

A THEORETICAL STUDY OF THE CHEMISTRY OF ISOQUINOLINE

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Abstract—A Hückel molecular-orbital treatment of isoquinoline, analogous to previously published treatments of quinoline and of some five-membered ring heterocycles, is presented. It is shown that the apparently anomalous orientations observed in some electrophilic substitution reactions can be explained in terms of the molecular-orbital results. A new mechanism, similar to that previously proposed for some electrophilic substitutions in quinoline, is proposed to account for the orientation of bromination and mercuration of isoquinoline.

The high reactivity of the 1- and 3-positions of isoquinoline towards nucleophils is also predicted by the theoretical results. Radical attack is briefly considered also.

The values of parameters found appropriate in a previous study of quinoline are confirmed by the present work. Bounds for an additional parameter relating to the energy of a localized π -electron adjacent to a heteroatom are indicated by the present analysis.

CONSIDERABLE progress has been made recently in elucidating the chemical properties of some nitrogen and oxygen heterocycles. On the one hand mechanisms of some substitution reactions have been investigated¹⁻³ and more precise observation of the orientation of some electrophilic substitutions have been reported.⁴⁻⁹ On the other hand the analysis of chemical properties in the light of simple Hückel molecular-orbital calculations, which suggested the possibility of preliminary protolysis of secondary nitrogen in certain cases,^{10,11} and protonation of tertiary nitrogen in others,¹²⁻¹⁴ has provided a basis for interpretation of many apparently anomalous observations.¹³⁻¹⁵ Some new reaction mechanisms have also been suggested as a consequence of these studies.^{4,13,14} In addition values of the hetero-parameters which occur in the Hückel method have been settled to within narrow limits in this work^{14,15} and these values are in good agreement with independent theoretical estimates¹⁶ based on the variable-electronegativity-self-consistent-field molecular orbital method. The present theoretical study of the chemistry of isoquinoline can therefore be based largely on values of the Hückel parameters already established.

¹ R. D. Brown, H. C. Duffin, J. C. Maynard and J. H. Ridd, *J. Chem. Soc.* 3937 (1953).

² J. H. Binks and J. H. Ridd, *J. Chem. Soc.* 2398 (1957).

³ R. D. Brown, B. A. W. Coller and M. L. Heffernan, *J. Chem. Soc.* 1776 (1958).

⁴ M. J. S. Dewar and P. M. Maitlis, *J. Chem. Soc.* 944 (1957).

⁵ M. J. S. Dewar and P. M. Maitlis, *J. Chem. Soc.* 2521 (1957).

⁶ M. J. S. Dewar and D. S. Urch, *J. Chem. Soc.* 345 (1957).

⁷ M. J. S. Dewar and D. S. Urch, *J. Chem. Soc.* 3079 (1958).

⁸ P. B. D. de la Mare, M. Kiamud-Din and J. H. Ridd, *Chem. & Ind.* 361 (1958).

⁹ R. D. Brown, unpublished experiments.

¹⁰ I. M. Bassett and R. D. Brown, *J. Chem. Soc.* 2701 (1954).

¹¹ R. D. Brown, *Aust. J. Chem.* 8, 100 (1955).

¹² R. D. Brown and M. L. Heffernan, *J. Chem. Soc.* 4288 (1956).

¹³ R. D. Brown, *Current Trends in Heterocyclic Chemistry* p. 13. Butterworths, London (1958).

¹⁴ R. D. Brown and R. D. Harcourt, *J. Chem. Soc.* In press.

¹⁵ R. D. Brown and B. A. W. Coller, *Aust. J. Chem.* 12, 152 (1959).

¹⁶ R. D. Brown and M. L. Heffernan, *Aust. J. Chem.* 12, 319 (1959).

Previous molecular-orbital studies of isoquinoline^{5,17,18} were based on parameter values now considered to be unsatisfactory and are not nearly as detailed as the present investigation.

METHOD

Details of the method have been set out previously.^{14,15} Values of π -electron densities and localization energies were computed as functions of the coulomb parameter h and the auxiliary inductive parameter h' of the nitrogen atom. The CN resonance integral was assigned the standard value β° because previous studies have shown that π -electron densities are insensitive to the value of this integral and only for positions adjacent to the heteroatom are the localization energies appreciably dependent upon its value.

As has previously been mentioned¹⁴ the value to be assigned to the energy of a localized electron when computing localization energies at positions adjacent to heteroatoms is uncertain. If the auxiliary inductive effect is still fully operative at localized centres then the value $\alpha^\circ + h'\beta^\circ$ is appropriate, if it is no longer operative then the value α° is appropriate. Wheland¹⁹ has suggested that some intermediate value should be used and the quantum mechanical mechanism currently envisaged for the auxiliary inductive effect¹⁶ implies an intermediate value since localization will probably considerably reduce the value of the nearest neighbour electron repulsion integral $\gamma_{\mu\nu}$. The present investigation provides the first direct evidence, based on prediction of chemical properties, that such intermediate values should be assigned to energies of localized electrons.

RESULTS AND DISCUSSION

(a) *Electrophilic substitution*

Two main types of orientation of electrophilic substitution have been observed experimentally. Bromination^{20,21} and mercuriation²² lead to 4-substituted isoquinolines while in concentrated sulphuric acid sulphonation²³ and nitration⁵ yield mainly 5-substituted quinolines, with the 8-substituted quinolines as minor products. From the calculated π -electron densities (Figs. 1 and 2) neither of these orientations can be reconciled with direct substitution in the free base because for physically acceptable values of the coulomb parameters the expected order of reactivity is $5 > 7 > \text{others}$. The electrophilic localization energies for the free base (Figs. 3 and 4) can be reconciled with 5,8-orientation but from our studies on quinoline¹⁴ it seems probable that the isoquinolinium cation is the reacting species when this orientation is observed. The preferential attack at the 4-position can however be explained in terms of a mechanism similar to that proposed to explain 3-substitution in quinoline.¹⁴ Preliminary 1:2-addition of EB (electrophil and nucleophil) produces a 1:2-dihydroisoquinoline system, the charge densities for this being shown in Figs. 5 and 6. This would be expected to be attacked by electrophils preferentially at the 4-position. On this basis

¹⁷ H. C. Longuet-Higgins and C. A. Coulson, *Trans. Faraday Soc.* **43**, 87 (1947).

¹⁸ I. Samuel, *C.R. Acad. Sci., Paris* **236**, 2510 (1953).

¹⁹ G. W. Wheland, *J. Amer. Chem. Soc.* **64**, 900 (1942).

²⁰ J. J. Padbury and H. G. Lindwall, *J. Amer. Chem. Soc.* **67**, 1268 (1945).

²¹ F. W. Bergstrom and J. H. Rodda, *J. Amer. Chem. Soc.* **62**, 3030 (1940).

²² T. Ukai, *Chem. Abstr.* **25**, 5427 (1931).

²³ F. T. Tyson, *J. Amer. Chem. Soc.* **61**, 183 (1939).

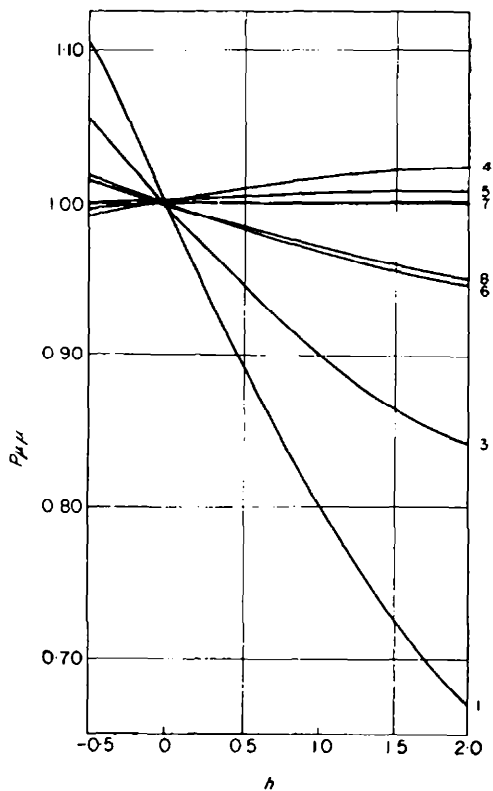


FIG. 1. π -Electron densities of isoquinoline as a function of h (for $h' = 0$).

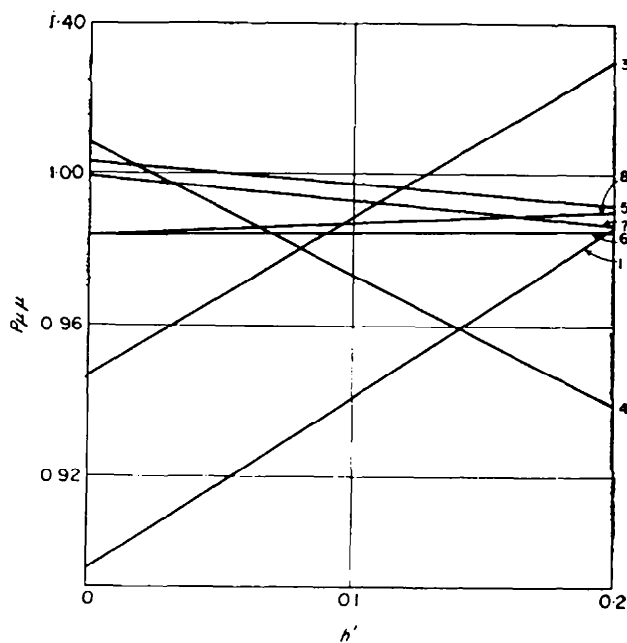


FIG. 2. π -Electron densities of isoquinoline as a function of h' (for $h = 0.5$).

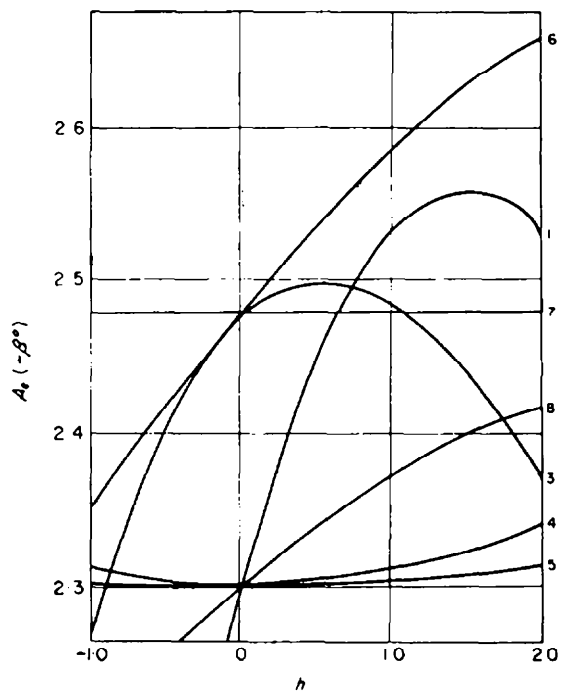
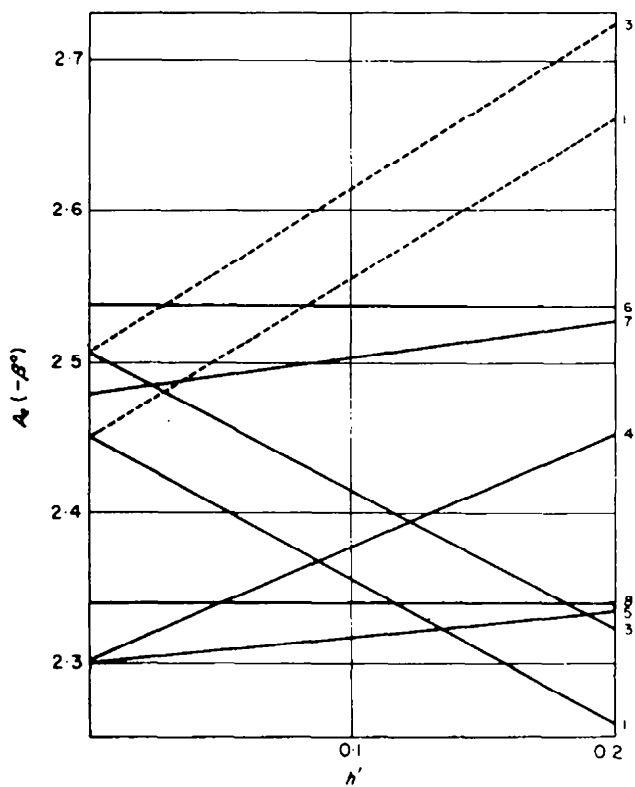


FIG. 3. Electrophilic localization energies of isoquinoline as a function of h (for $h' = 0$).

FIG. 4. Electrophilic localization energies of isoquinoline ($h = 0.5$) as a function of h' . (For positions 1 and 3: Broken line, $\delta = 0$; full line $\delta = 1$.)



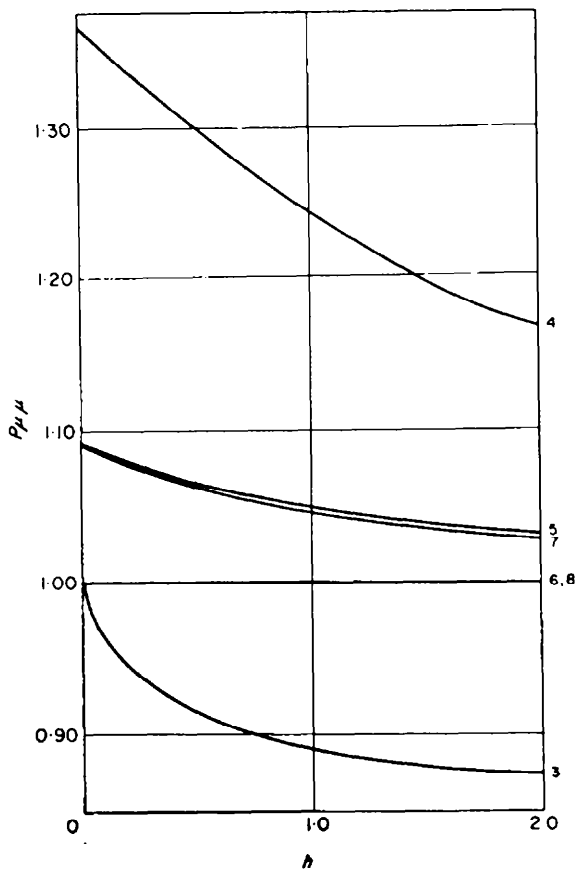


FIG. 5. π -Electron densities of 1:2-dihydroisoquinoline as a function of h (for $h' = 0$).

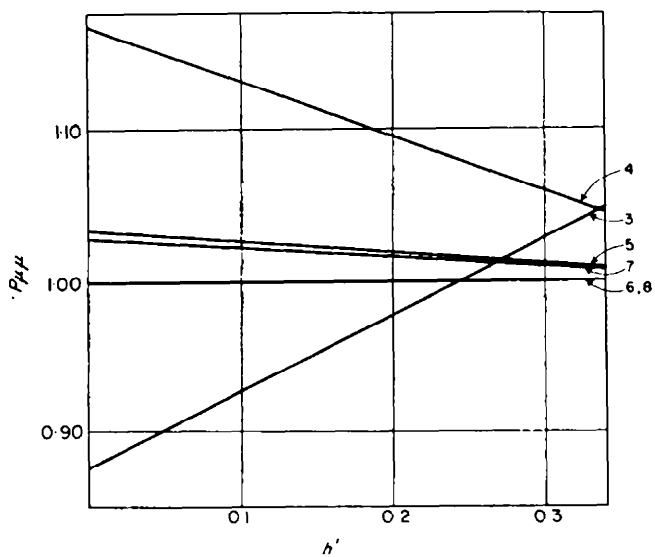
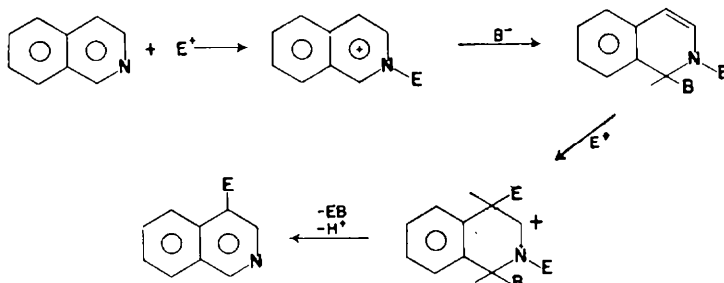


FIG. 6. π -Electron densities of 1:2-dihydroisoquinoline as a function of h' (for $h = 2$).

we should expect the nitration of isoquinoline in acetic anhydride to yield 4-nitroisoquinoline, but it has been reported to yield intractable products.⁴



In concentrated sulphuric acid the concentration of free base is probably too low for it to take a significant part in the reaction, the relatively unreactive isoquinolinium cation being the species probably undergoing substitution. The orientation might therefore be expected to be predicted by electrophilic localization energies rather than

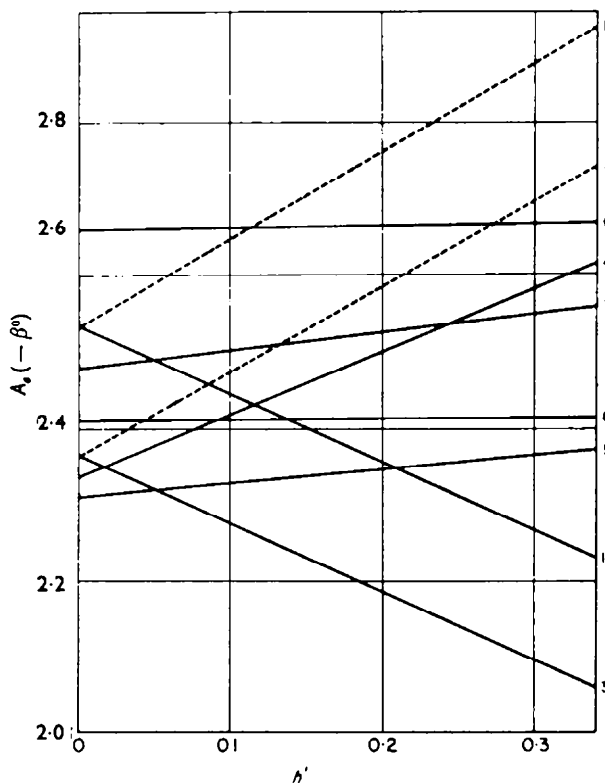


FIG. 7. Electrophilic localization energies of isoquinolinium ($h = 2$) as a function of h' . (For positions 1 and 3: Broken line, $\delta = 0$; full line, $\delta = 1$.)

by π -electron densities.^{13,14} Electrophilic localization energies are shown in Figs. 3 and 7 and for physically acceptable values of the coulomb parameters ($h = 2$, $h' = 0.2-0.25$) predict the reactivity order $5 > 8 > \text{others}$ provided that the energy of an electron localized at the 1 or 3 positions is taken as $\alpha^{\circ} + \delta h' \beta^{\circ}$ where $\delta < 0.43$. Thus

if the general reliability of the simple Hückel method is accepted we now have a definite indication of the upper limit for δ , confirming Wheland's suggestion¹⁹ that δ should be appreciably less than unity.

(b) *Nucleophilic attack*

Attack by nucleophiles on isoquinoline always occurs primarily at the 1-position²⁴⁻²⁶ and a methyl substituent is most reactive towards benzaldehyde and analogous reagents when at the 1-position, a methyl substituent at the 3-position being next

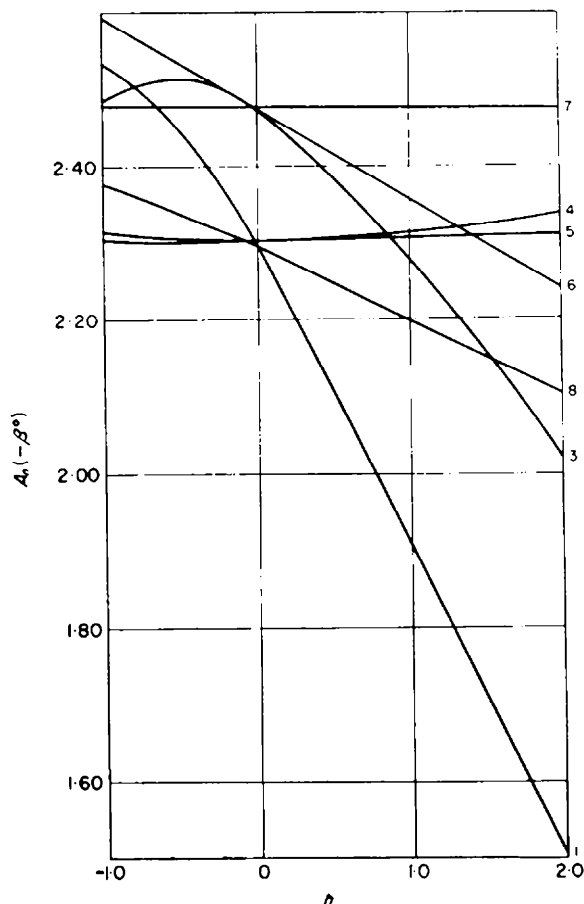


FIG. 8. Nucleophilic localization energies of isoquinoline as a function of h (for $h' = 0$).

in reactivity.^{27,28} Although there is some small uncertainty as to whether these attacks occur on the free base or on "electrophilated" isoquinoline (see discussion of comparable problem for quinoline¹⁴) the relative reactivities point to an order of π -electron densities of $1 < 3 < \text{others}$ and this order is found in the molecular-orbital calculations

²⁴ F. W. Bergstrom, *Liebigs Ann.* **515**, 34 (1934); *J. Org. Chem.* **2**, 414 (1937).

²⁵ F. W. Bergstrom and S. H. McAllister, *J. Amer. Chem. Soc.* **52**, 2845 (1930).

²⁶ A. E. Tschitschibabin and A. I. Kursanova, *Chem. Abstr.* **25**, 2727 (1931).

²⁷ W. H. Mills and J. L. B. Smith, *J. Chem. Soc.* **121**, 2724 (1922).

²⁸ H. Erlenmeyer, H. Baumann and E. Sorokin, *Helv. Chim. Acta* **31**, 1978 (1948).

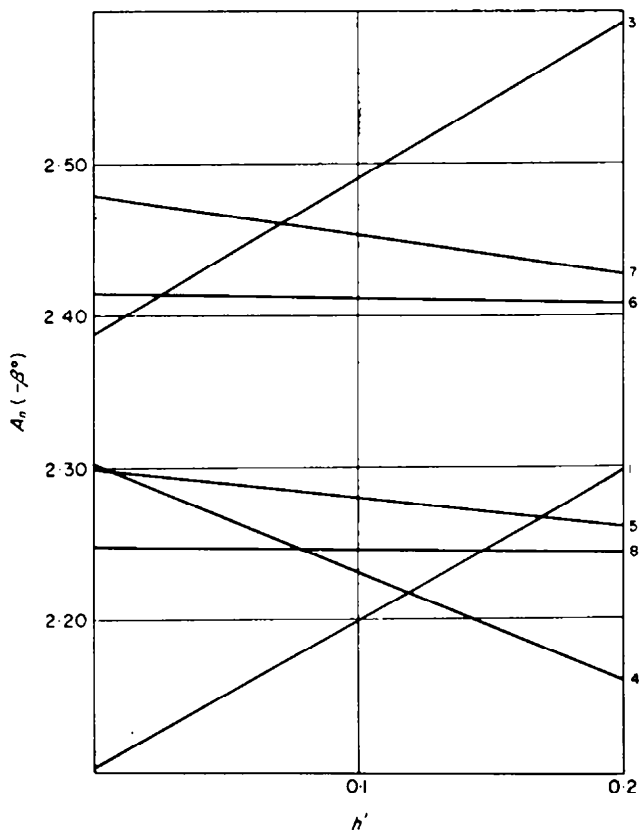


FIG. 9. Nucleophilic localization energies of isoquinoline ($h = 0.5$) as a function of h' .

for both isoquinoline and the isoquinolinium cation (Figs. 1 and 2). N-alkylisoquinolinium ions are also attacked by nucleophils preferentially at the 1-position^{29,30} and methyl substituents in the 1-position and, to a lesser extent, at the 3-position react with aldehydes.^{27,28} This accords with the calculated π -electron densities for the isoquinolinium system.

Nucleophilic localization energies for isoquinoline and the isoquinolinium cation are shown in Figs. 8, 9 and 10.

(c) Radical attack

Radical localization energies for isoquinoline are shown in Figs. 11 and 12. There is no clearcut experimental evidence on the orientation of radical attack, but vapour phase bromination, which may involve radical attack by bromine atoms, yields 1-bromoisoquinoline.³¹ This orientation is in agreement with the localization energies for physically reasonable values of h and h' provided that the "localized energy" parameter δ is greater than 0.80 (for $h = 0.5$, $h' = 0.085$). This is a greater value than was required when considering electrophilic substitution but clearly this value is likely to vary with the nature of the localizing entity.

²⁹ M. Freund, *Ber. Dtsch. Chem. Ges.* **37**, 4666 (1904).

³⁰ M. Freund and G. Bode, *Ber. Dtsch. Chem. Ges.* **42**, 1746 (1909).

³¹ H. E. Jansen and J. P. Wibaut, *Rec. Trav. Chim.* **56**, 699 (1937).

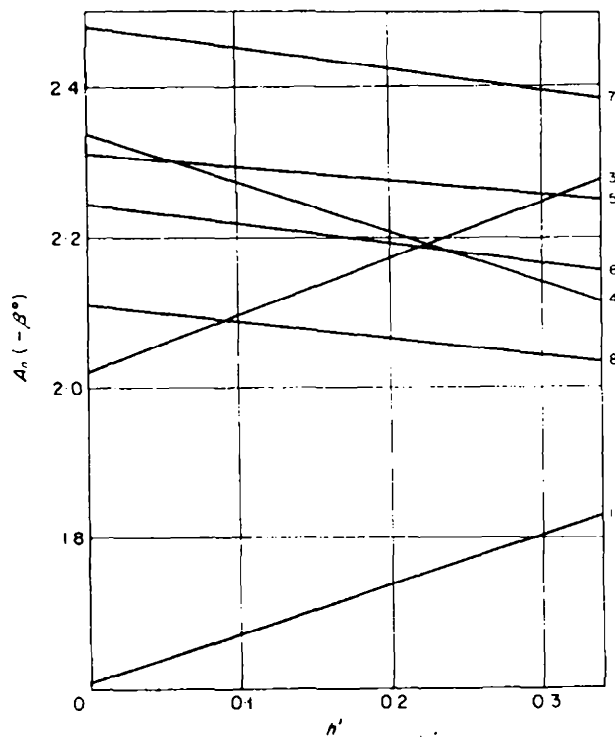
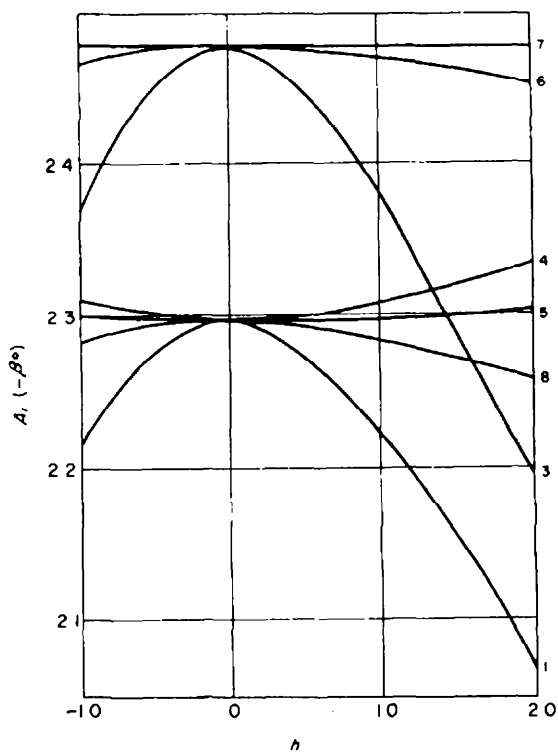


FIG. 10. Nucleophilic localization energies of isoquinolinium ($h = 2$) as a function of h' .

FIG. 11. Radical localization energies of isoquinoline as a function of h (for $h = 0$).



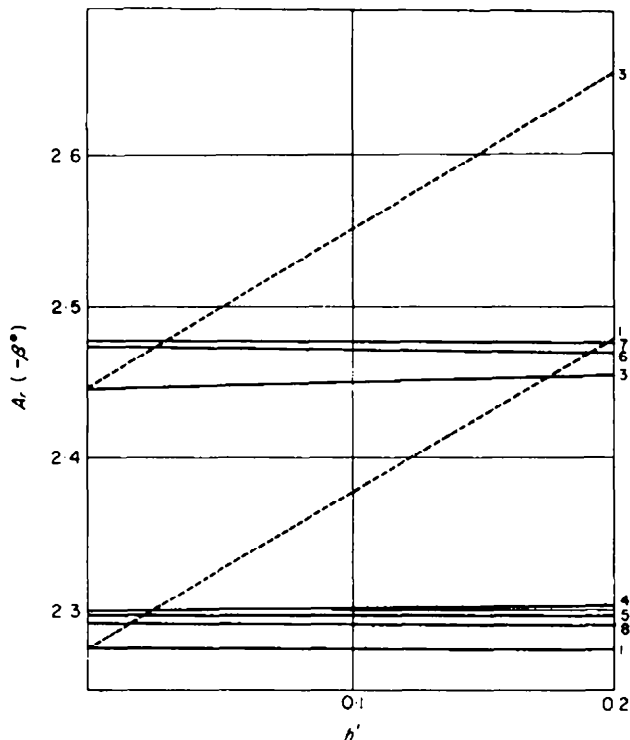


FIG. 12. Radical localization energies of isoquinoline ($h = 0.5$) as a function of h' .
(For positions 1 and 3: Broken line, $\delta = 0$; full line, $\delta = 1$.)

CONCLUSION

It has been possible to account fully for the observed chemistry of isoquinoline in terms of simple Hückel MO calculations and using values of the heteroparameters similar to those found suitable for interpreting the chemistry of other heterocycles. In fact these values of parameters have now been tested sufficiently to suggest that they should be suitable for theoretical treatments of other nitrogen heterocycles, the values being

$$\beta_{CN}^{\circ} - \beta^{\circ}$$

tertiary N: $h = 0.5, h' = 0.085$
secondary N: $h = 2, h' = 0.2$.

In addition some more definite indications of the appropriate procedure for computing localization energies for positions adjacent to heteroatoms have been obtained. These do not affect our previous study of quinoline because the position adjacent to the quinoline nitrogen (the 2-position) plays no part in electrophilic substitution while localization energies for nucleophilic substitution do not incorporate the energies of electrons localized at the 2-position. The vapour phase bromination of quinoline was tentatively interpreted in terms of radical localization energies for the quinolinium system and, as in the present case of vapour phase bromination of isoquinoline, the lowest localization energy is found for the observed position of bromination provided that the value used for δ is not too small.