deuterated diacid by addition to 30 mL of 10% deuterium chloride in deuterium oxide, followed by removal of the solvent in vacuo. Decarboxylation was effected by refluxing the deuterated diacid with 10% deuterium chloride in deuterium oxide (3 mL for each gram of diacid) under nitrogen for 4 h. The mixture was extracted with ether, and the extracts were dried and fractionated to yield 91% of 2-phenylpropionic-*2-d₁* acid, bp 71–72 °C (2 mm), >98% d_1 by NMR.

2-Phenylpropanol-*2-d₁* was obtained by reduction of ethyl 2-phenylpropionate-*2-d₁* or 2-phenylpropionic-*2-d₁* acid by lithium aluminum hydride. Workup by the procedure of Amundsen and Nelson[32] gave 74% (from the ester) or 81% (from the acid) of 2-phenylpropanol-*2-d₁*, bp 98–99 °C (1.0 mm) (lit.[33] 65 °C (0.1 mm)).

2-Phenylethanol-*2,2-d₂* was prepared by the reduction with lithium aluminum hydride of ethyl phenylacetate-*2,2-d₂* (obtained from diethyl phenylmalonate by the procedure of Saunders and Edison[23]). Workup as above yielded 79% of 2-phenylethanol-*2,2-d₂*, bp 68–69 °C (0.5 mm) (lit.[23] 110 °C (20 mm)), >98% d_2 by NMR.

2-Phenylethyl-*2,2-d₂* *p*-toluenesulfonate was obtained by the

method of Tipson in 70% yield, mp 38–39 °C (lit.[23] 37.4–38 °C).

2-Phenylpropyl-*2-d*₁ *p*-toluenesulfonate was prepared as above in 72% yield, mp 46.5–47.5 °C.

2-Phenylethyldimethylamine was prepared from 2-phenylethyl bromide and dimethylamine by the method of Saunders and Edison[23] in 58% yield, bp 50–51 °C (0.8 mm) (lit.[23] 110 °C (20 mm)).

2-Phenylpropyldimethylamine was prepared as above from 2-phenylpropyl bromide[33] and dimethylamine in 85% yield, bp 46–47 °C (2.0 mm) (lit.[34] 79–80 °C (10 mm)).

2-Phenylethyl-*2,2-d₂*-dimethylamine was obtained as above from 2-phenylethyl-*2,2-d₂* *p*-toluenesulfonate and dimethylamine in 58% yield, bp 50–50.5 °C (0.5 mm).

2-Phenylpropyl-*2-d*₁-dimethylamine was obtained as above from 2-phenylpropyl-*2-d*₁ *p*-toluenesulfonate and dimethylamine in 60% yield, bp 46–47 °C (2.0 mm).

2-Phenylethyldimethylamine oxide was prepared by the method of Cope and Bumgardner.[22] Removal of water from the product by rotoevaporator left an essentially quantitative yield of a pale yellow, viscous syrup which was shown by NMR to contain 1.4 mol of water per mol of amine oxide.

2-Phenylpropyldimethylamine oxide was prepared as above, and contained 1.6 mol of water per mol of amine oxide.

2-Phenylethyl-*2,2-d₂*-dimethylamine oxide was prepared as above, and contained 1.2 mol of water per mol of amine oxide.

2-Phenylpropyl-*2-d*₁-dimethylamine oxide was prepared as above, and contained 1.2 mol of water per mol of amine oxide.

Solvents. Dimethyl sulfoxide (Baker Analyzed, or Fisher Spectroanalyzed) was refluxed over calcium hydride for 6 h and distilled. The first 10% was discarded and the remainder collected. Tetrahydrofuran (Fisher Analytical grade) was refluxed over lithium aluminum hydride and distilled just prior to use. *tert*-Butyl alcohol was refluxed over sodium *tert*-butoxide for 3 h and distilled. The first 10% was discarded and the remainder collected. Distilled water was redistilled from potassium permanganate. The percentage compositions of mixed solvents refer to mole percent (mole fraction × 100).

Kinetic Procedure. Reactions were carried out in a thermostatically controlled (±0.05 °C) oil bath. Sufficient amine oxide to give an initial concentration of 0.004 M was added to a 100-mL volumetric flask containing 20 mL of the appropriate solvent which had been equilibrated to the desired temperature. For reactions with long (>2 h) half-lives, 0.1-mL aliquots of the reaction mixture were withdrawn with a 0.25-mL syringe and quenched with 5 mL of 95% ethanol. For reactions with shorter (<2 h) half-lives, ca. 0.5–1.0 mL was quickly withdrawn by pipet and added to a flask chilled with dry ice–acetone. A 0.1-mL aliquot of this sample was then withdrawn and quenched as above. The absorbances of the ethanol solutions were determined

with a Beckman DB-GT spectrophotometer at 250 nm for styrene and α-methylstyrene. At least eight points were determined for each run, and A_∞ was taken as the absorbance after 6 or more half-lives. The rate constant was determined from the slope of the best straight line plot of $\ln (A_\infty - A_t)$ vs. t.

References and Notes

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