Stereoelectronic Control of α Proton Abstraction from Iminium Ions

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Summary The first direct evidence for stereoelectronic control in α deprotonation of iminium ions has been obtained by observation of selective abstraction of axial α protons from iminium ions derived from the *trans*-decalones (**1**) and (**2**).

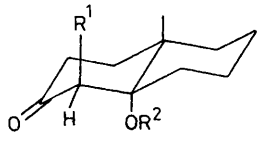
THE principle of 'stereoelectronic control'[1] is very widely accepted as a guide to the geometry of abstraction of protons α to carbonyl groups, although the evidence supporting this principle is limited[1-3] and not without controversy.[4] For the closely related, biologically important phenomenon of deprotonation α to carbon–nitrogen double bonds[5] there has been no direct evidence for stereoelectronic control.[6] We report here that a significant degree of stereoelectronic control is indeed manifested in selective abstraction of axial α protons from iminium ions derived from the β-hydroxy-ketone (**1**) and β-acetoxy-ketone (**2**) during their conversions into the enone (**3**). These results were obtained by comparing the rates of α deprotonation of (**1**)[7] and (**2**)[8] *via* iminium ion formation with those of the specifically α axially monodeuteriated (**4**) and (**5**).†

† Compounds (**4**) and (**5**) were prepared in the same manner as (**1**) and (**2**), except that $LiAlD_4$ was used instead of $LiAlH_4$ to reduce the intermediate 1α,9α-oxy-2β-acetoxy-10β-methyldecalin (ref. 7). The stereochemistry of the deuterium in (**5**) was confirmed by H n.m.r. spectroscopy.

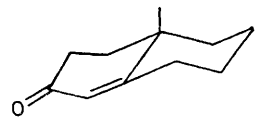
TABLE. Kinetic isotope effects and stereoelectronic factors for the formation of (3) under various conditions in H_2O at 25 °C with $\mu = 0{\cdot}4$ M

		Compound (1) *vs.* (4)			Compound (2) *vs.* (5)		
Catalyst	pK_a	Mechanism[a]	KIE_{obs}	SEF[b]	Mechanism[a]	KIE_{obs}	SEF[b]
OH^-	15·7	k_{OH}	5—6[c]		k_{OH}	6·2	130
$CF_3CH_2NH_2$	5·70	k_{AB}	5·3	18[d]	k_{AB}	7·4	110[d]
NH_2CH_2CN	5·34	k_{AB}	5·0	16[d]	k_{AB}	8·8	110[d]

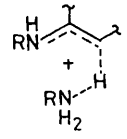
[a] An entry here means that the experiments were performed under conditions in which that catalytic term (*e.g.*, $k_{AB}[AM][AMH^+]$) accounted for >90% of reaction. [b] All SEF's are the average of at least two runs. [c] Estimated from initial slopes, owing to isotopic exchange. [d] From reactions at pH = pK_a, [buffer] = 0·4 M.



(1), $R^1 = R^2 = H$
(2), $R^1 = H$, $R^2 = Ac$
(4), $R^1 = D$, $R^2 = H$
(5), $R^1 = D$, $R^2 = Ac$



(3)



(6)

Catalysis of the conversion of (1) or (2) into (3) by weakly basic nontertiary amines occurs under appropriate conditions almost exclusively *via* iminium ion formation through transition state (6) (k_{AB} pathway).‡ When (4) and (5) were allowed to react under such conditions, using trifluoroethylamine or cyanomethylamine as catalyst, large primary kinetic isotope effects (KIE_{obs}) were observed. These results, shown in the Table, establish conclusively that there is preferential abstraction of the axial α proton.

Stereoelectronic factors ($SEF \equiv k^H_{ax}/k^H_{eq}$) can be calculated from values of KIE_{obs} if the amount of deuterium in excess of natural abundance in the product enone (3) is also known.§ The deuterium content of appropriate samples of (3) was determined by mass spectroscopy, and the resulting values of SEF are listed in the Table.

The values of SEF for (1) are smaller than those for (2). Since the overall rate of formation of (3) is largely determined by k^H_{ax}, and since the rate constants for (2) → (3) *via* (6) are only 2—4 times greater than those for (1) → (3)‡ (exactly the small difference which would be predicted on the basis of the inductive effects of hydroxy *vs.* acetoxy[9]), this difference in SEF's must arise predominantly from a difference in the rates with which the usually equatorial α protons are removed from (1) *vs.* (2). If one assumes that these deprotonations occur from a twist-boat conformation, in which abstraction of the usually equatorial protons is stereoelectronically favourable, the differences in SEF could arise either from acceleration with (1), caused by hydrogen bonding of catalyst to the hydroxy group, or from deceleration with (2), caused by steric hindrance to catalyst approach by the acetoxy group.

It is noteworthy that the SEF's for the conversion of (2) into (3) *via* (6) are roughly the same (*ca.* 10^2) as the SEF for direct α proton abstraction from (2) by hydroxide ion. These are the largest SEF's recorded for abstraction of an axial *vs.* an equatorial proton, and if an attempt were made, as has been done previously,[1,2] to take into account steric hindrance by the angular methyl group, the preference for the axial proton would appear even larger.

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‡ The kinetics of the amine-catalysed conversion of (1) and (2) into (3) (R. D. Roberts, H. E. Ferran, Jr., M. J. Gula, and T. A. Spencer, unpublished work) is exactly the same as that described previously for the conversion of the *cis*-fused isomers of (1) and (2) into (3): ref. 8, and D. J. Hupe, M. C. R. Kendall, and T. A. Spencer, *J. Amer. Chem. Soc.*, 1973, **95**, 2271.

§ $SEF \equiv k_{ax}{}^H/k^H{}_{eq} = KIE_{obs}[(k^D{}_{ax}/k^H{}_{eq}) + 1] - 1$, where $KIE_{obs} = (k^H{}_{ax} + k^H{}_{eq})/(k^D{}_{ax} + k^H{}_{eq})$ and $k^D{}_{ax}/k^H{}_{eq}$ can be calculated from the amount of D in excess over natural abundance in the product. The same analysis was apparently used in ref. 2.

[1] E. J. Corey, *J. Amer. Chem. Soc.*, 1954, **76**, 175; E. J. Corey and R. A. Sneen, *ibid.*, 1956, **78**, 6269.
[2] G. Subrahmanyam, S. K. Malhotra, and H. J. Ringold, *J. Amer. Chem. Soc.*, 1966, **88**, 1332.
[3] G. B. Trimitsis and E. M. Van Dam, *J.C.S. Chem. Comm.*, 1974, 610.
[4] F. G. Bordwell and R. G. Scamehorn, *J. Amer. Chem. Soc.*, 1968, **90**, 6749.
[5] Biochemical examples include reactions involving aldolases, *e.g.* C. Y. Lai O. Tchola, T. Cheng, and B. L. Horecker, *J. Biol. Chem.*, 1965, **240**, 1347, R. G. Rosso and E. Adams, *ibid.*, 1967, **242**, 5524; dehydratases, *e.g.*, D. Portsmouth, A. C. Stoolmiller, and R. H. Abeles, *ibid.*, p. 2751, D. L. Nandi and D. Shemin, *ibid.*, 1968, **243**, 1236, R. Jeffcoat, H. Hassall, and S. Dagley, *Biochem. J.*, 1969, **115**, 977, J. R. Butler, W. L. Alworth, and M. J. Nugent, *J. Amer. Chem. Soc.*, 1974, **96**, 1617; and pyridoxal phosphate, *e.g.*, H. C. Dunathan, *Adv. Enzymol.*, 1971, **35**, 79.
[6] J. Hine, M. S. Cholod, and R. A. King, *J. Amer. Chem. Soc.*, 1974, **96**, 835 have inferred stereoelectronic control in deprotonation of iminium ions on the basis of observations in a study of bifunctional amine catalysts.
[7] H. B. Henbest and J. McEntee, *J. Chem. Soc.*, 1961, 4478.
[8] Compound (2) was synthesised by a pathway analogous to that used to prepare its *cis*-fused isomer: D. J. Hupe, M. C. R. Kendall, and T. A. Spencer, *J. Amer. Chem. Soc.*, 1972, **94**, 1254.
[9] R. A. More O'Ferrall and P. J. Warren, *J.C.S. Chem. Comm.*, 1975, 483; R. A. More O'Ferrall, personal communication; P. Ahlberg, *Chemica Scripta*, 1973, **3**, 183.