The Acidity of Weak Carbon Acids. Part 5.[1] The Kinetic Acidities of Substituted Benzyl Cyanides using Substituted Benzylamines as Bases

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The rate coefficients for the base-catalysed detritiation of a series of *meta*-substituted benzyl cyanides in DMSO have been measured at 25.0 °C. The bases are a series of *meta*/*para*-substituted benzylamines. Brønsted coefficients, α and β, have been calculated from both the known pK_a values of the substrates and measured pK_a values of the conjugate acids of the bases in DMSO. The mean α and β values of *ca.* 0.72 and 0.64 are close. There is no selectivity–reactivity relationship apparent. The results are related to Marcus and related treatments.

The acidity of benzyl and arylalkyl cyanides has been of interest for some time. The pK_a values of such carbon acids have been measured using H_- acidity function methods in aqueous and ethanolic dimethyl sulphoxide (DMSO)-containing base.[2,3] However, a comprehensive study of the ionisation of many carbon acids in DMSO has been made by Bordwell *et al.*,[4] which includes a large number of arylalkyl cyanides. The reactivity and stereochemistry of the carbanions derived from such arylalkyl cyanides has been studied in depth by Cram.[5] More recently, the kinetic and equilibrium acidities of 4-nitro- and 2,4-dinitrobenzyl cyanide and 9-cyanofluorene in 50% aqueous DMSO have been investigated by Bernasconi *et al.*[6,7]

In Part 3 of this series the kinetic acidities of substituted benzyl cyanides were studied by measuring the rates of detritiation by secondary aliphatic amines and guanidines.[8] A matrix of rate coefficients allowed a series of complementary Brønsted α and β values to be generated, which enabled conclusions to be derived regarding the 'nature' of the transition state for the reaction. A more ideal system in which to study such effects would be to construct the matrix using non-proximate polar substituents in both acid and base to vary the acid/base strength with a constant and relatively sterically unhindered reaction site. In the present study we report the rate of detritiation of a series of *meta*-substituted benzyl cyanides in DMSO by a series of *meta*/*para*-substituted benzylamines. The rates are discussed in terms of reactivity-selectivity and the structure of the transition state.

Results

The rate coefficients, k_2, for the base-catalysed detritiation of a series of *meta*-substituted benzyl cyanides in DMSO at 25.0 °C are shown in Table 1. The bases used are a series of *meta*/*para*-substituted benzylamines. The reactions were found to be first order in the substrate and in the base. The rate coefficients, k_2, were calculated by dividing the base concentration into the observed first-order rate coefficients. Table 2 shows the pK_a values of both the carbon acids and the conjugate acids of the bases in DMSO. The Hammett equation (1) has been used to correlate the rates of detritiation using known σ values.[9] The results for the latter are shown in Table 3.

$$\log(k/k_0) = \rho\sigma \quad (1)$$

Discussion

As in our previous study[8] the kinetic acidities of the *meta*-substituted benzyl cyanides have been studied in DMSO. The present study employs as the bases primary amines, a series of *meta*/*para*-substituted benzylamines. Thus, in this study, both series of carbon acids and amines have constant and unvaried reaction centres, with the variation in the acidity and basicity arising from distant substitution. Both reaction centres are relatively sterically unhindered and it is possible to generate a matrix of ρ values as shown in Table 3. The ρ values for the equilibrium ionisation of the relevant benzyl cyanides is 5.65 in DMSO at 25.0 °C, as calculated previously.[8] The Brønsted coefficient, α, can be calculated by use of eqn. 2 below for this

$$\alpha = \rho_{k_2}/\rho_{K_a} \quad (2)$$

study using the reaction constants for both kinetic and equilibrium acidity. These values are shown in Table 2 and vary from 0.70–0.74. The parameter α has been interpreted as a measure of the extent to which the transition state resembles reactants or products.[10] The values observed in this study are very close to those observed previously[8] for secondary amines with α in the range 0.71–0.77. It has been suggested[11] that α should only be regarded as a 'rough' qualitative guide to transition state structure. Similarly, the Brønsted coefficient, β, can be calculated by use of eqn. (3) below for this study using

$$\beta = \rho_{k_2}/\rho_{K_b} \quad (3)$$

the reaction constants for both kinetic and equilibrium basicity. These values are shown in Table 2, where β varies from 0.57–0.69. However, the values of β found in our previous study[8] using secondary amines are significantly greater and are in the range 0.91–0.93.

As in our previous study,[8] there appears to be no evidence for a reactivity-selectivity relation[12] in the present investigation. The values of dβ/dpK_a (benzyl cyanides) and dα/dpK_a (benzylamines) are 0.03 ($\pm$0.003) and 0.03 ($\pm$0.01), respectively. These Hammond coefficients are effectively zero, notwithstanding the small ranges for the end atom effect variations.[12]

A likely possibility appears to be that the transition state is not a simple function of migration between substrate and the strongly resonance-stabilised, sp^2-hybridised carbanion product. The transition state could have involvement of sp^3-hybridised character.[8] The charge localisation on the α-carbon would be greater and give rise to greater dependence on the substituent polar effect. Hence, in this study, the transition state is 'viewed' from both acid and base and clearly conforms to such a picture of the reaction process.

Table 1. Rate coefficients, k_2, for the detritiation of *meta*-substituted benzyl cyanides by *meta/para*-substituted benzylamines in DMSO at 25.0 °C.[a]

	$k_2/10^{-4}$ dm^3 mol^{-1} s^{-1}					
	Substituent R[b]					
Substituent R[c]	H	4-Me	4-OMe	4-Cl	3-CF$_3$	3,4-Cl$_2$
H	13.4	19.8	24.7	7.13	4.26	3.01
Me	10.0	13.0	16.9	4.15	2.79	1.97
OMe	26.3	34.2	44.2	12.0	7.16	5.43
Cl	544	723	913	324	178	135
Br	604	857	1 080	348	192	149
CN	2 310	3 230	5 650	1 290	801	589
NO$_2$	10 200	14 200	16 400	6 490	3 590	2 790

[a] Rate coefficients are reproducible to ±3%. [b] In *meta/para*-substituted benzylamines, *m/p*-$RC_6H_4CH_2NH_2$. [c] In *meta*-substituent benzyl cyanides, *m*-$RC_6H_4CH_2CN$.

Table 2. pK_a values and Brønsted coefficients, α and β, for the *meta*-substituted benzyl cyanides and the conjugate acids of the *meta/para*-substituted benzylamines in DMSO at 25.0 °C.

		pK_a	α
Substituent R[a]	H	9.81	0.71
	4-Me	10.24	0.71
	4-OMe	10.32	0.70
	4-Cl	9.41	0.74
	3-CF$_3$	9.23	0.73
	3,4-Cl$_2$	8.96	0.74

		pK_a	β
Substituent R[b]	H	21.91	0.67
	Me	22.19	0.69
	OMe	21.62	0.68
	Cl	19.44	0.61
	Br	19.50	0.64
	CN	18.69	0.59
	NO$_2$	18.11	0.57

[a] In *meta/para*-substituted benzylamines, *m/p*-$RC_6H_4CH_2NH_2$. [b] In *meta*-substituted benzyl cyanides, *m*-$RC_6H_4CH_2CN$.

Table 3. Reaction constant, ρ, for the *meta/para*-substituted benzylamine-catalysed detritiation of *meta*-substituted benzyl cyanides in DMSO at 2.0 °C.[a]

		ρ	*s*	log k_0	*r*	*n*
	Base					
Substituent R[b]	H	4.020	0.115	−2.846	0.996	7
	4-Me	4.034	0.117	−2.713	0.996	7
	4-OMe	3.969	0.120	−2.603	0.996	7
	4-Cl	4.208	0.129	−3.175	0.995	7
	3-CF$_3$	4.140	0.127	−3.384	0.995	7
	3,4-Cl$_2$	4.184	0.123	−3.525	0.996	7
	Acid					
Substituent R[c]	H	−1.076	0.016	−2.890	0.999	6
	Me	−1.111	0.047	−3.065	0.994	6
	Me	−1.092	0.041	−2.639	0.995	6
	Cl	−0.976	0.029	−1.292	0.997	6
	Br	−1.020	0.026	−1.286	0.998	6
	CN	−0.951	0.025	−0.667	0.998	6
	NO$_2$	−0.919	0.030	−0.010	0.996	6
Ionisation of the conjugate acids of the *meta/para*-substituted benzylamines		1.603	0.108	9.88	0.991	6

[a] *s* = standard deviation, *r* = correlation and *n* = number of points. [b] In *meta/para*-substituted benzylamines, *m/p*-$RC_6H_4CH_2NH_2$. [c] In *meta*-substituted benzyl cyanides, *m*-$RC_6H_4CH_2CN$.

Bell[13] considered that there is no thermodynamic requirement for α and β to be equal. In some systems, very different values of α and β have been found.[14,15] This study has values of α and β equal to 0.71 (benzylamine) and 0.67 (benzyl cyanide), which are close. It seems very likely that this 'coincidence' arises because of the absence of any 'important' steric interactions in the transition state unlike those in our previous study.[8]

The formalisation provided by Marcus theory has enabled Bernasconi[14] to put forward eqn. (4) shown below. This relates

$$\log k'_0 = \log k_1 + \beta \log K_1 \qquad (4)$$

the intrinsic rate coefficient, k'_0, to the forward rate coefficient for ionization, k_1, for the situation where $\Delta G^0 = 0$, *i.e.* $K_1 = 1$. This treatment has been applied in our previous study[8] to benzyl cyanide–piperidine in DMSO to give log k'_0 as 9.76. The value calculated for benzyl cyanide–benzylamine from the present results is 6.38, assuming a tritium isotope effect of 14. The two values for benzyl cyanide are quite different and can be compared to the values of 3.70 and 2.70 reported[6] for 4-nitro- and 2,4-dinitrobenzyl cyanide, respectively, in 50% aqueous DMSO. It has been considered that high intrinsic barriers are associated with a lack of synchronization between bond formation/cleavage and charge or resonance development, *etc.*[15]

Eqn. (5) has been developed from Marcus theory to enable

$$\beta = \frac{\Delta G^{\ddagger}}{\Delta G^0} - \left[\left(\frac{\Delta G^{\ddagger}}{\Delta G^0}\right)^2 - \left(\frac{\Delta G^{\ddagger}}{\Delta G^0}\right)\right]^{\frac{1}{2}} \qquad (5)$$

the calculation of the Brønsted coefficient.[16] The calculated and observed values for β can then be compared. Thus, β can be calculated as 0.68 using benzyl cyanide and piperidine. This is in excellent agreement with the observed value of 0.67. An alternative treatment developed by Lewis–More O'Ferrall[16] gives eqn. (6) below. The value of β calculated from this

$$\beta = (2 - \Delta G^0/\Delta G^{\ddagger})^{-1} \qquad (6)$$

expression is 0.81, which is in poor agreement with the observed value.

pK_a *Values of the Conjugate Acids of the Benzylamines.*—The pK_a values of the conjugate acids of the *meta*/*para*-substituted benzylamines, shown in Table 2, have been measured in DMSO at 25 °C. The ρ value obtained is *ca.* 1.60, as shown in Table 3. The corresponding value for the substituted benzylamines in water at 23 °C is 1.23.[17] The corresponding values for the substituted anilines in water and in DMSO are 2.89 [18] and *ca.* 4.6,[19] respectively. The effect on ρ values for the protonation of these amines on transferral from water to DMSO is similar, but unlike those for a number of other acid types.[4]

Experimental

Materials.—The *meta*-substituted benzyl cyanides were prepared, purified and tritiated or deuteriated as previously described.[8] The 3-, 4- or 3,4- substituted benzylamines were available commercially as pure compounds, with the exception of 3-trifluoromethybenzylamine. The latter was prepared by the method of Cherbuliez *et al.*[20] They were then redistilled before use. Other solvents and materials were prepared as previously described.[8]

Kinetic Measurements.—The rates of detritiation were studies as described previously.[8]

pK_a *Determinations.*—The pK_a values of the benzylamines were measured as described by others [21] using a potentiometric method in DMSO at 25.0 ($\pm$0.1) °C with titration by sulphuric acid in DMSO. A direct reading pH meter, the Pye-Unican model PW9409, together with a glass electrode (401E07) and reference electrode (AgCl/DMSO),[21,22] was used. The pH scale was checked before and after use with 0.1 mol dm^{-3} sulphuric acid in DMSO.

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Paper 0/01969K
Received 3rd May 1990
Accepted 13*th August* 1990