Relative Catalytic Abilities of Nitrogen and Dipolar Oxygen Bases in Chlorobenzene

By PHILIP W. ARANA, CHIH-WU SU, and JOSEPH W. WATSON*

(*Department of Chemistry, University of California, San Diego, La Jolla, California* 92037)

Summary The enhanced catalytic abilities of dipolar oxygen bases relative to nitrogen bases in two general base catalysed reactions in chlorobenzene is reported and its possible relevance to enzyme reactions is indicated.

IN low-dielectric aprotic solvents dipolar oxygen bases form stronger hydrogen bonds with acids than nitrogen bases of equal aqueous pK_a.[1] This is illustrated in the Table by the hydrogen-bond formation constants, K_f, in CCl_4 for the reaction

$$p\text{-F}\cdot C_6H_4\cdot OH + B \overset{K_f}{\rightleftarrows} p\text{-FC}_6H_4OH\text{ - - - }B \qquad (1)$$

Dipole moments, μ, are also listed in the Table.

Dipole moments and equilibrium and rate constants of catalysts

	μ	pK_a	K_f	$k_2 \times 10^3$, M^{-1} sec^{-1a}	k_3, M^{-2} sec^{-1b}
n-Butylamine	1·4	10·59	130	(42,000)^c	0·062
N-Methylimidazole	3·6	7·00		275	0·19
Pyridine	2·20	5·22	76	45	0·018
Dimethylacetamide	3·79	−0·63	242	1·84	0·15
2-Pyridone		0·75		32	1·5^d
N-Methyl-2-pyridone	4·15	0·32		6·0	0·21
Dimethyl sulphoxide	3·9	−1·8	338	2·04	0·20
Triphenylphosphine oxide	4·31	−4·4	1456	4·14	0·57

[a] For t-butyl performate decomposition; [b] for n-butylaminolysis of *p*-nitrophenyl acetate; [c] the k_2 value is for triethylamine catalysis; [d] not corrected for dimerization of catalysts (ref. 5).

We report that this enhancement of the basicities of dipolar oxygen bases relative to that of nitrogen bases also occurs for two base catalysed reactions in chlorobenzene solvent; the heterolytic decomposition of t-butyl performate at 90° and the aminolysis of *p*-nitrophenyl acetate at 25°.†

Pincock has presented evidence for the nitrogen-base (anilines, pyridines, and triethylamine) catalysed decomposition of t-butyl performate proceeding by the heterolytic mechanism[2]

$$\mathrm{B} + \mathrm{HCO_3Bu^t} \xrightarrow{k_2} \mathrm{BH^+} + \mathrm{CO_2} + {}^-\mathrm{OBu^t} \xrightarrow{\text{fast}} \mathrm{B} + \mathrm{CO_2} + \mathrm{HOBu^t} \qquad (2)$$

The k_2 values (Table) for catalysis of this reaction by oxygen bases are $>10^3$ times greater than would be predicted by the Brønsted relationship ($\log k_2 = 0{\cdot}64\ \mathrm{p}K_a - 5{\cdot}35$) observed by Pincock for catalysis by nitrogen bases. Products and formyl kinetic isotope effects (k_H/k_D *ca.* 4) support the formulation of the catalysis by oxygen bases as general base catalysis.

The n-butylaminolysis of *p*-nitrophenyl acetate follows the rate equation:

$$\frac{\text{Rate}}{[\text{Ester}][\mathrm{Bu^tNH_2}]} = k_{2\mathrm{obs}} = k_2 + k_3[\mathrm{Bu^nNH_2}] + k_3'[\text{Cat.}]$$

with k_2 being undetectable ($< 2 \times 10^{-4}$M^{-1}sec^{-1}).[3] Because k_3 and k_3' tend to vary with increasing concentrations of dipolar catalysts, the k_3' values in the Table are from linear plots of $k_{2\mathrm{obs}}$ *versus* [$\mathrm{Bu^nNH_2}$] with the catalyst concentration constant at approximately 0·01 M. Except for 2-pyridone, which can act as a bifunctional catalyst,[4] we prefer to consider the aminolysis as being general-base catalysed by the oxygen bases. Nucleophilic catalysis is given a lower preference, but not ruled out, by the second-order dependence on [$\mathrm{Bu^nNH_2}$] and the non-occurrence of the release of *p*-nitrophenol when *p*-nitrophenyl acetate and valerolactam are allowed to react in the absence of n-butylamine. However, catalysis of the anilinolysis of benzoyl chloride in benzene by oxygen bases has been explained in terms of nucleophilic rather than general-base catalysis.[5]

Although 2-pyridone is considered to catalyse ester aminolysis and other reactions by bifunctional catalysis,[4] the catalytic abilities (Table) for *N*-methyl-2-pyridone and the other oxygen bases incapable of bifunctional catalysis indicate that 2-pyridone can be quite catalytic without the occurrence of bifunctional catalysis.

For aminolysis of aryl esters in ether solvents a large second-order term, k_2, is observed.[6] The strong correlation between hydrogen bonding ability as measured by K_f and k_3 supports the attribution of this second-order term to catalysis by the ether solvent (K_f *ca.* 10).

As with the dramatic increases in the nucleophilicity of small anions when hydrogen bonding solvation of the anion is removed,[7] the increase in the basicities of the dipolar oxygen bases relative to the basicities of the less polar nitrogen bases on transference from aqueous to aprotic solvents can be attributed to the loss of hydrogen bonding solvation of the negatively charged oxygen atoms; *i.e.* hydrogen bonding solvents have a greater basicity lowering effect on dipolar oxygen bases than on nitrogen bases. As has been observed,[8] the data (Table) indicate that the actual nucleophilicity order observed in a particular solvent is dependent on the bonding characteristics of the reaction being investigated. In the piperidinolysis of fluorodinitrobenzene in benzene tertiary amides are not catalytic while nitrogen bases are effective catalysts.[9]

The relative catalytic abilities observed in this work indicate that free amide groups should be considered along with imidazyl and amino groups as potential basic or nucleophilic catalysts in enzymes considered to have non-polar aprotic active sites.[10]

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† More detailed discussions of this work will appear in subsequent full papers. The kinetic procedures were essentially those of references 3 and 4.

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