Basicity of the Carbonyl Group. Part 11.[1] A Re-examination of the Electrophilic Substituent Constants for Amino-substituents from Thermodynamic Measurements

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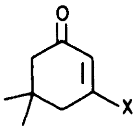
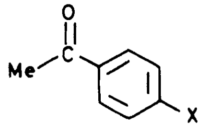
Hammett–Brown correlations between $\sigma_p{}^+$ and pK_{BH^+} values or enthalpies of complexation, $\Delta H°$, with boron trifluoride for three series of carbonyl compounds, 3-substituted 5,5-dimethylcyclohex-2-enones, 4-substituted acetophenones, and benzaldehydes, have enabled a re-evaluation of electrophilic substituent constants for various amino-groups to be made. A relationship is obtained between $\sigma_p{}^+$ (NR^1R^2) and $\Sigma\sigma^*(R)$. The electron-releasing ability of the amino-groups is found to be larger, in a given series, than those expected from the Brown–Okamoto classical values and other more recent estimates. The discrepancies are attributed to charge delocalisation on the probe, steric inhibition of resonance, and to specific solvent associations with the amino-substituents. Owing to their large $\sigma_p{}^+$ values, we suggest deletion of amino-group data when using a non-linear treatment of substituent effects.

Recently, we used thermodynamic pK_{BH^+} values in aqueous sulphuric acid and $\Delta H°$ values of complex formation with BF_3 in CH_2Cl_2, as measures of Brønsted and Lewis basicities of the carbonyl group in a series of 3-substituted cyclohex-2-enones.[1,2] These basicity scales were very well correlated with $\sigma_p{}^+$ constants,[1] if amino-substituents are not included.[3] Thus, protonation and BF_3 co-ordination of the carbonyl group of α-enones seem to be in the class of ' electrophilic ' reactions or equilibria in which correlations with the σ^+ scale show deviations in the case of strong electron-donor substituents such as NH_2 and NMe_2. In the literature, several interpretations of this behaviour have been put forward. (i) The low accuracy of these constants computed from very fast reactions [4-9] prompted attempts to generate more accurate σ^+ constants from ^{13}C chemical shifts;[10-13] these new data do not resolve all the problems and the discrepancies arise again for highly polarizable groups. (ii) The non-constancy of σ^+ was attributed to substituent solvation.[11] (iii) In recent years, a number of papers have been devoted to the concept of the ' electron demand ' made on a substituent. Hitherto, two qualitative analyses of this concept have been proposed in the formalism of dual substituent parameters.[14-17] In our opinion, these treatments suffer from three drawbacks. First, they are only founded on n.m.r. data [14,15] or molecular orbital calculations.[16,17] Secondly, the increasing complexity of the corresponding equations [14,15] needs calculation of at least three unknowns, the two transmission coefficients (ρ_I, ρ_R) and a ' demand ' parameter ε. The use of too many parameters may serve to mask some special effects peculiar to one or several substituents of the same family. Finally, the predominant weighting of extreme substituents of a set, such as NR_2, may lead to an overevaluated ' electron demand ' coefficient of the function. Thus, the monoparametric equation is still a useful tool for assessment of ' abnormal ' behaviour such as curvature [18] or systematic deviations. Since such deviations were observed in our studies of thermodynamic basicities for strongly conjugated systems, we decided to re-examine the $\sigma_p{}^+$ values of amino-substituents using pK_{BH^+} and $\Delta H°$ values obtained from three series of carbonyl compounds, 3-substituted-5,5-dimethylcyclohex-2-enones (I), 4-substituted acetophenones (II), and 4-substituted benzaldehydes (III).



(I)



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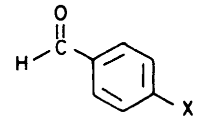


(III)

Results and Discussion

(a) *Basicity Measurements and Hammett-Brown Correlations*.—The new basicity parameters for series (II) and (III) obtained in this work are presented in Table 1.

Table 1. New enthalpies for complex formation with BF_3 in CH_2Cl_2 ($\Delta H°$) used in this work [a]

Substituent	$-\Delta H°$/kJ mol^{-1} [b]
A Revised values for series (III)	
$N(CH_3)_2$	103.21 ± 0.38
OCH_3	84.81 ± 0.42
CH_3	79.62 ± 0.56
F	76.14 ± 0.36
H	74.88 ± 1.00
Cl	73.51 ± 0.54
CN	65.06 ± 0.44
NO_2	62.32 ± 0.18
B New value for series (II)	
$N(CH_3)_2$	98.84 ± 0.23

[a] Other data used in correlation analysis reported in this work are taken from refs. 1—3 and 19. [b] Quoted errors are at the 95% confidence level.

For series (III), the $\Delta H°$ values published previously [20] are affected by 95% confidence intervals as large as 4 kJ mol^{-1}. An improvement in our microcalorimetric technique [21,22] enabled us to realise a better accuracy on a larger set of *para*-substituted benzaldehydes. Other data obtained for series (I) and (II) were published previously.

Protonation of amino-substituted acetophenones and benzaldehydes takes place on the nitrogen atom.[23,24] Thus, the corresponding pK_{BH^+} values are not relevant to our discussion and are not reported. In the case of compounds bearing one or two hydrogen at the nitrogen atom or a hydroxy-group, it was not possible to measure the enthalpies of complex-formation.

In previous work,[1] we obtained the regression equations (1) and (2a) for series (I) (amino groups excluded).

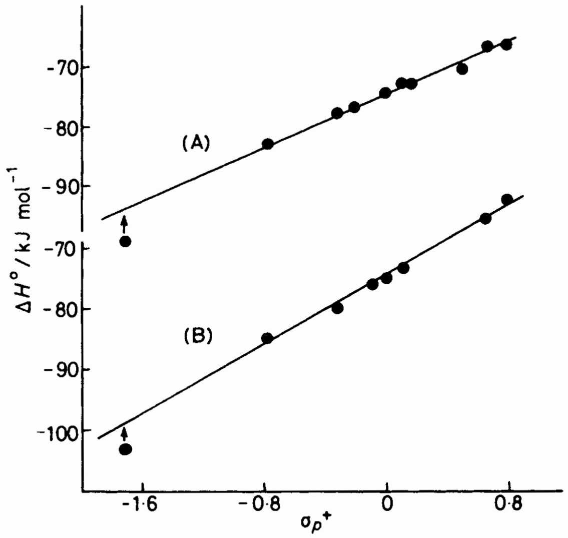
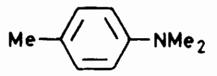
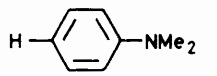


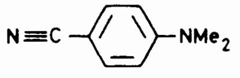
Figure 1. Relationship of $\Delta H°$ and $\sigma_p{}^+$ in *para*-substituted acetophenones (A) and *para*-substituted benzaldehydes (B)



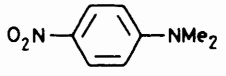
(A)
ΔH° -111·17



(B)
-109·16



(C)
-87·12



(D)
-78·13 kJ mol⁻¹

$$\text{p}K_{\text{BH}^+} = (-2.82 \pm 0.12)\,\sigma_p{}^+ - 3.10 \qquad (1)$$

correlation coefficient *r* 0.9923, standard deviation *s* 0.18, number of data points *n* 11

$$\Delta H°_{\text{I}}/\text{kJ mol}^{-1} = (23.89 \pm 0.87)\,\sigma_p{}^+ - 82.05 \qquad (2a)$$
$$r\ 0.9941,\ s\ 1.34,\ n\ 11$$

Data for series (II) and (III) treated in the same way as series (I) (NMe_2 group excluded) lead to equations (2b and c).

$$\Delta H°_{\text{II}}/\text{kJ mol}^{-1} = (10.36 \pm 0.41)\,\sigma_p{}^+ - 74.77 \qquad (2b)$$
$$r\ 0.9945,\ s\ 0.58,\ n\ 9$$

$$\Delta H°_{\text{III}}/\text{kJ mol}^{-1} = (14.46 \pm 0.56)\,\sigma_p{}^+ - 74.59 \qquad (2c)$$
$$r\ 0.9963,\ s\ 0.74,\ n\ 9$$

Whatever the value of the $\sigma_p{}^+$ constant available in the literature for amino-groups,[25] corresponding compounds ($X = NH_2$, NHPh, NMe_2) show a systematic deviation in correlation equations (1) and (2). This behaviour is exemplified in Figure 1 (see also Figure 1 of ref. 3). This abnormality could be considered to result from *N*-protonation and *N*-complexation. A detailed study has shown that the carbonyl group is the basic site in the cyclohexenone series.[3]

For *p*-dialkylaminobenzaldehydes, Rabinovitz *et al.* have demonstrated that the kinetically favoured complex is the one in which BF_3 is linked to the carbonyl oxygen and that the *N*-complexed form is the thermodynamically favoured form.[24,26] In our heat-flow Calvet microcalorimeter, we measured the fast acid–base reaction heat, and n.m.r. spectra obtained on the calorimetric solution allowed us to conclude unambiguously that co-ordination with oxygen occurred.[20]

Table 2. ¹H Chemical shifts of the aromatic protons in free and complexed *para*-substituted acetophenones of series (II) (in p.p.m. relative to Me_4Si; 0.5 mol dm⁻³)

Substituent	Free form		Complexed form	
	H_{ortho} *	H_{meta} *	H_{ortho} *	H_{meta} *
$N(CH_3)_2$	7.81	6.64	8.03	6.81
OCH_3	7.86	6.90	8.21	7.03
CH_3	7.78	7.24	8.09	7.43
C_6H_5	8.00	7.72	8.29	7.85
H	7.90	7.50	8.25	7.70
Cl	7.83	7.43	8.13	7.58
Br	7.75	7.50	8.07	7.73
$COCH_3$	8.00	8.00	8.18	8.18
CN	7.80	8.03	7.94	8.29
NO_2	8.06	8.20	8.22	8.29

* Position from the $COCH_3$ group.

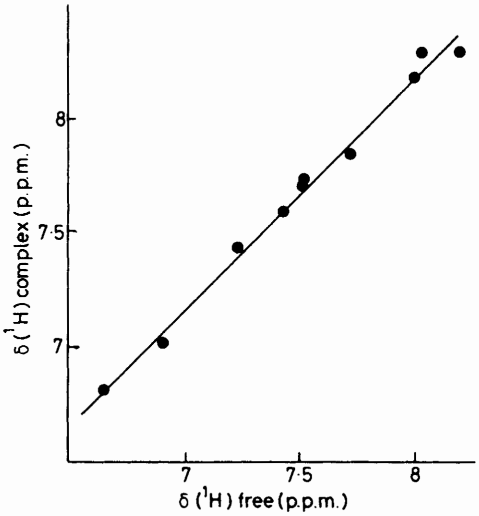


Figure 2. Relationship of δ^1H_{meta} (complex) and δ^1H_{meta} (free base) for *para*-substituted acetophenones

A string of converging arguments shows the carbonyl oxygen to be the basic site for BF_3 co-ordination of *p*-dimethylaminoacetophenone. (i) There is chemical and spectroscopic evidence that the nitrogen of the dimethylamino-group is the basic site for anilines (A)—(D) [27] and the expected $\Delta H°$–$\sigma_p{}^-$ correlation (3) holds. The Lewis basicity calculated from

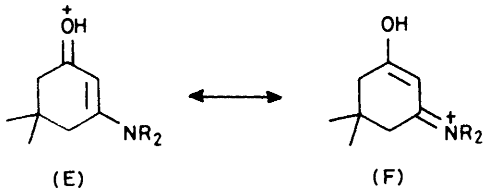
$$\Delta H°/\text{kJ mol}^{-1} = 22.73\,\sigma_p{}^- - 108.33 \qquad (3)$$
$$r\ 0.9964,\ s\ 1.71\ \text{kJ mol}^{-1},\ n\ 4$$

equation (3) for *p*-dimethylaminoacetophenone ($\sigma_p{}^-$ $COCH_3$ 0.874, $-\Delta H°_{\text{calc}}$ *ca.* 88.5 kJ mol⁻¹) is much weaker than the experimental basicity ($-\Delta H°_{\text{exp}}$ 98.84 kJ mol⁻¹). (ii) For the chemical shifts of the aromatic proton *meta* to the $COCH_3$ group (Table 2), we observe a very good relationship (4)

$$\delta^1H_{meta}(\text{complex}) = (1.00 \pm 0.04)\,\delta^1H_{meta}(\text{free}) + 0.15 \qquad (4)$$
$$r\ 0.9949,\ s\ 0.054\ \text{p.p.m.},\ n\ 10$$

Table 3. New σ_p^+ constants for amino-substituents

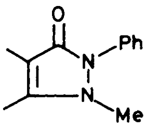
Substituent	σ_p^+ from series (I) Equation (5)	σ_p^+ from series (I) Equation (6)	σ_p^+ from series (II) Equation (6)	σ_p^+ from series (III) Equation (6)	σ_p^+ from series (I) Equation (7)	σ_p^+ from series (I) Equation (8)	Selected values of σ_p^+
NMe_2	−2.21	−2.11	−2.32	−1.98	−2.18	−2.11	−2.15
NHPh	−1.86				−1.89		−1.87
NH_2	−2.10				−2.10		−2.10



(E) (F)

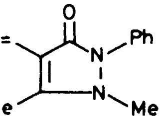
(IV) Y = Z = Ph

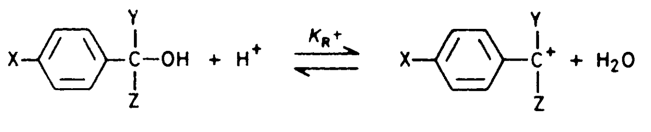
(V) Y = Z =



(VI) Y = Z = p-$NMe_2C_6H_4$

(VII) Y = p-$NMe_2C_6H_4$, Z =





between free and co-ordinated forms including the amino-derivative (Figure 2). Other proton chemical shifts (H_{ortho} and CH_3) do not differ sufficiently as a function of the substituent to be a meaningful probe of the complexation site.

(b) *Determination of* σ_p^+ *Constants.*—The nature of the basic site for the amino-derivatives in series (I)—(III) is now firmly assigned and we can postulate that the significant deviations [18] from equations (1) and (2) are induced by inadequate σ_p^+ values of the amino-groups. The excellent quality of correlations allows us to re-estimate the σ_p^+ constants for amino-groups by using equations (5) and (6). The results are reported in Table 3.

$$\sigma_p^+ = (\mathrm{p}K_{\mathrm{BH}^+\mathrm{X}} - \mathrm{p}K_{\mathrm{BH}^+\mathrm{O}})/\rho_1^+ \qquad (5)$$

$$\sigma_p^+ = (\Delta H^\circ_{\mathrm{X}} - \Delta H^\circ_{\mathrm{O}})/\rho_2^+ \qquad (6)$$

For the dimethylamino-group, the two values obtained from equations (1) and (2) with series (I) are in good agreement. This can be explained if we consider that the solvation effect on dialkylamino-groups is weak and does not affect σ_p^+ constants for this type of highly 'electrophilic' reaction. Indeed, we have recently shown that solvation effects on Lewis (in CH_2Cl_2) and Brønsted (in H_2O) basicities are not very important in 3-substituted cyclohexenones including numerous *NN*-dialkylamino-groups and we have obtained a single extrathermodynamic relationship between $\mathrm{p}K_{\mathrm{BH}^+}$ and ΔH° for 29 compounds.[3]

Literature data reveal a significant difference between the σ_p^+ values of NH_2 and NMe_2;[7] the difference observed in this work is much smaller. We should keep in mind that our values are calculated from a protonation reaction developing a partial positive charge on the nitrogen [canonical form (F)] and compared with dialkylamino-groups, we can expect stabilisation by hydrogen bonding with a hydrogen-bond acceptor solvent (HBA) in the case of NHR or NH_2 groups.[3]

Recently, $\mathrm{p}K_{\mathrm{BH}^+}$ and ΔH° values of 30 3-aminocyclohex-2-enones bearing NH_2, NHR^1, or NR^1R^2 groups (R^1,R^2 = alkyl, aryl) have been investigated and excellent linear relationships between the basicity parameters and the sum of σ^* constants of alkyl and aryl substituents in the nitrogen atom have been obtained.[3] From these correlations and those of Table 2, we obtain the direct relationships (7) and (8) between the σ_p^+ constants of amino-groups and σ^* of R^1 and R^2. Although these relationships are limited to alkyl and weakly electron-withdrawing R^1 or R^2 groups, they can be used to estimate new σ_p^+ constants useful in correlating reactions similar to our reference reactions (Table 3).

From $\mathrm{p}K_{\mathrm{BH}^+}$

$$\sigma_p^+ = 0.41\,\Sigma\sigma^* - 0.16h - 2.18 \qquad (7)$$

h = number of hydrogens on the nitrogen atom

From ΔH°

$$\sigma_p^+ = 0.41_5\Sigma\sigma^* - 2.11 \qquad (8)$$

only for $R^1, R^2 \neq H$

(c) *Limits of Applicability of New* σ_p^+ *Constants.*—Analysis of literature data shows a large dependence of amino-group σ_p^+ values on the type of 'electrophilic' probe in a given solvent. We have examined this dependence for several classes of reactivity and spectroscopic properties. The first class can be exemplified by the acid–base equilibria of four arylcarbinol bases (IV)—(VII).[28] $\mathrm{p}K_{\mathrm{R}^+}$ values were correlated with σ_p^+ [equation (1), NMe_2 value excluded] and σ_p^+ (NMe_2) was calculated according to equation (5). Series (IV)—(VII) lead to the following values, −2.74, −2.38, −1.82, and −1.89, respectively. Values obtained from series (IV) and (V) militate in favour of a much larger electron-donating effect than those anticipated by the literature values.[25] In these cases, we notice that the positive charge is much more localised on the functional carbon than in series (VI), where the powerful donor effect of Y and Z induces charge delocalisation leading to a σ_p^+ estimate closer to the classical constant.[4] Compared with series (IV) or (V) and (VI), series (VII) exhibits intermediate behaviour owing to the opposing effects of the Y and Z groups. In the same way, we observe that σ_p^+ (NMe_2) obtained from the $\mathrm{p}K_{\mathrm{R}^+}$ of symmetrically disubstituted diarylcarbinols $(Ar)_2CHOH$ is −2.00 whereas in the case of symmetrically trisubstituted triarylcarbinols $(Ar)_3COH$, where the charge of the conjugate cation is more delocalised, one obtains only −1.55.[4] In addition steric crowding around the cationic centre may restrain coplanarity with the phenyl ring, thereby reducing through-conjugation.*

Apart from ionization equilibria of two carbinols, only kinetic parameters measured in hydroxylic media were used by Clementi and Linda[9] in their reinvestigation of the σ_p^+ values for some strong resonance donor substituents. They obtained −1.31 and −1.50 for amino- and dimethylamino-groups, respectively. Compared with our calculations, the increase of these values is attributed to solvation of the nitrogen atom of the substituent by the hydrogen-bond donor (HBD) solvent.

The ^{13}C substituent chemical shifts of the carbon bearing the cyano-groups in *p*-substituted ββ-dicyanostyrenes is a typical example because it was used to calculate substituent constants.[11b,12b] In spite of the two strong electron-withdrawing groups bonded to the probe, the value calculated as previously[11b,12b] for $\sigma_p^+(NMe_2)$ shows a large dependence on the solvent: −1.80† and −2.22† for $CDCl_3$[12b] and $(CH_3)_2SO$.[11b]

^{13}C N.m.r. results obtained from other ββ-disubstituted styrenes[12b] bearing $-R$ groups bonded to the probe are in agreement with the observation above of polar aprotic solvent effects. Recent ^{17}O n.m.r. results[29] on *para*-substituted nitrobenzenes dissolved in acetonitrile suggest the same trend for NEt_2 and NH_2 groups. Such effects are also obtained from i.r. results in dipolar solvents.[30,31]

Conclusions.—We have demonstrated that $\sigma_p^+(NR_2)$ depends largely on the strength of the $-R$ power of the function and on solvent properties (acidity, basicity, and polarity). In the σ_p^+ scale there is a marked lack of substituents between the medium donors, such as OMe or OH and the strong donors NR_2. Thus, when we observe an apparent deviation in a plot for NR_2 groups using Brown–Okamoto σ_p^+ values[4] care must be exercised concerning the treatment of the phenomenon. Is it a curvature of the ρ^+–σ^+ plot? Is it an inadequate use of substituent constants? To answer these points, and before undertaking a sophisticated non-linear multiparametric treatment,[14–17,32] which includes all substituents, it is necessary to consider structural or specific solvent effects on the amino-substituents, making use of values obtained in this work. We further suggest that attempts be made to determine the electrophilic substituent constants of NR^1R^2 groups, where R is an electron-withdrawing substituent, *e.g.* CH_2F, $CH_2C{\equiv}N$, *etc.*, in order to fill the σ_p^+ gap between −0.9 and −2.0.

Experimental

The preparation of cyclohexenones (I) and their spectroscopic properties are described in refs. 33—35. Methods for pK_{BH^+} and ΔH° measurements have been previously reported in refs. 2 and 3 and 21 and 22, respectively.

^1H Chemical shifts for the complexed form were obtained under conditions for complete complex formation. Calorimetric measurements show a proportionality between the heat evolved and the amount of Lewis acid injected in the cell for all the compounds used in this work. Only much weaker bases have shown a sizeable amount of dissociation.[21] In several instances, we have also observed that the complexation chemical shift and the BF_3 : base ratio are proportional, leading to the same conclusion.

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* We are indebted to a referee for this remark.

† Only data available in both solvents were used in the regressions.

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