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ALKYLATION OF NITROGEN HETEROCYCLES—II

SEMI-EMPIRICAL CALCULATIONS OF THE ELECTRON DISTRIBUTION IN CINNOLINES

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Abstract—A partial optimisation of the geometry in cinnoline is reported and calculations by the INDO and CNDO methods are made of the electron distribution in cinnoline and its 3-and 4-monomethyl and 3,4-dimethyl derivatives and their 1- and 2- protonated species. It is concluded that there is little significant difference in electron density at N-1 and N-2 in the neutral compounds, while preferential 2- protonation arises from a more favourable electronic energy for 1- protonation being offset by greater nuclear repulsion.

IN THE previous paper two of us expounded the hypothesis that the observed differences in reactivity at the 1- or 2- positions of cinnoline or 1- and 3- of quinoxaline are largely if not exclusively, the result of steric hindrance to reactivity at an α-position by the peri(8-) proton rather than any inherent electronic activation at the β-positions. A study of methylation reactions for a series of cinnolines where such steric effects were balanced by a substituent in the 3- position supported this view.[1] We now report detailed studies of the electron distribution in some simple cinnolines which are again consistent with the above hypothesis. The methods used are the self-consistent field LCAO-MO methods with complete or intermediate neglect of differential overlap (CNDO and INDO respectively).[2] These are the two most widely used[3] semi-empirical methods and are known to give reasonable energy minima near the correct geometry for simple molecules. The charge distributions lead to dipole moments, calculated in the point charge approximation after correction for sp polarization ("hybrid moment"), which are in reasonable agreement with experiment. Of the present methods, CNDO and INDO, the latter is mathematically superior, being slightly closer to the ab initio methods in that less electron repulsion integrals are equated to zero. It will also be seen that some inconsistencies are observed in the present results using CNDO. We had hoped to include studies using the modified INDO (MINDO) method[4] which has been widely used to determine heats of formation among related molecules, but the version available to us[5] often fails to diagonalize the eigenvalue matrix successfully, and this was common in the present work.

Geometry determination and total energy calculations. No experimental determinations of the geometry of cinnolines have been reported. Comparison of the structures of pyridine and the diazines with benzene,[6] and various bicyclic heterocycles[7] with naphthalene shows that carbon–carbon distances vary little between the carbo- and heterocyclic compounds, the shorter C–N lengths being largely offset by angle changes. A method of continuous (but non-iterative) approximation towards the real geometry of cinnoline was made starting with the naphthalene skeleton. A series of

CNDO calculations of total energy and electron distribution were made and after each run one or more geometric feature were changed; the criterion for a satisfactory change was increase in binding energy. The constraint of having to force ring closure in these processes in fact assists the process to converge. The four main changes tried are shown in I to IV, and it is clear that only small energy changes are likely to result from further refinements. It is interesting to note that the actual differences in electron distribution calculated for I to IV are very small, although the overall dipole moment is rather more sensitive (Table 1). The geometry IV was then used for subsequent work. Methyl substitution in the 3- and for 4- positions was carried out using the CH_3 geometry of toluene: the calculated and measured rotation barrier for methyl groups in aromatics is small, and for simplicity the methyl group was taken with one hydrogen (say H_1) in plane in the least hindered position. Under these conditions the E group orbital (H_2-H_3) of the C_{3v} methyl hydrogens is hyperconjugative with the π-electron system: at 90° to this the other E orbital ($2H_1$-H_2-H_3) is hyperconjugative.

TABLE 1. TOTAL ENERGIES, DIPOLE MOMENTS AND GEOMETRIC FEATURES OF CINNOLINES

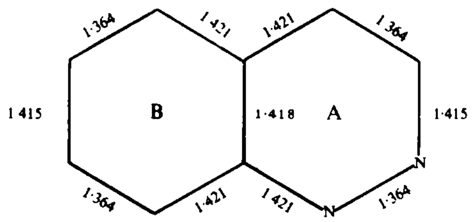
CNDO Method	*Total Energy (a.u.)*	*Electronic Energy (a.u.)*	*Dipoles Moment (d)*
I	−84·64678	−311·86138	3·941[a]
II	−84·66309	−312·34186	3·881[a]
III	−84·66971	−314·33024	3·846[a]
IV	−84·66992	−314·03758	3·849[a]
3-Me, I	−93·26390	−364·86740	3·844
3-Me, IV	−93·36854	−367·66272	3·784[c]
4-Me, IV	−93·36745	−371·41313	4·106[b]
3,4-Me$_2$, IV	−102·06519	−431·09865	4·026
(1-H, I)$^+$	−85·10720	−321·75880	2·879
(2-H, I)$^+$	−85·11260	−321·09130	6·690
INDO Method			
IV	−81·61952	−310·98719	3·726
3-Me, IV	−90·06307	−364·35726	3·676
4-Me, IV	−90·06199	−368·10766	3·873
3,4-Me$_2$, IV	−98·50531	−427·53827	3·865
(1-H, I)$^+$	−82·10644	−319·11451	1·870
(2-H, I)$^+$	−82·13763	−318·74103	4·732
(1-H, IV)$^+$	−82·17855	−321·36702	1·888
(2-H, IV)$^+$	−82·18360	−320·75759	4·820

[a] The observed value is 4·14D (M.T. Rogers and T. W. Campbell, *J. Am. Chem. Soc.* **75**, 1209 (1953)

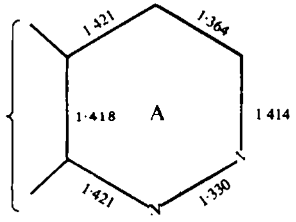
[b] The observed value is 4·53D (see footnote *a*)

[c] The estimated value from cinnoline and its 4-Me derivative (above) is 3·83D.

The preferred site of protonation is unequivocally N-2: this arises from the nuclear repulsion being sufficiently high in the N-1 protonated case that the more favoured electronic energy of the latter is outweighed. The dangers of calculations using electronic energy only as the criterion of geometry (such methods occur normally in Hückel type procedures) are apparent here.



I



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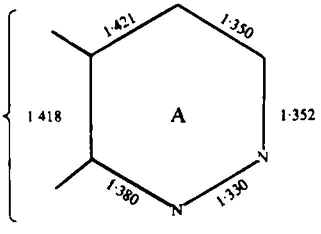

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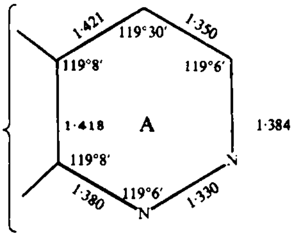

IV

Charge distribution and dipole moments. The calculated and observed dipole moments for cinnoline and its 4-Me derivative are about 10% too low; no figure is reported for 3-methylcinnoline but the estimated value from the unsubstituted and 4-Me compounds is 3·83D, in good agreement with calculation. It seems probable that the major charge distributions, N-1, N-2, C-3, C-4 etc (Table 2) are substantially realistic in each molecule studied. The overall electron releasing effect of the Me groups is evident in each case (the CNDO calculation on the 4-Me compound is inconsistent and this is a further reason for preferring the INDO results). The Me groups are apparently electron withdrawing through the π-hyperconjugative orbitals, and we have found this generally true with Me substituted aromatics such as toluene or 4-picoline. Tables of eigenvectors are not included here but will be supplied on request. The net charges by both INDO and CNDO methods on the ring atoms confirm that the charge densities are essentially equal at N-1 and N-2. There is a strong but possibly fortuitous correlation between these total charges and those reported by Cobb and Memory[8] for PPP π-electron only SCF calculations, where of course an unpolarized σ-skeleton is assumed: thus although their assumptions (such as all equal bond lengths etc.) and methods are very different the final results are very similar.

In Table 3 we give the individual components of the electron density at the N atoms by both methods. We propose that in reactions such as alkylation through attack on the σ-skeleton, where the mechanism is similar, that in sterically balanced systems the relative rates of reaction at different centres should be proportional not necessarily to total electron density, but to the electron density along the axis of the approaching reagent. Thus for cinnoline, taking for simplicity all angles as 120°, the axes are p_y:for N-1 and $\frac{1}{2}(p_y - \sqrt{3}\, p_x)$ for N-2. To determine these values the P_x and P_y eigenvectors at N-2 are conveniently rotated to correspond to radial $(\frac{1}{2}p_y - \sqrt{\frac{3}{2}}p_x)$ and tangential $(\sqrt{\frac{3}{2}}p_y - \frac{1}{2}p_x)$ eigenvectors. The electron densities calculated in this way for cinnoline are $(\text{N-1})p_y = 1{\cdot}4671$, $(\text{N-2})(\frac{1}{2}p_y - \sqrt{\frac{3}{2}}p_x) = 1{\cdot}5050$. Thus overall,

TABLE 2. TOTAL NET CHARGES ON CINNOLINE RING ATOMS

	N-1	N-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10
INDO Method										
IV	−0·097	−0·093	+0·105	+0·105	+0·016	+0·016	+0·031	+0·004	+0·103	+0·026
3-Me, IV	−0·094	−0·106	+0·114	+0·006	+0·012	+0·028	+0·028	+0·006	+0·099	+0·026
4-Me, IV	−0·103	−0·092	+0·092	+0·032	+0·013	+0·026	−0·031	+0·004	+0·104	+0·014
3,4-Me_2, IV	−0·102	−0·105	+0·102	+0·019	+0·012	+0·028	+0·029	+0·005	+0·099	+0·016
CNDO Method										
IV	−0·078	−0·072	+0·061	+0·005	−0·003	+0·009	+0·010	−0·009	+0·089	+0·026
3-Me, IV	−0·074	−0·089	+0·097	−0·015	−0·006	+0·011	+0·006	−0·007	+0·072	+0·080
4-Me, IV	−0·059	−0·068	+0·142	+0·141	−0·003	+0·007	+0·012	−0·011	+0·082	+0·012
3,4-Me_2, IV	−0·083	−0·085	+0·079	+0·021	−0·006	+0·010	+0·008	−0·008	+0·075	+0·014

although the total electron densities are essentially equal at N-1 and N-2, we feel that a very slight preference for reactivity at N-2 might be expected. In the present work it is unlikely, even in the sterically balanced cases, that we would detect such small differences in reactivity; in work with triazoles and related compounds there is a wider spread of electron density and some support for these proposals is apparent.

TABLE 3. COMPONENTS OF ELECTRON DENSITY AT THE NITROGEN ATOMS IN CINNOLINES

		Total	1s + 2s	$2p_x$	$2p_y$	$2p_z(\pi)$
INDO Method						
IV	N-1	7·0970	3·5741	1·0276	1·4541	1·0411
	N-2	7·0930	3·5513	1·3245	1·1905	1·0267
3-Me, IV	N-1	7·0939	3·5737	1·0323	1·4595	1·0284
	N-2	7·1061	3·5609	1·3195	1·1823	1·0434
4-Me, IV	N-1	7·1028	3·5744	1·0244	1·4515	1·0525
	N-2	7·0921	3·5507	1·3265	1·1985	1·0163
3,4-Me, IV	N-1	7·1021	3·5742	1·0298	1·4573	1·0408
	N-2	7·1050	3·5601	1·3213	1·1903	1·0333
CNDO Method						
IV	N-1	7·0830	3·5263	1·0495	1·4671	1·0351
	N-2	7·0690	3·5071	1·3446	1·1986	1·0218
3-Me, IV	N-1	7·0737	3·5266	1·0564	1·4733	1·0174
	N-2	7·0893	3·5139	1·3387	1·1903	1·0462
4-Me, IV	N-1	7·0892	3·5259	1·0439	1·4628	1·0566
	N-2	7·0682	3·5074	1·3488	1·2076	1·0044
3,4-Me$_2$, IV	N-1	7·0828	3·5260	1·0505	1·4688	1·0375
	N-2	7·0852	3·5139	1·3433	1·1984	1·0296

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