The Basicities of Substituted *N*-Trimethylammoniophenylacetamidates and *N*-Trimethylammoniocinnamamidates. The Hammett Correlations and the Thermodynamics of Protonation

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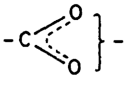
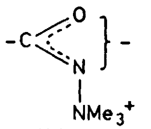
The pK_a values of a number of substituted *N*-trimethylammoniophenylacetamidates and *N*-trimethylammoniocinnamamidates have been determined over a range of temperature and the thermodynamic functions of protonation (ΔH° and ΔS°) derived. Both reaction series obey the Hammett equation very well, the ρ values at 25 °C being 0.639 ± 0.026 and 0.709 ± 0.049, respectively. It is found that the ratio of these ρ values to the ρ values for the ionization of the corresponding carboxylic acids is constant at 1.50 ± 0.04, regardless of the structure of the rest of the molecule, and is thus a characteristic of the amidate group. An analysis of the pK_a data for these acid–base series and comparison with the pK_a data for the corresponding carboxylic acid series leads to the conclusion that mesomeric electron donation by the benzene ring to the basic groups (a) and (b) is more important in the carboxylates than in the amidates, consistent with the greater overall electronegativity of the carboxylate group. The thermodynamic functions of protonation, ΔH° and ΔS°, broadly show a similar behaviour to that of the *N*-trimethylammoniobenzamidate series, although the entropies of protonation are more positive.

THE recently published study of the basicities of *N*-trimethylammonioacetamidate and of substituted *N*-trimethylammoniobenzamidates[1] has led to some interesting observations on the Hammett correlation of the pK_a values and on the thermodynamic functions of protonation of these compounds. The question of the extent of mesomeric interaction of the benzene ring with the carboxylate group (a), on the one hand, and the amidate group (b), on the other, was raised on the basis of the results obtained, but remained unanswered. For this reason, it seemed of interest to examine two further acid–base series, *N*-trimethylammoniophenylacetamidates (1) in which the mesomeric interaction is blocked by the methylene group, and *N*-trimethylammoniocinnamamidates (2) in which the mesomeric interaction is operative, being transmitted by the ethylene group.


(a)


(b)

We also wished to find out whether the correlations of thermodynamic functions of protonation found for the benzamidate series[1] would also hold for these two series, and therefore thermodynamic functions of protonation were also determined. The results provide some answers to these questions.

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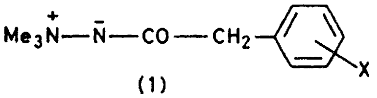
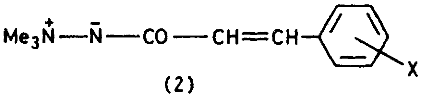
[1] W. H. Beck, M. Liler, and D. G. Morris, *J.C.S. Perkin II*, 1977, 1876.

EXPERIMENTAL

Materials.—The *p*-substituted *N*-trimethylammonioamidates in both series (1) and (2) were prepared and characterized by A. M. Murray (Thesis, Glasgow, 1975) and the *meta*-derivatives in series (2) were synthesized by J. D. Stephen (unpublished results), using methods already described.


(1)

X = H, *p*-Br, *p*-F, *p*-MeO, *p*-Me, *p*-NO_2, *p*-Cl


(2)

X = H, *p*-Me, *p*-F, *p*-Cl, *p*-NO_2, *p*-Br, *p*-CF_3, *p*-MeO, *m*-F, *m*-Cl, *m*-Me, *m*-NO_2, *m*-CF_3, *m*-MeO

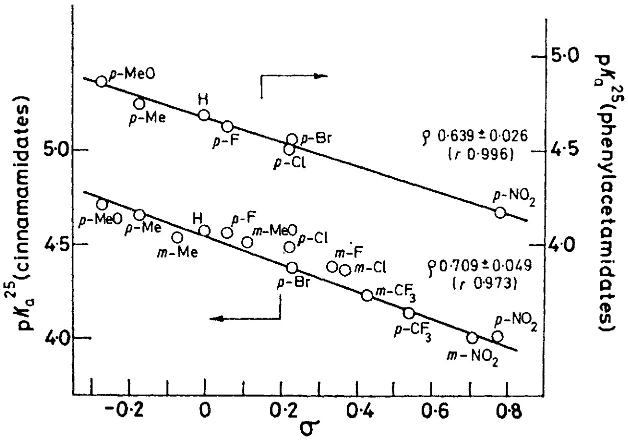
Measurements.—pH Measurements were carried out as before,[1] except that the pH meter used was the EIL model 7050. The temperature range was again 15—55 °C. The samples were shown by titration to contain generally less than 5% impurity, except the cinnamamidate and its *p*-fluoro derivative, which contained up to 12% impurity (probably NaI). Measurements were carried out on 0.1M (or a little less concentrated) half-neutralized solutions. A few derivatives showed insufficient solubility of either the amidate itself (*m*-bromocinnamamidate) or of its hydrochloride salt (*m*-cyanocinnamamidate). The results for these derivatives, being of probably lower accuracy, are not reported.

The thermodynamic pK_a values and the thermodynamic functions of protonation were calculated as before.[1] The correlation coefficients for the plots of pK_a *versus* $1/T$ were comparable with those for benzamidates. All the plots were linear to the eye, except those for *p*-trifluoromethyl-, *p*-bromo-, and *p*-chloro-cinnamamidates, which showed upward curvature. The results for both the pK_a values at 25 °C and the thermodynamic functions of protonation, $\Delta H°$ and $\Delta S°$, are summarized in Tables 4 and 5.

RESULTS AND DISCUSSION

The Hammett Correlations.—The two Hammett plots, both with very high correlation coefficients, are shown in the Figure. The pK_a ranges for the two series are closely similar, hence the relative shift of the ordinates by 0.5 pK_a units. Both correlations are seen to be with σ constants, as was found for the benzamidate series also.[1] As expected, there is an attenuation in the transmission of substituent effects due to the bridging groups in both series. The attenuation factors or transmission coefficients ($\pi = \rho/\rho_0$, where ρ_0 is the value for the benzoic acid derivatives) were calculated using the ρ values obtained from the Figure and the value, $\rho = 1.51$, earlier obtained for the benzamidate series.[1] For the ethylene group, data on pK_a values for the cinnamamidates give a π value of 0.470, closely similar to that obtained from the *trans*-cinnamic acid series ($\pi \equiv \rho = 0.466$).[2] For the methylene group, a variety of ρ values were reported,[2,3] based on different treatments of the pK_a values of phenylacetic acids. For this reason, a straightforward Hammett plot of the pK_a values from two literature sources[3,4] was constructed and yielded a ρ value ($\equiv \pi$) of 0.438 (*r* 0.990). The pK_a values of the phenylacetamidates studied here yield a somewhat lower value, π 0.423. Thus, from these results, the ethylene bridging group transmits substituent effects distinctly better than the methylene group.

The other quantity of interest arising from Hammett plots is the ratio of ρ values for *N*-ammonioamide cations to those for the corresponding carboxylic acids. For the *N*-trimethylammoniobenzamides, this ratio is 1.51 (≡ ρ for the benzamidate series[1]). Table 1 summarizes the ρ values and the corresponding ratios for the acid–base series studied in this work. It can be seen that the value for *N*-trimethylammoniocinnamamides is



Hammett correlations of the pK_a^{25} values for substituted *N*-trimethylammoniophenylacetamidates and *N*-trimethylammoniocinnamamidates

TABLE 1

A comparison of ρ constants for some carboxylic acid and *N*-trimethylammonioamide acid series

Parent acid	δ	Ratio	Ref.
Benzoic	1.00	1.51	By definition
N-Trimethylammoniobenzamide	1.51		*a*
Cinnamic (*trans*)	0.466	1.52	*b*
N-Trimethylammoniocinnamamide (*trans*)	0.709		Present work
Phenylacetic	0.438	1.46	*c*
N-Trimethylammoniophenylacetamide	0.639		Present work

[a] Ref. 1. [b] Ref. 2. [c] From a Hammett plot based on the combined data from refs. 3 and 4.

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[2] H. H. Jaffé, *Chem. Rev.*, 1953, **53**, 191.

[3] A. Fisher, B. R. Mann, and J. Vaughan, *J. Chem. Soc.*, 1961, 1093.

[4] J. F. J. Dippy and F. R. Williams, *J. Chem. Soc.*, 1934, 161.

virtually the same as that for *N*-trimethylammoniobenzamides, whereas the value for *N*-trimethylammoniophenacetamides is a little lower (probably just outside the limits of error). This shows that the characteristics of the two basic groups (in particular, the polarizability of the basic centres) remain the same, whatever the structure of the rest of the molecule. The conjugative interaction between the basic groups (a) and (b) and the benzene ring thus seems to have no effect (or perhaps only a very small effect) on their polarizability.

This conclusion is further supported by a quantity closely related to the ratios of ρ values in Table 1, *i.e.* the ratio of ΔpK_a values, obtained by substituting the phenyl group into acetic acid and into *N*-trimethylammonioacetamidate, respectively (see Table 2). The ratio of ΔpK_a values shown in Table 2 is 1.60 ± 0.08 (assuming an uncertainty of only ± 0.01 in the pK_a values of the amidates), *i.e.* it is not very different from the ratios in Table 1.

TABLE 2

Some pK_a differences involving derivatives of acetic acid

Acid	pK_a^{25}	ΔpK_a	Ref.
Acetic	4.756	0.445	*a*
Phenylacetic	4.311		*b*
N-Trimethylammonioacetamide ion	5.39	0.71	*c*
N-Trimethylammoniophenylacetamide ion	4.68		Present work

[a] G. Kortüm, W. Vogel, and K. Andrussow, ' Dissociation Constants of Organic Acids in Aqueous Solution,' Butterworths, London, 1961. [b] Ref. 3. [c] Ref. 1.

Some Comparisons of pK_a *Differences.*—In the previous paper,[1] it was argued that the much greater ΔpK_a between *N*-trimethylammonio-acetamidate and -benzamidate (1.13 p*K* units) compared with ΔpK_α between acetic and benzoic acids (0.56 p*K* units) is due partly to the more effective inductive electron withdrawal by the benzene ring from group (b) compared with group (a), and possibly partly to a difference in the extent of mesomeric electron release by the ring towards these two groups. The further pK_a data obtained in this work shed more light on this question. The relevant comparisons and ΔpK_a values are shown in Table 3. The first point to note [part (A) of Table 3] is that the *N*-trimethylammonioamidate group is a good deal more basic than the carboxylate group, when attached to a methyl group, which serves as a reference with regard to inductive and mesomeric effects in these systems. The first two pK_a values in Table 3 therefore reflect, in a sense, the ' intrinsic ' basicities of groups (a) and (b). When a phenyl group is introduced as a substituent into the methyl group to give a benzyl group, the basicity of both (a) and (b) groups is reduced, but that of the *N*-trimethylammonioamidate group more so, leading to a smaller ΔpK_a value. This can be ascribed to the more effective inductive electron withdrawal by the phenyl group due to the greater polarizability of group (b) compared with group (a) (in particular, the polarizability of the basic centre, the nitrogen) (see refs. 1 and 5). The same inductive effect is operative in the absence of the bridging methylene group [part (B) of Table 3] and is certainly amplified several times for both groups (a) and (b), which should result in a further reduction in their basicity and in the ΔpK_a. Only a small further reduction in basicity is in fact observed, especially for the carboxylate group, because of the intervention of the mesomeric effect in the opposite direction. This leads to a very small ΔpK_a between benzoate and *N*-trimethylammoniobenzamidate, and also between cinnamate and *N*-trimethylammoniocinnamamidate. It can be estimated, using the pK_a values from part (A) of Table 3, that the operation of the inductive effect of the ring alone would lead to ΔpK_a values in part (B) almost twice as large. The mesomeric effect reduces the difference by operating more effectively (in the sense of electron release) in the carboxyaltes than in the amidates. This is a reasonable conclusion, since one would expect greater electron release towards a group of overall greater electronegativity, as the carboxylate group is, compared with amidate. [The lower ' intrinsic ' basicity of the carboxylate group (a) compared with the amidate group (b) is itself a reflection of its greater electronegativity.]

TABLE 3

Some pK_a differences showing the effect of mesomerism involving the benzene ring

Acid	pK_a^{25}	ΔpK_a	Ref.
(A) Mesomerism absent			
Acetic acid	4.76	0.63	*a*
N-Trimethylammonioacetamide ion	5.39		*b*
Phenylacetic acid	4.31	0.37	*c*
N-Trimethylammoniophenacetamide ion	4.68		Present work
(B) Mesomerism present			
Benzoic acid	4.20	0.06	*a*
N-Trimethylammoniobenzamide ion	4.26		*b*
Cinnamic acid (*trans*)	4.44	0.13	*a*
N-Trimethylammoniocinnamamide ion (*trans*)	4.57		Present work

[a] G. Kortüm, W. Vogel, and K. Andrussow, ' Dissociation Constants of Organic Acids in Aqueous Solution,' Butterworths, London, 1961. [b] Ref. 1. [c] Ref. 3.

The Thermodynamic Functions of Protonation.—As expected, the thermodynamic functions of protonation in both reaction series (Tables 4 and 5) are broadly similar to those reported for *N*-trimethylammonioacetamidate and substituted *N*-trimethylammoniobenzamidates:[1] all protonations are exothermic and involve an entropy

TABLE 4

pK_a Values and thermodynamic functions for the protonation of the *N*-ammoniophenylacetamidates

Substituent	pK_a	$\Delta H°$ / kJ mol^{-1}	$T\Delta S°$ / kJ mol^{-1}	$\Delta S°$ / J K^{-1} mol^{-1}
H	4.68	5.51 ± 0.00	21.22 ± 0.06	71.17 ± 0.20
p-Br	4.55	6.01 ± 0.29	19.95 ± 0.35	66.91 ± 1.17
p-F	4.62	4.91 ± 0.26	21.49 ± 0.32	72.06 ± 1.07
p-Me	4.74	5.52 ± 0.32	21.55 ± 0.38	72.27 ± 1.27
p-NO_2	4.17	5.08 ± 0.16	18.74 ± 0.22	62.85 ± 0.74
p-Cl	4.51	5.62 ± 0.16	20.13 ± 0.22	67.52 ± 0.74
p-MeO	4.86	6.68 ± 0.48	21.04 ± 0.54	70.57 ± 1.81

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[5] M. Liler and D. G. Morris, *J.C.S. Perkin II*, 1977, 909.

increase. It is interesting to note, however, that the entropy increases for the protonation of the parent compound in both series (ΔS° +71.2 for the phenylacetamidate and +61.9 J K^{-1} mol^{-1} for the cinnamamidate) are closely similar to that in the protonation of *N*-ammonioacetamidate (ΔS° 65.2 J K^{-1} mol^{-1}) and much higher than the value for *N*-ammoniobenzamidate (ΔS° +51.0 J K^{-1} mol^{-1}). This suggests that the restrictions on the rotation of the benzene ring in the conjugate acid that were thought to be responsible for the low ΔS° value for *N*-ammoniobenzamidate, are absent in the conjugate acids of *N*-ammonio-phenylacetamidate and -cinnamamidate. This seems reasonable, because the bridging groups force the benzene ring out of the sphere of direct steric and/or charge influence of the hydrazinium part of the cation.

TABLE 5

pK_a Values and thermodynamic functions for the protonation of the *N*-ammoniocinnamamidates

Substituent	pK_a	$-\Delta H^0$ kJ mol^{-1}	$T\Delta S^0$ kJ mol^{-1}	ΔS^0 J K^{-1} mol^{-1}
H	4.57	7.63 ± 0.31	18.46 ± 0.37	61.92 ± 1.24
p-Me	4.65	9.38 ± 0.37	17.17 ± 0.42	57.60 ± 1.41
p-F	4.56	8.80 ± 0.65	17.23 ± 0.70	57.80 ± 2.35
p-Cl	4.48	7.97 ± 0.74	17.61 ± 0.80	59.06 ± 2.68
p-NO_2	4.02	3.82 ± 0.40	18.23 ± 0.42	61.14 ± 1.41
p-Br	4.37	6.12 ± 0.60	18.83 ± 0.66	63.14 ± 2.21
p-CF_3	4.13	5.71 ± 0.51	17.87 ± 0.57	59.94 ± 1.90
p-MeO	4.71	6.50 ± 0.13	20.39 ± 0.18	68.39 ± 0.60
m-F	4.37	6.38 ± 0.20	18.57 ± 0.24	62.28 ± 0.80
m-Cl	4.36	6.95 ± 0.00	17.94 ± 0.06	60.17 ± 0.19
m-Me	4.53	7.49 ± 0.50	18.37 ± 0.56	61.61 ± 1.87
m-NO_2	3.97	4.09 ± 0.00	18.57 ± 0.06	62.28 ± 0.19
m-CF_3	4.22	4.93 ± 0.40	19.06 ± 0.46	63.93 ± 1.53
m-MeO	4.51	8.77 ± 0.50	16.98 ± 0.55	56.95 ± 1.87

The correlations of ΔH° and $-T\Delta S^\circ$ values with pK_a are not as good for the present two series as they were found to be for the *N*-ammoniobenzamidates (Figure **3** of ref. 1), partly because of the smaller spread of the pK_a values themselves. Nevertheless, the general trend of both ΔH° and $-T\Delta S^\circ$ values for the proton ionization of *N*-ammoniophenylacetamide cations is roughly parallel to that for *N*-ammoniobenzamide cations, the $-T\Delta S^\circ$ values being higher, and the ΔH° values consequently lower than those for the *N*-ammoniobenzamide cations of comparable pK_a values. The $-T\Delta S^\circ$ values for the proton ionization of *N*-ammoniocinnamamide cations all fall within the range of 17—19 kJ mol^{-1} (except the value for the *p*-methoxy derivative, which is larger) and show virtually no correlation with the pK_a values. The values of ΔH° do show a correlation with pK_a values (*r* 0.847), with the exception of the *p*-methoxy derivative, which deviates substantially. A deviation of the *p*-methoxy derivative from the correlations shown by other derivatives (but in the opposite direction) was ative, which shows a substantial deviation. A deviation of the *p*-methoxy derivative from the correlations shown by other derivatives (but in the opposite direction) was also found in the benzoic acid series.[6] The reasons for these deviations are not clear. Thus the evidence for the solvation effects in these acid–base reactions, which were discussed in ref. 1, is less clear from the thermodynamic functions of protonation for the *N*-ammoniocinnamamidate series, but the values for the *N*-ammoniophenylacetamidate series broadly confirm the kind of behaviour found for the *N*-ammoniobenzamidate series.[1]

[8/117 *Received*, 24*th January*, 1978]

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[6] P. D. Bolton, K. A. Fleming, and F. M. Hall, *J. Amer. Chem. Soc.*, 1972, **94**, 1033.