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THE EFFICIENCY OF INTRAMOLECULAR GENERAL BASE CATALYSIS IN NONAQUEOUS SOLVENTS

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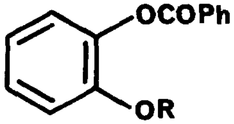
There is good evidence that intramolecular general base catalysis is much less efficient than intramolecular nucleophilic catalysis.[1] It has recently been suggested[2] that this is true only for reactions in aqueous solvents, and that in nonaqueous solvents - and perhaps also in enzyme active sites from which water is excluded - intramolecular general base catalysis may cause large rate accelerations.

This conclusion was based on data for the n-butylaminolysis of 2-hydroxyphenyl benzoate (1), and the corresponding methoxy compound (2), in acetonitrile. The reaction of 1 is first order in amine, and hundreds of times faster than the (second order) reaction with 2. The results were explained in terms of highly efficient intramolecular general base catalysis by the ionised (phenolate) group of 1. Our results with 2 suggest that the reaction involves general acid catalysis, and that its efficiency is unremarkable.



1, R = H
2, R = Me

The n-butylaminolysis of 2-methoxymethyl benzoate (2) is catalysed by n-butylammonium chloride. Senatore et.al.[2] attribute this to general base catalysis by chloride anion, but we find that the perchlorate salt is more effective than the chloride. Since tetra-n-butylammonium perchlorate does not affect the rate of the reaction appreciably[2] this catalysis must be due to the

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$BuNH_3^+$ cation, presumably acting as a general acid. The neighbouring OH group of 1 can also act as a general acid.* To gauge the effective molarity[4] of this group we need to know the rate constant for intermolecular catalysis by a phenol of similar pK_a, and we have estimated this by measuring rate constants for catalysis by two fluoroalcohols. In the presence of 0.5 M $BuNH_2$ the catalytic constants for CF_3CH_2OH and $(CF_3)_2CHOH$ (pK_a's 12.4 and 9.3 in water[5] and thus both probably weaker acids than phenol in acetonitrile) are 1.2×10^{-5} and 7.5×10^{-5} $dm^3\ mol^{-1}\ s^{-1}$, respectively. We can therefore estimate a value in the region of $10^{-4}\ dm^{-3}\ mol^{-1}\ s^{-1}$ for catalysis by phenol, and thus an effective molarity of the OH group of 1 (for which $k_{obs} = 2.88 \times 10^{-3}$ in the presence of 0.5 $BuNH_2$) of the order of 30M. This estimate is likely to be correct to well within a factor of two, and falls in the range of low effective molarities noted for reactions involving intramolecular general base catalysis in water.[1]

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* The Italian authors suggest that this OH group is fully ionised in the presence of > 0.2M $BuNH_2$, but known pK_a's of phenols and primary amines in acetonitrile[3] predict less than 0.5% of ionisation under these conditions. In fact the UV spectrum of 2-hydroxyphenyl benzoate in MeCN is essentially identical in the presence and absence of 0.5M $BuNH_2$, and readily distinguished from that of the anion.

References

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