Substituent Effects in Saturated Systems. An Assessment of the Transmission of Substituent Effects by the Field, σ-Inductive, and π-Inductive Effects in 3- and 6-Substituted Hexahydrocarbazoles

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Basicities of *N*-methyl-*cis*-1,2,3,4,4a,9a-hexahydrocarbazoles substituted at the 3- and 6-positions have been measured. For substituents of the type CH_2X polar effects are analysed in terms of the direct field effect operating from the 3-position and the field and π-inductive effect operating in concert across the aromatic portion of the molecule (from the 6-position). Empirical correlations and the results of calculations of ΔpK_a using the Kirkwood–Westheimer method show that the field effect is substantial but that relay by the π-inductive effect is greater by a factor of *ca.* 2.5.

Waters[1] first drew attention to the possibility of the transmission of polar substituent effects by other than the classical inductive effect. Using bond polarisability data he calculated the expected attenuation of induced charge in substituted benzenes, found it to be considerable, and concluded that induction was greatly exceeded by a direct electrostatic interaction. Since then many model systems, *e.g.* (1)—(10), have played a part in attempts to elucidate details of the relative importance of possible mechanisms for the transmission of polar substituent effects in organic molecules.

Most of the information now to hand suggests that the effects of polar substituents are, for separations of more than one or two bonds, relayed more effectively by coulombic interaction than by polarisation of σ-bonds. For instance polar effects upon ionisation of the saturated carboxylic acids (1),[2] (2),[3] and (3)[4] are significant and comparable with effects in 4-substituted benzoic acids. It is also significant that although the number of paths for relay by σ-bond polarisation varies within the group (1)—(3) the efficiency of transmission is not greatly affected. Furthermore dipolar substituents such as F, Cl, or CN, which normally strengthen acidity in arenecarboxylic acids, have the opposite effect[5] in the bridged anthracenes (4). This effect is, however, readily explained by the dipolar field effect; the C–X dipole is reversed at the 8-position *vis à vis* the 4-position. Even the acidity order of halogenoacetic acids can no longer be presented as proof of the operation of a σ-inductive effect; the acidity order in the gas phase is the reverse of that in aqueous solution[6,7] and the order seems to be governed by enthalpies of hydration.[8] Finally, quantitative theories,[9,10] based on the premise that the field effect greatly outweighs the σ-inductive effect, have been successful in accommodating measured changes in pK_a.

The importance or otherwise of the π-inductive effect is not so well established. There is also confusion about the definition of π-inductive effects.[11] We shall use the term in the sense adopted by Dewar[12] for benzenoid systems, namely the polarisation of a π-system by an electrostatic charge set up at a conjugated atom adjacent to the substituent. Such an effect is transmitted preferentially to the *ortho*- and *para*-positions. Transmission of the π-inductive effect apparently requires a conjugated π-system and does not depend on the greater polarisability of individual π-bonds; transmission of polar effects is not enhanced in systems such as (5) and (6)[4] compared with the saturated analogues. For the latter two series of compounds the reaction centre is not conjugated with the π-system. Investigation of chemical and spectroscopic properties of the systems (7)—(10) suggests however that a π-inductive effect can

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[1] W. A. Waters, *J. Chem. Soc.*, 1933, 1551.

[2] S. Siegel and J. M. Komarmy, *J. Amer. Chem. Soc.*, 1959, **82**, 2547.

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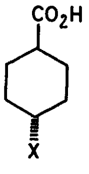
[10] M. J. S. Dewar and P. J. Grisdale, *J. Amer. Chem. Soc.*, 1962, **84**, 3548.

[11] A. R. Katritsky and R. D. Topsom, *J. Chem. Educ.*, 1971, **48**, 427.

[12] M. J. S. Dewar and P. J. Grisdale, *J. Amer. Chem. Soc.*, 1962, **84**, 3539.

be significant. In particular the increase in Hammett ρ values for acidities with increasing side chain unsaturation in the series, arylalkanoic acids[13,14] (7), *trans*-cinnamic acids[15] (8), and arylpropiolic acids[16] (9), suggests that polar effects are transmitted more efficiently through unsaturated systems than through saturated systems. For nitration of compounds of type (10), Ridd and his co-workers[17] have found that for positive pole substituents ($X = \overset{+}{N}R_3$, $\overset{+}{S}R_2$, or $\overset{+}{P}R_3$) a π-inductive effect must be invoked to account for the lack of correlation between deactivation of the *meta*-position and orientation of substitution; the variation of deactivation with the separation of the pole from the ring is, however, well explained by the field effect.

For compounds of type (10), with both charged and neutral substituents, the ^{13}C n.m.r. shifts[18,19] at the ring carbon atoms are affected by the polar nature of X in a manner which is best explained by a significant π-inductive effect.



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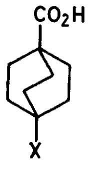

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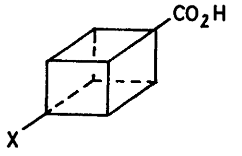

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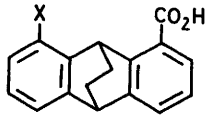

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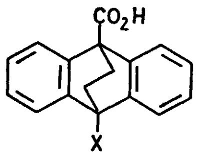

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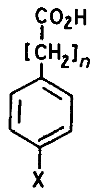

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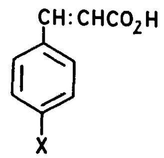

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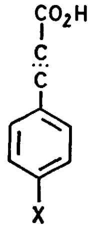

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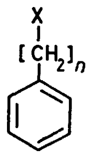

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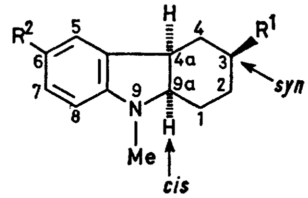
We report in this paper the results of basicity measurements on 3- and 6-substituted *cis*-hexahydrocarbazoles (11); the experiments are designed to assess the relative significance of the field and π-inductive effects. Previous work in this laboratory has concerned the synthesis,[20] stereochemistry,[21] and reactivity[22] of these compounds. The *cis*-hexahydrocarbazole system has a defined and rigid geometry and the basicity and reactivity of the compounds are sensitive to polar effects. We have recently[23] synthesised a number of *cis*-hexahydrocarbazoles with substituents of the type CH_2X at the 3- or 6-positions. The effect of such substituents upon the basicity of the nitrogen atom can therefore be examined in terms of the direct field effect (from the 3-position) or the π-inductive effect combined with the field effect (from the 6-position). An advantage of this model system is that, because only one type of compound is used, the comparison is made for a common reaction centre with constant steric and solvation requirements; previously conclusions have been based on comparisons from two or more series of compounds.



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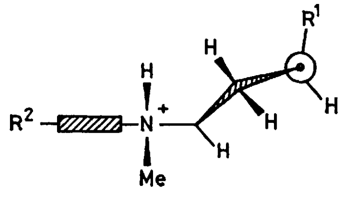
RESULTS AND DISCUSSION

pK_a Values.—These are displayed in Table 1; for comparison, related compounds involved in earlier work[22] are included. It is clear that the nitrogen basicity may be influenced by both polar and steric effects. The gross effects have been discussed previously and a key assumption,[22] supported by n.m.r. spectroscopic evidence, is that the conjugate acid is predominantly the isomer with the proton in the more crowded position (12).



(12)

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[20] A. Smith and J. H. P. Utley, *J. Chem. Soc.* (*C*), 1970, 1.

[21] D. Shaw, A. Smith, and J. H. P. Utley, *J. Chem. Soc.* (*B*), 1970, 1161.

[22] A. Smith and J. H. P. Utley, *J. Chem. Soc.* (*B*), 1971, 1201.

[23] J. H. P. Utley and S. O. Yeboah, *J.C.S. Perkin I*, 1978, 888.

With a *syn*-3-substituent a rigid boat conformation is adopted;[21] the base-weakening effect of 3-alkyl substituents is associated[22] with disturbance of regions of solvent order (cybotactic regions) in the conjugate acid. The bulky, hydrophobic, t-butyl group acts likewise from the 6-position. Similar base-weakening has been found in hindered aminocholestanes.[24]

TABLE 1

pK_a Values for substituted *N*-methyl-*cis*-hexahydrocarbazoles

syn-3-Substituent	6-Substituent	pK_a (293 K)[a]
H	H	4.35
H	H	(2.89)[b]
CH_3	H	3.87
CH_3	H	(2.18)[b]
CMe_3	H	(1.82)[b]
CH_2OH	H	3.85
CH_2OMe	H	3.67
CH_2CN	H	3.42
H	CH_3	4.72
H	CMe_3	4.11[c]
H	CMe_2CN	3.35
H	CH_2OH	4.17
H	CH_2OMe	4.05
H	CH_2CN	3.57

[a] Judged accurate to ±0.02 pK_a units. [b] Measured[22] in 20% v/v 2-butoxyethanol at 303 K. [c] In H_2O at 303 K.[22]

The pK_a values for the *cis*-hexahydrocarbazoles substituted in the 6-position with CH_2CN and CMe_2CN are consistent with the above rationalisation. Whilst the base-weakening effect of both substituents can be attributed to the electron-withdrawing effect of the nitrile group, the lower basicity, by 0.22 pK_a units, of the CMe_2CN substituted compound would not be predicted on polar grounds because electron withdrawal would be demanded of the methyl group. The large 6-CMe_2CN group would, however, be expected to inhibit solvation of the conjugate acid, as does the 6-CMe_3 group.

For the 3- and 6-substituted compounds the electron-withdrawing effects (base-weakening) of the CH_2OH, CH_2OMe, and CH_2CN groups mostly agree with qualitative expectation. However, the small difference (0.02 pK_a units) for *syn*-3-CH_3 and *syn*-3-CH_2OH is worth more discussion. Eaborn and his co-workers[25] have suggested that the polar effect of a CH_2Y group may be regarded as composed of two-thirds of the electron-releasing ability of the CH_3 group and the suitably attenuated polar effect of group Y, expressed by its σ_I constant. This approach need not assume a particular mechanism of transmission of polar effects. On this basis the CH_2OMe and CH_2OH groups have similar calculated polar substituent constants (σ_p *ca.* 0.04). However, a value of $\sigma_p = -0.04 \pm 0.03$ was recently found[26] for CH_2OH by measurement of the pK_a of *p*-hydroxymethylbenzoic acid, so calculation of absolute values by Eaborn's method may not be very reliable. From the results in Table 1 it is clear that, both for 3- and 6-substitution, the polar influence of CH_2OH is considerably smaller than for CH_2OMe, a result in line with the direct measurement[26] of σ_p. An attractive explanation of the small effect of the CH_2OH group is that, because of hydrogen bonding, the group is embedded in the solvent with effective dispersal of the group dipole. The field effect would therefore be greatly diminished and it is perhaps significant that for the 3-substituted compound, in which only the field effect may operate, the CH_2OH group has virtually no polar effect, whereas for the 6-substituted compound (field and π-inductive effect) a polar effect is observed albeit less than for the CH_2OMe derivative. A similar solvent effect has been proposed to account for anomalies in the influence of nitrogen pole substituents.[27]

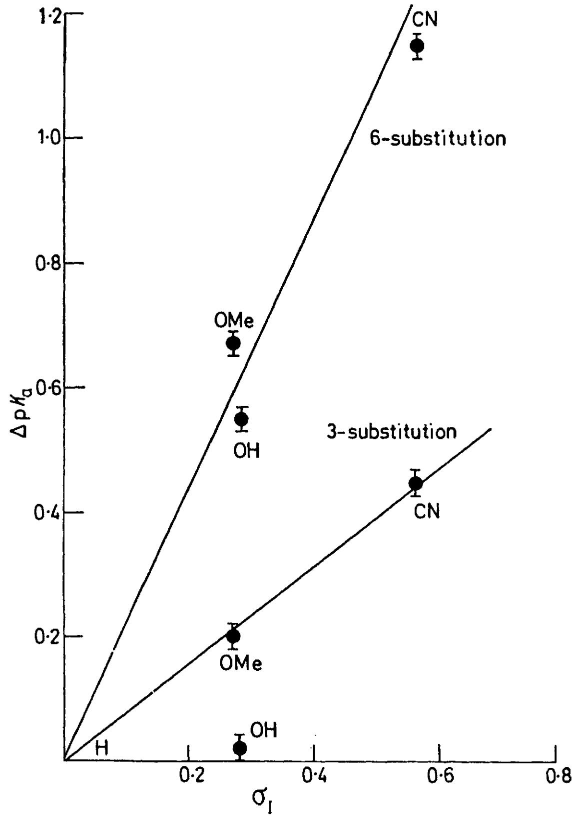

FIGURE 1 Plot of ΔpK_a *versus* σ_I

The Mode of Transmission of Substituent Effects. Empirical Correlations.—The relative efficiency of transmission of the substituent effect from the 3- and 6-positions has been assessed in two ways. Figure 1 contains for both sets of compounds plots of ΔpK_a *versus* σ_I constants[25] for CH_2Y groups. The ratio of the slopes of these plots is 2.82 and may be taken as a ratio of ρ values. Figure 2 shows the correlation between pK_a values for the two sets of hexahydrocarbazoles; the point for the CH_2OH group has been ignored in both figures. The slope (least squares method) for the plot in Figure 2 is 2.53. Two points emerge from the figures: (a) there is a moderately good linear correlation between

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[24] C. W. Bird and R. C. Cookson, *J. Chem. Soc.*, 1960, 2343.

[25] A. J. Cornish and C. Eaborn, *J.C.S. Perkin II*, 1975, 874.

[26] J. P. Girault and G. Dana, *J.C.S. Perkin II*, 1977, 993.

[27] M. Brickman, J. H. P. Utley, and J. H. Ridd, *J. Chem. Soc.*, 1965, 6851; D. E. Caddy and J. H. P. Utley, *J.C.S. Perkin II*, 1973, 1258.

substituent effects from the 3- and 6-positions, and (b) polar effects are relayed more effectively across the aromatic system by a factor of *ca.* 2.5.

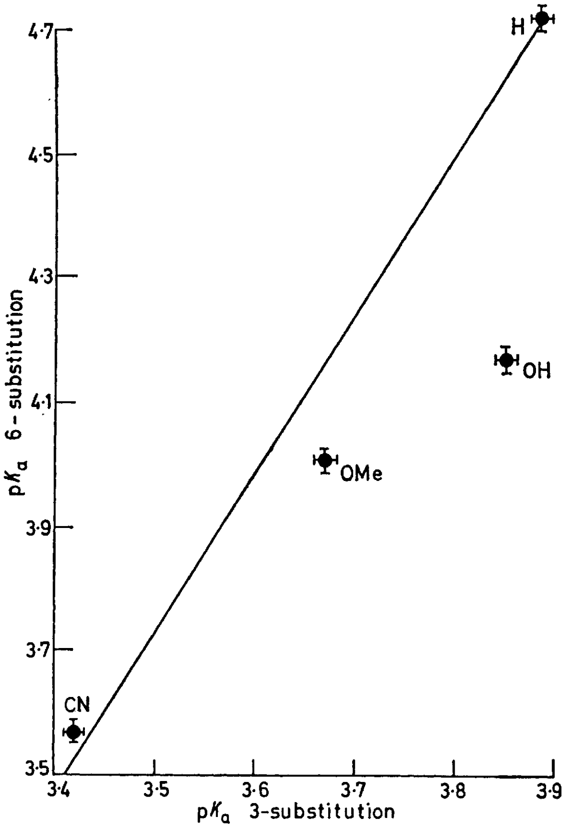
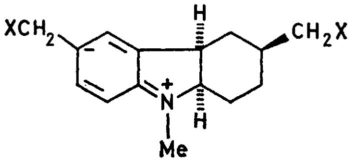


FIGURE 2 Relative substituent effects on pK_a

For the many reasons given in the introduction to this paper, the relay of polar effects by the σ-inductive effect is assumed to be insignificant. This assumption is supported by the results of calculations of ΔpK_a values (see below). The factor operating from the 6-position in addition to the field effect is most probably the π-inductive effect. The mode of operation is, perhaps, best expressed in terms of the canonical structure (13);



(13)

stabilisation of such a structure would stabilise the initial state and therefore be base-weakening. The negative charge at C-6 would be stabilised by both inductive and coulombic electron withdrawal and with only one methylene group insulating C-6 from the substituent an attempt at distinction is probably futile. The long range effect depends, however, on the π-system and it operates to reinforce the direct field at the nitrogen. Additional evidence for an important contribution from canonical forms such as (13) comes from the u.v. spectra of hexahydrocarbazoles and related compounds. Wepster and his co-workers [28] have shown that in a series of *ortho*-substituted *NN*-dimethylanilines $\lambda_{max.}$ is not altered by twisting of the NMe_2 group out of the plane of the benzene ring but the extinction coefficient is greatly lowered. For instance, in iso-octane solution, $\varepsilon_{max.}$ for *NN*-dimethylaniline is 15 500 whereas for *o*-t-butyl-*NN*-dimethylaniline $\varepsilon_{max.}$ is only 630. For 3- and 6-substituted *N*-methyl-*cis*-hexahydrocarbazoles, in 95% ethanol, values for $\varepsilon_{max.}$ are in the range [22] 15 400—8 100 (*cf.* 12 900 for *NN*-dimethylaniline). Clearly there is considerable interaction between the nitrogen atom and the π-system as demanded in (13).

Contribution of the Field Effect to ΔpK_a; *Calculations by the Kirkwood–Westheimer Method.*—Considerable success has been achieved in accounting for substituent effects on pK_a by simple calculations based on classical expressions for coulombic interactions. Equation (1) is the key expression,[9] in which e is, in our case, the charge on protonated nitrogen, μ the dipole moment of the substituent, θ the angle between the dipole axis and a line joining the nitrogen to the mid-point of the dipole, R the length of that line, D_E the relevant dielectric constant, with k and T having the usual significance.

$$\Delta pK_a = e\mu\cos\theta/2.303kTR^2D_E \qquad (1)$$

Much discussion has centred on the method of estimating D_E; the simplest adequate method has been to regard the molecule as an ellipsoidal cavity of dielectric constant 2.0 embedded in a continuous medium (the solvent). The substituent and reaction centre are then regarded as being at the foci and from the molecular dimensions the reciprocal (λ) of the eccentricity of the ellipsoid is obtained using equation (2). In equation (2) V is the volume per molecule, usually estimated by Traube's rules,[29] and R is as used in equation (1). In their early papers [9] Kirkwood and Westheimer have calculated

$$\lambda^3 - \lambda = 6V/\pi R^3 \qquad (2)$$

D_E as a function of λ; the dielectric constant relevant for the relay of electrostatic effects across a molecule in aqueous solution is, in this way, found to be of the order of 4.0—6.0 with few instances of much larger values.

An obvious difficulty in applying the above method to the *cis*-hexahydrocarbazole system is that the molecules cannot be as easily regarded as ellipsoidal as, say, can 4-substituted benzoic acids [30] or 4-substituted bicyclo-[2.2.2]octane-1-carboxylic acids.[3] However, because of the fairly small range of values of D_E found for apparently more suitable geometries, it seemed worthwhile to use the Kirkwood–Westheimer method to estimate the likely contribution of field effects to observed changes in pK_a. In the event we have found that for substituents capable

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[28] J. Burgers, M. A. Hoefnagel, P. E. Verkade, H. Visser, and B. M. Wepster, *Rec. Trav. chim.*, 1958, **77**, 491.

[29] J. R. Partington, 'An Advanced Treatise on Physical Chemistry,' Longman, Green and Co., London, 1951, vol. II, p. 24.

[30] F. H. Westheimer, *J. Amer. Chem. Soc.*, 1939, **61**, 1977.

of conformational mobility much greater uncertainty arises in estimating θ. This must presumably also be the case for some of the systems previously employed for such calculations; Golden and Stock[5] have commented briefly on this point. In the present work, averaged values of θ are used which take account of the most likely conformations of the CH_2X group. Distances were measured on Dreiding models of the compounds assuming boat geometry [*cf.* (12)] and angles calculated therefrom.

Table 2

Calculated and measured ΔpK_a Values in aqueous solution; the Kirkwood–Westheimer method

X in CH_2X	3-OH	6-OH	3-OMe	6-OMe	3-CN	6-CN
$V/Å^3$	328	328	360	360	341	341
$R/Å$ [a]	5.8	6.0	5.8	6.0	6.4	6.7
$\theta/°$ [a]	57	64	57	64	55	54
D_E	4.1	5.1	4.0	4.5	4.4	6.0
ΔpK_a (calc.)	0.17	0.10	0.17	0.09	0.58	0.40
ΔpK_a (obs).	0.02	0.55	0.20	0.67	0.45	1.15

[a] Averaged values, see text.

The results of ΔpK_a values for *cis*-hexahydrocarbazoles, calculated by the method described above, are given in Table 2. The main conclusion to be drawn from the results is simple and qualitative. The polar effect from the 3-position may be accounted for by the direct field effects whereas from the 6-position the calculations clearly underestimate the polar effect. This supports the conclusion drawn from Figures 1 and 2, *i.e.* the field effect accounts for a substantial relay of polar effects (all in the case of the saturated part of the molecule) but that the π-inductive effect is important in relaying effects from the 6-position. The calculations also confirm that OH and OMe should have similar polar effects whereas the observation is that the effect of the OH group is much diminished.

EXPERIMENTAL

Materials.—The preparation and characterisation of the 3- and 6-substituted *cis*-hexahydrocarbazoles have been described.[23]

pK_a *Measurements.*—A modification[22] of Albert and Sarjeant's method[31] was used. The concentration of substrate was *ca.* 1×10^{-4} M.

One of us (S. O. Y.) thanks the Ghana Government, University of Cape Coast, and the British Council for financial assistance.

[7/1855 *Received*, 21*st October*, 1977]

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[31] A. Albert and E. P. Sarjeant, 'Ionisation Constants of Acids and Bases,' Methuen, London, 1962.