Intramolecular Catalysis in the Aminolysis of 2-Pyridyl Esters

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Summary The second- and third-order butylaminolysis of 2-pyridyl *p*-nitrobenzoate in chlorobenzene are intramolecularly catalysed.

IN view of the general interest in intramolecular catalysis and the recent report of the use of 2-pyridylthiol esters in peptide synthesis,[1] we report on investigations of intramolecular catalysis in the reactions of 2-pyridyl compounds in order to correct the general assumption that intramolecular catalysis affects only the second-order term, first order in ester and amine.

The data in the Table provide strong evidence for

TABLE

Rate and physical constants for aryl and pyridyl compounds,[a] $k_{1\,obs} = k_2[A] + k_3[A]^2$

	A					
$NO_2{\cdot}C_6H_4{\cdot}CO_2X$-*p*	Butylamine		THP			
X	10^2k_2	10^2k_3	k_2	k_3	νC=O[b]	pK_a[c](HX)
$C_6H_4{\cdot}NO_2$-*p*	0·0	7·3	77·0	$1{\cdot}7 \times 10^5$	1755·9	7·2
4-Pyridyl	0·0	4·0	21·0	$3{\cdot}8 \times 10^4$	1754·4	7·67
2-Pyridyl	2·5	24·0	7·4	$6{\cdot}3 \times 10^3$	1752·7	8·66 9·09
$C_6H_4{\cdot}Cl$-*m*	0·0	0·2	0·0	$1{\cdot}4 \times 10^3$	1751·7	9·12
$C_6H_4{\cdot}NO_2$-*m*	0·0	1·2	1·1	$3{\cdot}8 \times 10^4$	1755·0	8·36

[a] Spectrophotometrically determined rates in chlorobenzene at 25°; k_2 and k_3 in units of sec.$^{-1}$M^{-1} and sec.$^{-1}$M^{-2}, respectively.
[b] Carbonyl stretching frequencies of *p*-nitrobenzoates in carbon tetrachloride.
[c] For 2- and 4-pyridyl compounds pK_a's of hydroxyl tautomers are given.[5]

intramolecular catalysis of the butylaminolysis of 2-pyridyl *p*-nitrobenzoate in chlorobenzene.

The occurrence of a dectable second-order term, k_2, only in the aminolysis of the 2-pyridyl ester indicates that its mechanism of aminolysis is different from that of the aryl and 4-pyridyl esters. A comparison of the third-order terms, k_3's, for the aminolysis of the 2-pyridyl and aryl esters of phenols with pK_a's similar to that of 2-hydroxypyridine indicates that the k_3 term for the 2-pyridyl ester is enhanced by a factor of between 20 and 100.

The relative susceptibilities of the esters to nucleophilic substitution in the absence of intramolecular catalysis are indicated by their carbonyl stretching frequencies[2] and their rate constants for reaction with 1,4,5,6-tetrahydropyrimidine (THP). Nucleophilic attack by the imine nitrogen of THP makes the direct proton transfer to the 2-pyridyl nitrogen required for intramolecular catalysis sterically impossible. This data supports intramolecular catalysis rather than thermodynamic instability[3] as the cause of the k_2 and large k_3 terms in the aminolysis of the 2-pyridyl ester.

Our results further indicate that the high reactivity of 2-pyridyl esters toward amines[1,3,4] may not be totally the result of a large second-order term, as might be assumed in the absence of detailed kinetic data, for at moderate to high concentrations of general base catalysts intramolecular catalysis of the third-order term may be the major cause of the high reactivity. Because basic solvents such as *NN*-dimethylformamide may act as general base catalysts, the observation of second-order kinetics is often not sufficient to establish the order of the intramolecularly catalysed term.

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