Cross correlation analysis of reactions of benzyl bromides with imidazoles and pyridines in nitrobenzene

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According to structure–reactivity cross correlations, the transition state in the reactions of imidazoles with benzyl bromides is more product-like than that in similar reactions involving pyridines; this accounts for the lower reactivity of imidazoles compared to that of pyridines.

Despite the fact that catalytic properties of imidazoles and pyridines in substitution reactions at carbonyl, sulfonyl and phosphoryl electrophilic centres are often interpreted in terms of a nucleophilic catalysis mechanism,[1–3] there are virtually no comparative data on the nucleophilic reactivities of these heterocyclic bases in simple non-catalytic processes. It is only known[3] that imidazoles react with methyl iodide in acetonitrile more slowly than pyridines of the same basicity in the same solvent. In the present study, we compare the joint influence of structural factors on the rates of reactions of imidazoles and pyridines with benzyl bromides in nitrobenzene at 40 °C. The kinetic data for reactions of imidazoles, listed in Table 1, and the published data[4] for reactions of pyridines have been subjected to cross correlation analysis, the results of which have been used to characterise the structures of transition states (TS) of the cross reaction series being compared. The course of the processes was monitored based on the quantity of bromide ions formed. Statistical processing of the experimental results was performed with a fiducial probability of 0.95. The inaccuracy in the determination of rate constants did not exceed 5%.

It can be seen from Table 1 that the second-order rate constants for reactions of benzyl bromides with imidazoles decrease following a decrease in their basicity and an enhancement of the electron-withdrawing properties of substituents in the substrate. Exceptions are provided by the reactions involving imidazole; their rates do not depend on the substituents in benzyl bromide. This situation is typical of the isoparametricity phenomenon, which has been found previously for nucleophilic substitution in benzylic substrates.[5]

The rate constants for the reactions of imidazoles (Table 1) and pyridines[4] are described adequately by Brönsted and Hammett equations. The corresponding β and ρ coefficients for partial reaction series calculated using the pK_a values in water and the Hammett σ-constants are presented in Table 2. The β_{Im} and β_{Py} values characterising the sensitivity of the process to the basicity of nucleophilic reagents increase with enhancement of the electron-withdrawing properties of fixed substituents Y in benzyl bromide, and $\beta_{Im} > \beta_{Py}$ for identical Y. The latter implies that in the case of imidazoles, the extent of bond formation in the TS is larger. On the other hand, an increase in the basicity of both imidazoles and pyridines causes a sharp, especially in the former case, decrease in the sensitivity to the structural changes in the substrate (see the behaviour of ρ_{Im} and ρ_{Py} in Table 2). These changes in the sensitivity parameters attest to an interaction between the jointly varied factors in both reaction series; its influence on the rate of the process can be taken into account by the cross-correlation relation:

$$\lg k = \lg k_{st} + \beta_{st} pK_a + \rho_{st}\sigma + \lambda pK_a\sigma, \quad (1)$$

where k_{st} is the rate constant under standard conditions (p$K_a = 0$, $\sigma = 0$), β_{st} and ρ_{st} are parameters for standard reactions at $\sigma = 0$ and p$K_a = 0$, respectively, and λ is the coefficient of cross interaction. Despite the fact that the steric accessibilities of the nucleophilic reactive sites in the imidazoles and pyridines are virtually identical,[6] a unified correlation dependence of their reactivity on the joint effects of structural factors does not hold. Separate processing of the experimental data for the two reaction series in terms of equation (1) using the standard multilinear regression analysis programme gave the following results [equations (2)–(3)].

$$\lg k_{Im} = (-6.48\pm0.11) + (0.53\pm0.02)pK_a - (1.23\pm0.23)\sigma + (0.17\pm0.04)pK_a\sigma \quad (2)$$

$N = 16$, $S = 0.056$, $R = 0.999$, $p\hat{K}_a = 7.23$, $\hat{\sigma} = -3.12$

$$\lg k_{Py} = (-5.39\pm0.02) + (0.48\pm0.01)pK_a - (0.91\pm0.06)\sigma + (0.08\pm0.01)pK_a\sigma \quad (3)$$

$N = 20$, $S = 0.033$, $R = 0.999$, $p\hat{K}_a = 10.8$, $\hat{\sigma} = -5.71$

Correlations (2) and (3) become poorer with omission of the cross term: the correlation coefficient R (standard deviation S) decreases (increases) to 0.995 and 0.996 (0.0847 and 0.0567) for the imidazole and pyridine series, respectively. Alternatively the λ values can be calculated using equations (4)–(7):

$$\beta_{Im} = (0.532\pm0.004)+(0.171\pm0.009)\sigma, \quad r = 0.997, \ s = 0.0046 \quad (4)$$

$$\rho_{Im} = (-1.22\pm0.04) + (0.171\pm0.007)pK_a, \ r = 0.998, \ s = 0.0191 \quad (5)$$

$$\beta_{Py} = (0.484\pm0.007) + (0.09\pm0.02)\sigma, \quad r = 0.997, \ s = 0.0109 \quad (6)$$

$$\rho_{Py} = (-0.95\pm0.02) + (0.088\pm0.005)pK_a, \ r = 0.994, \ s = 0.0192 \quad (7)$$

The coefficients for regressions (2) and (3) correspond to those calculated from individual correlations [*cf.* the values with the corresponding values in Table 2 and equations (4)–(7)], which confirms the high reliability of the estimate. The statistical significance of λ in both regressions makes it possible to calculate[5] isoparametric points $p\hat{K}_a = -\rho_{st}\lambda^{-1}$ and $\hat{\sigma} = \beta_{st}\lambda^{-1}$. All these points except one go far beyond the limits of experimental attainability. An exception is provided by the isoparametric point $p\hat{K}_a = 7.23$, which approximately corresponds to imidazole (p$K_a = 6.99$), the rate of reaction of which, as noted above, barely depends on the effects of the substituents in benzyl bromide (Table 1), so that $\rho_{Im} \cong 0$ (Table 2). At this point, synchronous S_N2 substitution occurs with identical extents of formation and rupture of bonds in the TS. In the rest of the reactions for which $\rho_{Im} < 0$ and $\rho_{Py} < 0$ (Table 2), the rupture of the bond predominates over formation.

It follows from the magnitudes of the constant terms of regressions (2) and (3) that at equal basicities in water (p$K_a = 0$), imidazoles are an order of magnitude less reactive than pyridines. This trend is retained over the whole experimental range of the variation of pK_a both in water and in acetonitrile. The lower reactivity of imidazoles is in agreement

Table 1 Rate constants ($k/10^{-5}$ dm^3 mol^{-1} s^{-1}) for reactions of benzyl bromides ($YC_6H_4CH_2Br$) with imidazoles in nitrobenzene at 40 °C.

Azole (pK_a)	Y			
	H	3-Cl	3-CN	3-NO_2
Imidazole (6.99)	153	145	151	149
4(5)-Phenylimidazole (6.10)	61.2	53.4	48.7	45.3
Benzimidazole (5.53)	34.5	26.3	23.1	21.1
5-NO_2-Benzimidazole (3.48)	2.25	1.18	0.943	0.831

Table 2 Coefficients of sensitivity β for the Brönsted equation and ρ for the Hammett equation for reactions of benzyl bromides ($YC_6H_4CH_2Br$) with imidazoles and pyridines (XC_5H_4N) in nitrobenzene at 40 °C.

Y	β_{Im}	β_{Py}	Azole	$-\rho_{Im}$	X	$-\rho^4_{Py}$
3,5-$(CH_3)_2$	–	0.47±0.02	Imidazole	0.02±0.02	3-CH_3	0.44
H	0.53±0.03	0.48±0.01	4(5)-Phenylimidazole	0.17±0.01	H	0.48
3-Cl	0.60±0.03	0.53±0.01	Benzimidazole	0.30±0.02	3-$COOC_2H_5$	0.67
3-CN	0.63±0.02	–	5-NO_2-Benzimidazole	0.62±0.06	3-Br	0.68
3-NO_2	0.65±0.03	0.54±0.01	–	–	3-CN	0.82

with the results of cross correlation in terms of equation (1) in which the coefficient λ characterises the interaction of the effects of the substrate and nucleophile structures on the formation of the bond in the TS. The higher the order of the bond being formed (*i.e.* the closer to the products the TS is located on the reaction coordinate), the larger is this coefficient. The fact that this coefficient in regression (2) is twice as much than that in regression (3) indicates that in the case of imidazoles the extent of bond formation in the TS is higher, *i.e.* this TS is shifted along the reaction coordinate toward the products with respect to the position of TS in the reactions involving pyridine. This, in turn, should result according to the Leffler–Hammond postulate in an increase in the activation barrier for the reactions of imidazoles and in a decrease in the reaction rates with respect to those for the reactions involving pyridines, as is actually observed in the experiment.

In conclusion, we note that the question of what makes the TS in imidazole reactions more product-like and thus accounts for their lower reactivity is still open. In view of the fact that imidazoles contain an easily polarised –NH–CH=N– moiety, which incorporates the nucleophilic 'pyridine' nitrogen atom =N–, and taking into account stabilisation of the TS due to the electron-releasing mesomeric effect of the pyrrole nitrogen atom –N(H)–, one should expect that they would be more reactive than pyridines in nucleophilic substitution. In this context, the lower reactivity of imidazoles observed in our study is a special phenomenon, which requires further investigation.

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