Thermodynamic Analysis of Substituent Effects on Proton Dissociation Equilibria of Substituted Pyridines

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Equilibrium constants for the dissociation of $RC_5H_4NH^+$ (R = 3- and 4-Br, 3- and 4-CN, and 2- and 3-NH_2) have been measured as a function of temperature in the range 5—65 °C. For these and other literature data (R = H, 2-, 3-, and 4-NO_2, 2-, 3-, and 4-Me, 2-, 3-, and 4-CHO, 2-, 3-, and 4-Ac, 2-CH_2NHMe, and 4-NH_2) thermodynamic functions (ΔG^0, ΔH^0, and ΔS^0) have been calculated by a thermodynamic optimization method and by the Clarke and Glew procedure. Substituent effects, the environmental parameter for the reaction series examined, and solvent–solute interactions are discussed on the basis of Hepler's dichotomized enthalpy–entropy model, and the approach developed by Bolton *et al.*

RECENT investigations[1-4] of thermodynamics of acid–base equilibria in terms of a dichotomized enthalpy–entropy model[5-8] have led to useful information about interpretation of substituent effects and solvent–solute interactions. In view of our interest in the thermodynamics of protonation of substituted pyridines and associated solvent effects, we have investigated the proton dissociation equilibria (1) (R = 3- and 4-Br, 3- and 4-CN, and 2- and 3-NH_2) of some monosubstituted

$$RC_5H_4NH^+ \underset{H_2O}{\overset{K_a}{\rightleftharpoons}} RC_5H_4N + H^+ \qquad (1)$$

pyridinium ions in aqueous solution as a function of temperature. To these data and to those of other

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papers,[9,10] as well as to other selected literature data, we have applied the approach developed by Hepler [5-8] and Bolton [1-4] and their co-workers, in order to assess quantitatively the relative importance of solvation factors in the effect of substituents.

EXPERIMENTAL

Measurements of pK_a.—The technique employed was the same as that already used in earlier work.[9-11]

RESULTS AND DISCUSSION

Equilibrium (1) was measured as a function of temperature in the range 5—65 °C. Determination of the acid–base concentration ratio was carried out spectrophotometrically in buffered solutions at constant ionic strength (0·02M). The results in the form of pK_a values and their standard deviations are summarized in Table 1.

TABLE 1

pK_a (K_a in mol l^{-1}) Values for reaction (1) as a function of temperature

T/K	R = 3-Br	R = 4-Br	R = 3-CN	R = 4-CN	R = 2-NH$_2$	R = 3-NH$_2$
278·2	2·83 ± 0·016	3·87 ± 0·029	1·13 ± 0·018	1·47 ± 0·029	7·14 ± 0·03	6·36 ± 0·03
288·2	2·77 ± 0·021	3·77 ± 0·010	1·15 ± 0·013	1·475 ± 0·015	6·98 ± 0·03	6·25 ± 0·04
293·2					6·82 ± 0·02	
298·2	2·72 ± 0·013	3·68 ± 0·008	1·17 ± 0·022	1·48 ± 0·021	6·71 ± 0·02	6·03 ± 0·04
308·2	2·68 ± 0·025	3·60 ± 0·017	1·19 ± 0·012	1·485 ± 0·018	6·54 ± 0·02	5·91 ± 0·04
318·2	2·64 ± 0·012	3·53 ± 0·030	1·20 ± 0·023	1·49 ± 0·008	6·38 ± 0·03	5·77 ± 0·02
328·2	2·60 ± 0·023	3·46 ± 0·021	1·22 ± 0·019	1·493 ± 0·014		
338·2	2·55 ± 0·026	3·38 ± 0·026	1·13 ± 0·009	1·50 ± 0·012		

TABLE 2

Thermodynamic functions and constants for reaction (1)

R No.	3-Br 1	4-Br 2	3-CN 3	4-CN 4	2-NH$_2$ 5	3-NH$_2$ 6	4-NH$_2$ 7	2-NO$_2$ 8	3-NO$_2$ 9	4-NO$_2$ 10
ΔG^0/cal mol^{-1} at 298·2 K [a]	3711	5021	1596	2019	9154	8227	12429 [18]	−2811 [10]	1078 [10]	1678 [10]
A/cal mol^{-1} K^{-1}	4·00	7·00	−1·25	−0·20	19·90	15·60	27·50	−2·46	−1·97	−2·12
$\Delta H_0{}^0$/cal mol^{-1}	604	1033	−223	−63	2237	1664	3341	−4986	−1257	−468
I/cal mol^{-1} K^{-1}	33·20	53·24	−1·01	5·84	136·62	111·00	187·10	−6·73	3·40	−4·88
ΔG^0/cal mol^{-1} at 298·2 K [b]	3711	5021	1596	2019	9179	8265	12429	−2911	1078	1678
ΔH^0/cal mol^{-1} at 298·2 K [b]	1797	3120	−596	−123	8170	6315	11540	−5719	−1844	−1100
ΔS^0/cal mol^{-1} K^{-1} at 298·2 K [b]	−6·44	−6·39	−7·35	−7·17	−3·49	−6·64	−3·13	−9·72	−9·77	−9·50
ΔG^0/cal mol^{-1} at 298·2 K [c]	3711	5020	1596	2019	9170	8262	12431	−2669	1106	1702
ΔH^0/cal mol^{-1} at 298·2 K [c]	1768	3311	−750	−188	8288	7374	11211	−6809	−2022	−1079
ΔS^0/cal mol^{-1} K^{-1} at 298·2 K [c]	−6·52	−5·73	−7·87	−7·40	−2·95	−2·97	−4·09	−13·80	−10·49	−9·33
ΔC_p/cal mol^{-1} K^{-1} at 298·2 K [c]	−16·49	−17·45	1·74	−0·13	−63·38	−13·63	3·30	96·16	17·89	10·81
$d(\Delta C_p)/dT$/cal mol^{-1} K^{-2} [c]	2·05	1·88	0·08	−0·13	−8·80	−24·50	0·51	0·00	0·00	0·00

R No.	2-Me 11	3-Me 12	4-Me 13	2-CHO 14	3-CHO 15	4-CHO 16	2-Ac 17	3-Ac 18	4-Ac 19	H 20	H 21	2-CH$_2$-NHMe 22
ΔG^0/cal mol^{-1} at 298·2 K [a]	8117 [14]	7722 [14]	8186 [14]	5131 [15]	5045 [15]	6180 [15]	3601 [16]	4447 [16]	4788 [16]	7180 [9]	7080 [14]	12207 [17]
A/cal mol^{-1} K^{-1}	18·00	16·10	18·00	16·50	12·00	15·00	7·50	7·40	9·50	−2·70	12·50	27·25
$\Delta H_0{}^0$/cal mol^{-1}	2046	1871	2114	1800	1596	1678	1091	945	985	4830	1603	2548
I/cal mol^{-1} K^{-1}	122·87	111·31	122·87	105·14	79·90	100·52	51·13	53·89	66·85	−7·85	89·55	187·22
ΔG^0/cal mol^{-1} at 298·2 K [b]	8117	7722	8186	5131	5045	6180	3601	4447	4788	7120	7080	12207
ΔH^0/cal mol^{-1} at 298·2 K [b]	7412	6671	7480	6719	5173	6150	3327	3151	3817	4020	5329	10536
ΔS^0/cal mol^{-1} K^{-1} at 298·2 K [b]	−2·45	−3·71	−2·45	5·24	0·38	−0·17	−0·96	−4·39	−3·50	−10·40	−5·93	−5·19
ΔG^0/cal mol^{-1} at 298·2 K [c]	8125	7725	8184	5130	5031	6170	3618	4451	4794	7112	7075	12205
ΔH^0/cal mol^{-1} at 298·2 K [c]	7572	7055	7029	6946	5564	6237	3502	2622	3560	4352	6409	10592
ΔS^0/cal mol^{-1} K^{-1} at 298·2 K [c]	−1·85	−2·24	−3·87	6·09	2·32	0·22	−0·38	−6·13	−4·13	−9·25	−2·23	−5·50
ΔC_p/cal mol^{-1} K^{-1} at 298·2 K [c]	78·92	47·68	−275·33	52·85	5·64	39·54	0·70	−2·06	15·57	20·74	−116·15	375·00
$d(\Delta C_p)/dT$/cal mol^{-1} K^{-2} [c]	−17·06	−14·06	65·77	−0·79	−7·30	4·86	−7·06	7·65	4·43	−3·14	2·37	−65·80

[a] Experimental values (and standard deviation). [b] Calculated values [thermodynamic optimization method, equation (2)]. [c] Values obtained by the Clarke and Glew procedure.

For the calculation of thermodynamic functions from equilibrium data, two procedures were employed. In the first, which had been already used in previous papers,[9,10] the free energy changes ΔG^0 of reaction (1) were fitted to the thermodynamic equation (2) which

$$\Delta G^0 = \Delta H_0{}^0 + AT \ln T + IT \qquad (2)$$

represents ΔG^0 as a function of temperature in the particular case in which the difference (ΔC_p) between molar heat capacities of products and reactants ($A = \Delta C_p = d\Delta H^0/dT$) may be considered constant in the temperature range investigated. The values of the constants $\Delta H_0{}^0$, A, and I were obtained by an optimization procedure and are given in Table 2.

The thermodynamic functions were also calculated by the method developed by Clarke and Glew.[12] Computation was carried out by the regression equation containing only three temperature-dependent variables, as the precision of the data did not allow a greater

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complexity than this. The application of this procedure to acid ionization data has been thoroughly discussed.[1-4,13] The recommended procedure was followed, with minor differences, such as that of calculating temperature variables by a suitable subroutine program.

By both calculation methods [use of equation (2), which we shall call hereafter the thermodynamic optimization method, and the Clarke and Glew procedure], the free energy (ΔG^0), enthalpy (ΔH^0), and entropy (ΔS^0) of reaction (1) could be evaluated as continuous, well-behaved functions of temperature. Their values at 298·2 K as well as those for equilibrium (1) with R = H and 2-, 3-, and 4-NO_2 are reported in Table 2. pK_a Values for these latter equilibria were taken from previous measurements[9,10] which had previously been fitted only to equation (2).

The same type of treatment (*cf.* Table 2) was also applied to other literature data for the proton dissociation of monosubstituted pyridinium ions in aqueous solution which meet the requirement of having been measured over the temperature range 5—65 °C. They include ions where R = H,[14] 2-, 3-, and 4-Me,[14] 2-, 3-, and 4-CHO,[15] 2-, 3-, and 4-Ac,[16] 2-CH_2NHMe,[17] and 4-NH_2.[18]

The free energy and the enthalpy changes for the proton dissociation of pyridinium ions are linearly correlated. The points which deviate most are those for *ortho*-pyridinium ions (2-Ac, 2-CHO, 2-CH_2NHMe) and those for CHO and Ac groups (after excluding data for these derivatives $\Delta G^0_{298\cdot2\,K}$/cal mol^{-1} = 0·836$\Delta H^0_{298\cdot2\,K}$/cal mol^{-1} + 2453; correlation coefficient r = 0·9881 by the Clarke and Glew treatment; $\Delta G^0_{298\cdot2\,K}$/cal mol^{-1} = 0·911$\Delta H^0_{298\cdot2\,K}$/cal mol^{-1} + 2274; r = 0·9892 by the thermodynamic optimization method).

The anomalous behaviour of CHO and Ac groups is also shown by the Hammett σ plot and may be explained, partly at least, in terms of hydrogen bonding, since the protonated nitrogen of a pyridinium ion is one of the most electron-attracting side chains which can be visualized.[19]

Experimental data for unsubstituted pyridine deserve more comment. While measurements of pK_a by Perkampus and Prescher[14] substantially agree with those of a previous paper[9] in the range 20—30 °C, a certain discrepancy arises at higher temperatures, so that the data of these authors yield for the enthalpy of reaction at 298·2 K a value of 6·41, by the Clarke and Glew method, and 5·33 kcal mol^{-1} by the thermodynamic optimization method, as compared with 4·35 and 4·02 kcal mol^{-1} respectively (see Table 2) obtained from the experimental data of ref. 9. The latter values are 0·45—0·78 kcal mol^{-1} below the calorimetric value;[20] those derived from Perkampus and Prescher exceed it by 1·21—0·53 kcal mol^{-1}. The reason for this is not clear; it may be simply attributed to experimental uncertainties, particularly in the measurements of pK_a at high temperatures. This explanation, however, is not entirely satisfactory, since in this circumstance the same scattering should be observed for all other points.

As it has been observed for a limited number of data,[10] and can be assessed more clearly now for the comprehensive series of ions examined in this paper (*cf.* Table 2), entropy changes, associated with solvation factors, are scarcely influenced by substituents. The correlation $\Delta S^0_{298\cdot2\,K}$ *vs.* $\Delta H^0_{298\cdot2\,K}$ shown graphically in Figure 1*a* ($\Delta S^0_{298\cdot2\,K}$/cal mol^{-1} K^{-1} = 5·63 × 10^{-4} $\Delta H^0_{298\cdot2\,K}$/cal mol^{-1} − 8·087; r = 0·8133, by the Clarke and Glew procedure) reaches the limit of acceptability only when *ortho*-derivatives, as well as those containing CHO and Ac groups, are excluded. The points for unsubstituted pyridine and for 4-aminopyridine are the most scattered, notwithstanding the fact that the experimental data for the latter[18] are to be considered among the most reliable: their exclusion leads to the better correlation of Figure 1*b* ($\Delta S^0_{298\cdot2\,K}$/cal mol^{-1} K^{-1} = 7·51 × 10^{-4} $\Delta H^0_{298\cdot2\,K}$/cal mol^{-1} − 8·03; r = 0·9678). It has been shown that such isoequilibrium relationships[21] derive, by thermodynamics, from the Hammett $\sigma\rho$ equation and the assumption $\delta\Delta C_p = 0$ (where δ indicates the difference between substituted and unsubstituted substrates) both of which are valid over a range of temperatures. The significance and limitations of enthalpy–entropy relationships have been critically discussed.[22]

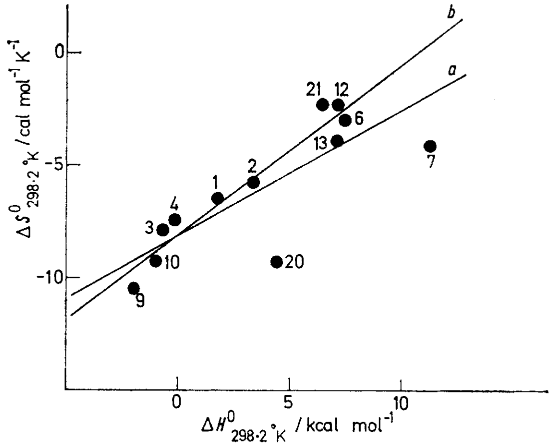

FIGURE 1 Proton dissociation of substituted pyridinium ions in aqueous solution. Entropy *vs.* enthalpy of reaction (1) at 298·2 K (numbers as in Table 2)

In the model proposed by Hepler for substituent and solvent effects, thermodynamic functions are taken to be sums of environmental contributions (solvent–solute

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interactions) and internal contributions (intrinsic to the molecules of acid and base taking part in the acid ionization). With the assumption that $\delta\Delta S^0_{int}$ *ca.* 0 for symmetrical reactions (as a consequence: $\delta\Delta S^0 \approx \delta\Delta S^0_{env}$) and that $\delta\Delta H^0_{int}$ is independent of temperature, this model leads to an isoequilibrium relationship, between substituent-induced changes in enthalpy ($\delta\Delta H^0$) and entropy ($\delta\Delta S^0$), of the form (3) where β_{env} is the

$$\begin{aligned}\delta\Delta H^0 &\approx \beta_{env}\delta\Delta S^0 - [(1+\gamma)/(d\gamma/dT)]\delta\Delta S^0 \\ &\approx \beta_{env}\delta\Delta S^0 + (1+\gamma)\delta\Delta H^0_{int} \qquad (3) \\ &\approx \beta_{env}\delta\Delta S^0 + \delta\Delta G^0\end{aligned}$$

environmental parameter,' and γ is a parameter (' solvent parameter ') that depends on the solvent and the temperature. The evaluation of these parameters has limited the practical application of equation (3). On the other hand, it should be considered a fundamental possibility of obtaining useful information about solvent–solute interactions. Bolton and Hall[2] have derived a method of calculating the environmental parameter β_{env}, based on the comparison of enthalpy changes of two reaction series, A and B, which may be assumed to be proportional [equation (4)]. Expression (5) was

$$\delta\Delta H^0_A = \theta\delta\Delta H^0_B \qquad (4)$$

$$\delta\Delta H^0_A = \theta\delta\Delta H^0_B - \theta\beta_{env_B}\delta\Delta S^0_B + \beta_{env_A}\delta\Delta S^0_A \qquad (5)$$

then obtained. By a set of experimentally measurable quantities, θ, β_{env_A}, and β_{env_B} could thus be evaluated.

Equation (5) was applied to the thermodynamic data (A) examined in the present paper, by using as reference system the corresponding data for anilinium ions (B), for which the value of β_{env_B} of 413 K determined by Bolton and Hall[2] was employed. The problem was thus reduced to a set of systems relating two unknown constants θ and β_{env_A}. Only the thermodynamic functions of proton dissociation of *m*- and *p*-bromo- and nitro-pyridinium ions which were common to both reaction series could be used. From the values of thermodynamic functions of Table 2 and those reported[2] for *m*- and *p*-substituted anilinium ions $\beta_{env_A} = 417 \pm 219$ K and $\theta = 1{\cdot}21 \pm 0{\cdot}80$ were calculated, the uncertainties being given as standard deviations. Elimination of the pair of equations for R = 3- and 4-NO_2, which showed the greatest scattering in β_{env_A} and θ values, led to the values $\beta_{env_A} = 351 \pm 146$ K, and $\theta = 0{\cdot}956 \pm 0{\cdot}419$.

From the known value of environmental parameter the $\beta_{env}\delta\Delta S^0$ and $(1+\gamma)\delta\Delta H^0_{int}$ terms were calculated by equation (3). Results are summarized in Table 3. The $(1+\gamma)\delta\Delta H^0_{int}$ values, which equal $\delta\Delta G^0$ [*cf.* equation (3)], show an excellent correlation with the substituent constant σ as shown in Figure 2. Furthermore, they agree fairly well with experimental $\delta\Delta G^0$ values which are reported in Table 3 for comparison. Determination of environmental ($\delta\Delta H^0_{env} = \beta_{env}\delta\Delta S^0 + \gamma\delta\Delta H^0_{int}$) and intrinsic ($\delta\Delta H^0_{int}$) enthalpy contributions is not possible without knowing the value of the solvent parameter γ. The term $\beta_{env}\delta\Delta S^0$ gives quantitative information on the differential enthalpy effects brought about by substituents for the system in different states of solvation.

The good agreement of the β_{env} value for pyridinium ions with that for anilinium ions, which are of the same charge type, satisfies the requirements of Hepler's model. However, evidence indicating that the environmental parameter is approximately equal to the temperature of the solution should be considered as a consequence of the approximations involved, rather than thought to have any other physical meaning. This statement, in fact, directly follows from assumptions made in Hepler's theory and equation (3) itself.

TABLE 3

Comparison of $\beta_{env}\delta\Delta S^0$ and $(1+\gamma)\delta\Delta H^0_{int}$ terms in equation (3) with experimental $\delta\Delta G^0$ values, at 298·2 K

R	$\beta_{env}\delta\Delta S^0$/ cal mol^{-1} [a]	$(1+\gamma)$ $\delta\Delta H^0_{int}$ cal mol^{-1} [a]	$\beta_{env}\delta\Delta\delta^0$/ cal mol^{-1} [b]	$(1+\gamma)$ $\delta\Delta H^0_{int}$/ cal mol^{-1} [b]	$\delta\Delta G^0$/ cal mol^{-1} [c]
3-CN	−1180	−5179	−2352	−4807	−5508
4-CN	−1815	−4782	−2256	−4341	−5089
3-Br	−1506	−3135	−1789	−2852	−3397
4-Br	−1228	−1870	−1460	−1638	−2087
3-NH_2	260	705	309	656	1119
4-NH_2	−653	5455	−776	5578	5321
3-NO_2	−2889	−5542	−3432	−4999	−6030
4-NO_2	−2492	−4996	−2961	−4527	−5430
3-Me	−3·5	650	−4·1	650	614
4-Me	−576	1196	−684	1304	1078
3-Ac	−1369	−2418	−1626	−2161	−2661
4-Ac	−667	−2182	−792	−2057	−2320

[a] Calculated values with $\beta_{env} = 351$ K. [b] Calculated values with $\beta_{env} = 417$ K. [c] Experimental values.

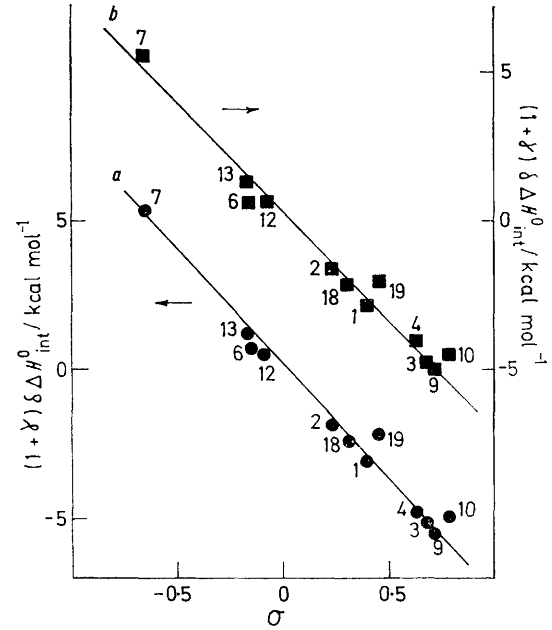

FIGURE 2 Proton dissociation of substituted pyridinium ions, $(1+\gamma)\delta\Delta H^0_{int}$ at 298·2 K *vs.* substituent constants σ: *a*, (ordinate to the left) with $\beta_{env} = 351$ K; *b*, (ordinate to the right) with $\beta_{env} = 417$ K (numbers as in Table 2)

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