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AN APPLICATION OF THE SEMI-EMPIRICAL MO-LCAO METHOD TO INDOXAZENE AND ANTHRANIL

G. Del Re*
RIAS, Baltimore, Maryland

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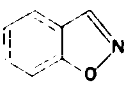
Abstract A discussion, in the light of a simple MO-LCAO treatment with inclusion of overlap, of the structure and properties of the two benzisoxazoles, indoxazene and anthranil, is given. After a few comments about the method used, the results of calculations by use of Orgel's parameters are given. The practically equal values of the dipole moments of the two molecules are substantially reproduced and explained. The main points about the structure and reactivity of indoxazene and anthranil are re-examined, pending further experimental investigation.

I. INTRODUCTION

The two possible benzisoxazoles, indoxazene (I) and anthranil (II), are both known. While indoxazene behaves substantially as any 4,5-disubstituted isoxazole, anthranil is very reactive, unlike the other 3,4-disubstituted isoxazoles. Its sensitivity to carbonyl reagents led its discoverers[1] to propose for it a lactam structure III, which, after a long and bitter dispute,[2] was finally disproved, together with structure IV by means of optical investigations.[3] The establishment of a benzisoxazole structure makes the properties of anthranil an indication of a peculiar electron distribution. This is also indicated by the fact that the dipole moments of I and II are practically equal,[4] notwithstanding the difference in the σ-skeletons and the quinoid structure which the classical formula for anthranil is bound to contain.



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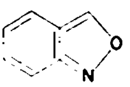

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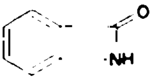

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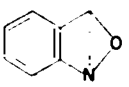

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The preceding remarks induced us to carry out a semi-empirical investigation about the compounds I and II, with the purpose of finding an electronic picture of these molecules and of deducing possible interpretations of their properties.

II. METHOD

The Hückel approach to molecular π-electron states has been used.

It is not intended here to give a detailed discussion of the validity and limitations of this method; however, a few comments about its present position, especially with respect to heterocyclic compounds, are appropriate.

Although an alternative procedure has been given,[5] the separation between σ and

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* On leave from Scuola di Perfezionamento in Fisica Teorica e nucleare, University of Naples, Italy.

[1] P. Friedländer and R. Henriques, *Ber. Dtsch. Chem. Ges.* **15**, 2105 (1882); **28**, 1382 (1895).

[2] The main arguments in this dispute are summarized by E. Bamberger, *Ber. Dtsch. Chem. Ges.* **36**, 819 (1903).

[3] K. Von Auwers, *Liebigs Ann.* **437**, 63 (1924).

[4] K. A. Jensen and M. Friediger, *Kgl. Danske Videskab. Selzk* XX, No. 20 (1943).

[5] G. G. Hall, *Proc. Roy. Soc.* A **213**, 102, 113 (1952).

π states has been proved to be a reliable approximation.[6] The general connection between the Hückel approach and more strictly mathematical approximation to the properties of ground states of molecules has been discussed, both in the light of the Hartree–Fock scheme and its SCF–MO–LCAO form[7] and in the light of approximations including configuration interaction:[8] in the latter case, it has been concluded that the Hückel approach, with appropriate parameters, can give a good description of the ground states of molecules.

The investigations mentioned, and others of a similar type, however, have not attacked the problem of giving a sounder foundation to the physical picture which underlies the MO–LCAO method. Consequently, they are not especially illuminating as to the significance of such quantities as charge- and bond-orders, which, nevertheless, are extremely useful in chemical applications. In this connection it can be said that the only proof of the validity of the MO-LCAO picture of molecules lies in the usefulness in interpreting the properties of molecules. A short review of the present position in this respect has been given:[9] it supports fully the view that, in comparing similar molecules, the Hückel method can be very illuminating. The papers mentioned above show that, if used cautiously, it can give much better quantitative agreement with experiment than usually expected.

Mainly in connection with the latter point, one particular topic is of interest here, namely the so-called "non-orthogonality problem." While Dewar[9] seems to think that introduction of overlap is probably pointless, others[10] have pointed out that possibly much better quantitative results as well as the elimination of some serious inconsistencies would result from the inclusion of overlap in Hückel calculations. The theoretical problem of such an inclusion, and of correlating the results with those of an equivalent overlap neglecting calculation, has long since been solved;[11] also, it can be shown that, under certain very plausible assumptions, the inclusion of overlap does not affect the calculation of dipole moments and the definition of atomic charges, while the eigenvalues are modified according to a simple linear transformation,[12] as we shall briefly summarize in the next section.

III. INCLUSION OF OVERLAP

If one assumes that the overlap integrals, $\beta_{\mu\nu}$, are proportional to the corresponding bond integrals, $S_{\mu\nu}$, through a general constant λ,[7] the basic equation of the MO–LCAO method

$$\mathbf{HC} = (\mathbf{1} + \mathbf{S})\mathbf{C}\boldsymbol{\epsilon} \tag{1}$$

can be shown to be equivalent to an equation of the form

$$\mathbf{H'C'} = \mathbf{C'}\boldsymbol{\epsilon}' \tag{2}$$

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[6] P. G. Lykos and R. G. Parr, *J. Chem. Phys.* **24**, 1166 (1956).

[7] R. S. Mulliken, *J. Chem. Phys.* **46**, 497, 675 (1949).

[8] R. McWeeny, *Proc. Roy. Soc.* A **232**, 114 (1955); R. McWeeny and T. E. Peacock, *Proc. Phys. Soc.* **70**, 41 (1957).

[9] M. J. S. Dewar, *Ann. Rep. Chem. Soc.* **53**, 126 (1956). About charges and bond-orders see also N. S. Ham and K. Ruebenderg, *J. Chem. Phys.* **29**, 1195, 1215, 1229, 1232 (1958).

[10] P. O. Löwdin, *J. Chem. Phys.* **21**, 496 (1953) and references therein.

[11] P. O. Löwdin, *Arkiv. Mat. Astr. Fys.* **35A**, 9 (1947); *A Theoretical Investigation into some Properties of Ionic Crystals* (Thesis) Almqvist and Wiksell, Uppsala, Sweden (1948); *J. Chem. Phys.* **18**, 365, (1950).

[12] G. Del Re, *On the Non-orthogonality Problem in the Semi-empirical MO-LCAO Method.* Quantum Chemistry Group of Uppsala University, Uppsala, Sweden, Techn. Rep. No. 20 (1958).

if the connexion between quantities in (2) and (1) is [primed quantities refer to (2)]:

$$\epsilon_i = \frac{\epsilon_i'}{1+\lambda\epsilon_i'}\,; \tag{3}$$

$$\alpha_\mu = \frac{\alpha_\mu'}{1+\lambda\alpha_\mu'}\,; \qquad \beta_{\mu\nu} = \frac{\beta_{\mu\nu}'}{\sqrt{(1+\lambda\alpha_\mu')(1+\lambda\alpha_\nu')}} \tag{4}$$

$$C_{\mu i} = \sqrt{\frac{1+\lambda\alpha_\mu'}{1+\lambda\epsilon_i'}}\,C_{\mu i}'. \tag{5}$$

In these equations the symbols have the usual meanings of orbital energies (ϵ_i), coulomb integrals (α_μ), bond-integrals ($\beta_{\mu\nu}$) and coefficients of the expansion of the i-th molecular orbital in the atomic orbitals ϕ_μ ($\epsilon_{\mu i}$). Their importance is connected with the fact that, since the diagonal and off-diagonal elements α_μ' and $\beta_{\mu\nu}'$ of **H**$'$ have the same one-atom and one-bond dependence as the corresponding elements of **H**, they can be taken as empirical parameters—provided a physical meaning is given only to quantities appearing in equation (2).

Now, it can also be shown that, provided the atomic orbitals are not very different in "size" and the overlap integrals are comparatively small (which is the case with π-electron systems) the dipole moments of π-electrons in a conjugated system can be described very well by atomic charges derived directly from (2), i.e. just as in calculations neglecting overlap. The preceding deductions can also be phrased as follows: *for applications where only energies and charges are required, one can start directly from an overlap-neglecting calculation, and overlap can then be taken into account through the linear transformation* (3) *of the eigenvalues.*

IV. PARAMETERS

As usual, we shall use α and β as standard reference parameters. For atoms μ and ν we shall therefore write:

$$\begin{aligned} \alpha_\mu &= \alpha + \delta_\mu\beta, \\ \alpha_\nu &= \alpha + \delta_\nu\beta, \\ \beta_{\mu\nu} &= \eta_{\mu\nu}\beta. \end{aligned} \tag{6}$$

As to the values of the quantities δ and η, their choice is subject, as is well known, to a large degree of arbitrariness: this, however, does not influence very much the semi-quantitative significance of the results, so that, provided certain general requirements are fulfilled, the particular choice of the parameters is not too important. Anyway, since we are interested both in considering dipole moments and in getting as good charges as possible, we shall use the set of parameters given in Table 1, which has been suggested just to predict the dipole moments of heterocyclic molecules, for instance isoxazole[13].

Two objections to the choice of this set deserve some comments. First, the introduction of 'inductive effects' into δ_C has been criticized as being theoretically unsound.[8] Such a criticism seemed also supported by the remark that a Hückel Hamiltonian corresponding to a more rigorous one does not show any increase in

[13] L. E. Orgel, T. L. Cottrell, W. Dick and L. E. Sutton, *Trans. Faraday Soc.* **47**, 113 (1951).

parameters for carbon atoms surrounding a heteroatom. However, it turns out (for instance in the case of furan and anisole) that it is practically impossible to find a set of parameters which predict a correct charge distribution for different molecules if no 'inductive effect' is taken into account. A similar remark has been made by others.[14] Therefore, the argument in the original paper[15] where the use of 'inductive' corrections was suggested appears to be rather well based from the empirical point of view. One could also introduce a sort of intuitive argument to justify this procedure. In the Hückel method, as is well known, the integrals $\alpha_\mu = \int \phi_\mu^* \mathscr{H}_{\text{eff}} \phi_\mu \, d\tau$ are taken as not depending upon the actual molecule one is considering in each case. If a physical meaning is to be given to this assumption, this is that the field generated at the center μ by neighbouring atoms (which only matters in a nearest neighbour approximation is practically independent of their nature; a statement which would be true enough if it were taken to mean that neighbours are "seen" from an atom μ as if, so to say, the same effective charge always correspond to their cores. Now, even if such a drastic simplification were justified in general, it certainly would not if one of more of the neighbours of μ happened to exhibit abnormal covalency, as for instance nitrogen in pyrrole, since then the cores would be quite different. The introduction of a correction in δ_μ is therefore necessary, at least in these cases, especially if δ_μ is so low that a slight change in it can affect strongly the charge distribution. It is easy to see how the preceding argument can be used to justify the actual way this "inductive effect" is introduced; however, it should be remembered that intuitive arguments as the one above cannot be taken too literally, and the best justification for the form given to the 'inductive effect' is that it works.

Table 1. Parameters used in these calculations

δ_C	$= 0{\cdot}1\Sigma\delta_x{}^a$	η_{CC}	$= 1{\cdot}0$
δ_{N_C}	$= 1{\cdot}0$	η_{CN}	$= 1{\cdot}2$
$\delta_{N<}$	$= 2{\cdot}0$	η_{CO}	$= 1{\cdot}4$
δ_{O-}	$= 2{\cdot}0$	η_{NO}	$= 0{\cdot}6$
$\delta_{O<}$	$= 3{\cdot}2$	λ	$= 0{\cdot}25$

ax denotes heteroatoms adjacent to C.

The second objection to the parameters chosen arises from the fact that the dipole moments obtained by Orgel *et al.* for the π-systems of heteromolecules are larger by a factor 1·6 than the experimental value; as a matter of fact, a correction in the parameters would be welcome. However, the proportionality between the calculated and experimental moments stands in favour of the correctness of the "relative" distributions of charges: and, for our purpose, the absolute magnitudes of the latter are not important. As to the energies, they too are obviously dependent upon the choice of parameters: but, even for these, we can consider their relative values, if a comparison between similar molecules is our only purpose.

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[14] B. Pullman and A. Pullman, *Proc. Nat. Acad. Sci.* **45**, 136 (1959).

[15] L. Pauling and G. W. Wheland, *J. Amer. Chem. Soc.* **57**, 2086 (1935).

The last parameter we must consider is λ (see section II): to it we have attributed a value of 0·25 because this value has usually been attributed to the overlap integral of the CC π-bond.

V. RESULTS AND DISCUSSION

The diagrams of Fig. 1 and Fig. 2 show the results for charge- and bond-orders for isoxazole (as calculated by Orgel *et al.*[13]) and for the two molecules under study here. Tables 2, 3 and 4 show some results about energies and dipole moments.

We shall first of all discuss energies, then the structures of the molecules under study in the light of results about dipole moments, charge- and bond-orders. In another section we shall use these results to discuss reactivities.

A. Total and delocalization energies

The main use one can make of energies calculated for ground states of molecules by means of the semi-empirical MO-LCAO method is for comparisons between different molecules. We have therefore included additional data to make such comparisons easier in Tables 2 and 3. Table 2 contains (a) total calculated energies, (b) delocalization energies, (c) delocalization energies per electron.

According to a remark by Orgel *et al.*,[13] we have avoided introducing resonance energies, but have used instead delocalization energies, simply calculated as the differences between total energies and the energies obtained by assigning the electrons to the various atomic orbitals with energies α_μ [see equation (4)]. In calculating the latter energies we have made no allowance for the "inductive effect," since we consider it as an effect of the binding.

The introduction of delocalization energies per electron deserves some comments. We have calculated them by dividing the whole delocalization energy by the number of electrons, with the purpose of comparing stabilities with a different number of π-electrons. These quantities, of course, are not strictly related to experimental quantities, since they are averages: nevertheless in our opinion they can be taken as a measure of the degree of delocalization of a system, since they are independent of the number of electrons.

From Table 2 it is immediately seen that the degree of delocalization of isoxazole is rather poor: this is not surprising, since the aromaticity of five-membered heterocyclics is always small, as is experimentally well known.[16] In fact, the total delocalization energy of isoxazole is only slightly larger than that of butadiene. As to the two molecules under study here, Table 2 shows that their aromatic nature is enormously increased with respect to isoxazole, because of the butadiene bridge linking two adjacent carbon atoms of the isoxazole unit. The fact that anthranil appears to be less stabilized than indoxazene clearly corresponds to the prevailing quinoid structure of the former compound. However, it is remarkable that the difference in delocalization energy per electron between the two benzisoxazoles is quite small, compared with the variation of this quantity when two isolated double bonds are allowed to interact (cf. ethylene and butadiene): this is an indication of the high weight of "ionic" structures in anthranil, as can be seen also from charge distributions. Table 2 also indicates that the increase in delocalization energy per electron from cyclopentadienyl to benzocyclopentadienyl is much less than the corresponding increase from isoxazole

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[16] L. Fieser and M. Fieser, *Organic Chemistry*. Reinhold, New York (1956).

to any of the two benzisoxazoles. This is but one more example of the well known stabilizing effect of condensed benzene rings on heterocyclics.

B. Partial localization energies

Though other conclusions can be drawn from Table 2, the figures given there do not allow a complete analysis of the numerical data, because they give no insight into the relationships between the energies of molecules and those of their "building blocks," on whose properties most of the purely chemical theory of reactions bases its predictions. In this connexion, a further elaboration of the results about energies is needed, and can be introduced by defining a *partial localization energy* as follows. Let the molecule under study be formed of two units, X and Y, linked to each other by any number of bonds (and, since we are considering π-systems, also conjugated to each other through these bonds). We shall call partial localization energy of the X unit in XY the difference between the total delocalization energy of XY and the delocalization energy calculated for Y. It corresponds to the energy needed to suppress the π-system of the X unit, by localizing its π-electrons, and gives an indication of the relative stability of X in a series of homologous molecules XY_1, XY_2, XY_3, etc.

TABLE 2. TOTAL AND DELOCALIZATION ENERGIES

Compound	(a)	(b)	(c)
Ethylene	$2\alpha + 1{\cdot}600\beta$	1·600	0·800
Allyl neg. ion	$4\alpha + 2{\cdot}090\beta$	2·090	0·522
Oxime group	$4\alpha + 6{\cdot}030\beta$	1·674	0·418
CON-group	$4\alpha + 5{\cdot}452\beta$	1·090	0·273
Butadiene	$4\alpha + 3{\cdot}375\beta$	3·375	0·844
Cyclopentadienyl[*] neg. ion	$6\alpha + 4{\cdot}808\beta$	4·808	0·801
Isoxazole[†]	$6\alpha + 8{\cdot}116\beta$	3·760	0·627
Benzene[*]	$6\alpha + 5{\cdot}867\beta$	5·867	0·978
Pyridine[*]	$6\alpha + 6{\cdot}786\beta$	5·986	0·998
Benzocyclopentadienyl ion[*]	$10\alpha + 8{\cdot}789\beta$	8·789	0·879
Indoxazene	$10\alpha + 12{\cdot}237\beta$	7·881	0·788
Anthranil	$10\alpha + 12{\cdot}039\beta$	7·683	0·768

[*] From: B. Pullman and A. Y. Pullman, *Les Théories Electroniques de la Chimie Organique*. Masson, Paris (1952).

[†] Ref. 13.

(a) Total energies (overlap included).

(b) Delocalization energies in units β.

(c) Delocalization energies per electron, units β.

The significance of such a quantity is clear if one considers the importance a reaction involving a whole unit can have for chemists—for instance, the oxidation of a polynuclear hydrocarbon. A quantity similar to these partial localization energies has been introduced by Brown[17] with respect to one bond, and hence called "bond fixation energy."

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[17] R. D. Brown, *J. Chem. Soc.* 1951 (1955).

As to the figures given in Table 3, the following remarks are important in connection with the present purpose:

(a) The 3,4-bond of isoxazole is more stable than the 4,5-bond, and indeed almost as stable as a CC-bond in a cyclopentadienyl system. This is not surprising, since it corresponds to the fact that localizing the two π-electrons of the 3,4-bond implies leaving a system whose only possibility of delocalization depends upon the tendency of oxygen to share its $2p\pi$ lone pair, which is obviously not very strong. On the other hand, fixing the 4,5-bond would leave the molecule with an oxime system, which is comparatively stable.

TABLE 3. PARTIAL LOCALIZATION ENERGIES (units β)

Compound	Fixated part	Energy required
Butadiene	C–C bond	1·875
Cyclopentadienyl ion	C–C bond	2·718
	CCC unit	3·208
Isoxazole	3,4 bond	2·670
	4,5 bond	2·080
CNO unit	CNO unit	2·160
	CON unit	2·160
Benzene	C–C bond	2·492
	butadiene unit	4·267
Benzocyclopentadienyl ion	CCC unit	2·922
	butadiene unit	3·981
	cyclopentad. ring	5·414
	benzene ring	6·699
Indoxazene	CNO unit	2·014
	butadiene unit	4·121
	isoxazole ring	4·505
	benzene ring	6·207
Anthranil	CON unit	1·816
	butadiene unit	3·923
	isoxazole ring	4·308
	benzene ring	6·593

(b) In benzocyclopentadienyl the benzene ring appears to be very stable, even more stable than benzene itself. The large amount of 'extra resonance energy' with respect to any two component units explains the fact that all units appear to be very stable. However, the cyclopentadienyl unit is less stabilized than the benzene unit, with respect to the isolated molecule. This situation is entirely reversed in indoxazene. In fact, while the benzene unit still appears to be deactivated, the isoxazole unit is much more stabilized with respect to isoxazole itself, and this is in agreement with experiment (*vide infra*): the isoxazole unit of indoxazene is comparatively stable.

(c) As to anthranil, it shows two interesting facts: first, the isoxazole unit is much less stabilized than the benzene unit; second, the latter appears to be more stabilized than in indoxazene. This is already a first indication of the peculiar reactivity of anthranil; we shall return later to this point. In the same connection, we note that the CON unit of anthranil shows an enormous increment of stability, with respect to its 'isolated' state, although it remains less stable than in isoxazole. This shows that its properties should be profoundly modified, with respect to its isolated, extremely unstable state, but that it should also be less stable than in isoxazole. In other words, anthranil should undergo more easily than isoxazole reactions which involve cleavage of one bond of the CON unit.

C. *Dipole moments*

As we pointed out in the introduction to the present paper, it is very surprising, at first sight, that the dipole moments of the two benzisoxazoles should be practically equal.[4] Indoxazene, judging from its chemical formula, is very similar to isoxazole, so that one should actually expect its dipole moment to be approximately the same as those of 4- and 5-phenylisoxazole, which are 3·0 and 3·2 D respectively.[18]

Table 4. Dipole moments (D)

Compound	μ_σ[a]	θ_σ[b]	μ_π[c]	θ_π[b]	μ_{tot}[d]	μ_{obs}[e]
Isoxazole[f]	1·9	155°	1·3	85°	2·7	2·8
Indoxazene	2·0	157°	1·3	119°	3·1	3·0
Anthranil	2·0	154°	2·6	82	3·6	3·1

a Dipole moment of the σ-frame according to reference 13.
b Angles measured with respect to the vertical axis (Fig. 1); the signs of the moments are taken according to the chemical convention.
c Dipole moments of the π-charge distribution.
d Total calculated moment
e Total observed moment (Ref. 4).
f All values from Ref. 13.

Anthranil, on the other hand, has a quinoid structure as a basic formula, so that it should be expected that highly polarized structures are essential for the stabilization of the whole system (*vide infra*). Therefore the result of the calculation of both dipole moments by means of the Hückel approach is particularly interesting, and Table 4 shows that the apparent equality of the dipole moments of the two benzisoxazoles is more or less an accident, due to the different orientation of the σ-moments in the two compounds, with respect to the corresponding π-moments. In fact, the π-dipole moment of anthranil is actually much larger than that of both isoxazole and indoxazene.

D. *Charge distributions*

It is instructive to discuss the dipole moments of the three compounds under study in connection with the charge distributions given in Fig. 1. An inspection of the charges in isoxazole suggests that two effects are superimposed in the π-system of this compound: one is the normal tendency of the charges to alternate, the other is the tendency of the electrons to concentrate on the nitrogen atom in such a way that the charge distribution tends to be symmetrical around the axis passing through the nitrogen atom. That the resulting charge distribution is not an accidental result of

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[18] P. Pino and G. Speroni, *Rend. Ist. Lomb. Sci. Lett., Classe Sci.* **88**, 331 (1955).

the rough approximation used to derive it is shown by the fact that the direction of the dipole moment found for isoxazole agrees very well with experimental results.[19] Therefore, we can reasonably believe that also for the other two compounds the situation is correctly described by the charge distribution given in Fig. 1. In indoxazene, the tendency of the charge to be symmetrical around the longitudinal axis passing through nitrogen is even more marked than in isoxazole, as is shown by the direction of the π-dipole moment. This is also true for bond orders, which, except for the CNO unit, are essentially symmetrical. In anthranil a quite different combination of the two effects is found. While the bond orders are symmetrical around the main longitudinal axis, thus supporting the fundamental quinoid structure of this benzisoxazole, the charge is very much concentrated on the nitrogen atom. This also corresponds to the fact that decreasing the bond order of the CN bond increases the charge of nitrogen; this may be considered as the Hückel equivalent of the introduction of ionic structures which would be required if resonance theory were applied to explain the 'aromaticity' of anthranil.

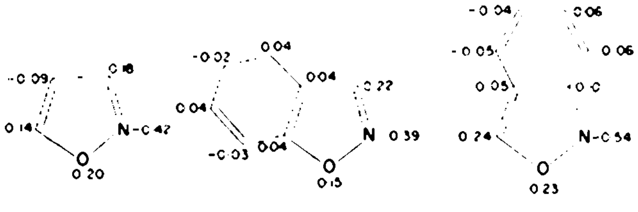


FIG. 1. Charge distributions found for (a) isoxazole[13], (b) indoxazene, (c) anthranil.

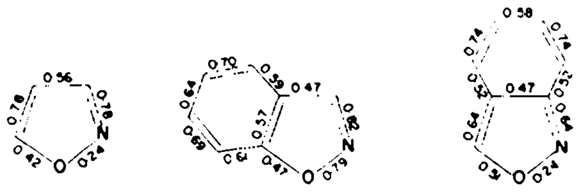
It is also useful to correlate the partial localization energies given in Table 3 with the molecular diagrams of Fig. 1. The isoxazole unit is stabilized by the condensed benzene ring both in indoxazene and in anthranil, but more in the former compound than in the latter. The stabilizing effect of the benzene ring, as we have pointed out before, is a well-known effect: here we only note that, at first sight, it seems to have very little to do with the charge distribution. In fact, there is no apparent general increase in bond-orders and no levelling of charges in passing from isoxazole to its two benzo-derivatives. However, if one considers the overall charge on the isoxazole ring, one understands where the correlation lies. In fact, the charge on the isoxazole ring, which is zero by definition in isoxazole, is —0·021 in indoxazene and —0·016 in anthranil, so that it clearly corresponds to the sequence indoxazene–anthranil–isoxazole suggested by partial localization energies. It is certainly remarkable that differences in localization energies of 0·554 and 0·752 should correspond to an excess of negative charge so small that we have been obliged to use three decimal figures to make the difference evident. However, this is no surprise if one considers that, especially in five-membered rings, this high sensitivity of energies to charges is the rule.

E. Bond orders

As to bond orders, there appears to be no easy way of connecting them with localization energies, also because, as we have pointed out in section III, they have no direct meaning if overlap is considered as important, except in a very rough way.

[19] G. Speroni and P. Pino, *Gazz. Chim. Ital.* **80**, 549 (1950); **82**, 269, 285 (1952); **84**, 760 (1954).

However, their qualitative distribution shows how close the structures of indoxazene and anthranil are to the classical structures one can draw for these compounds. In indoxazene, the benzene ring appears to be mainly in its normal kekule structures, except for an important contribution on the part of a quinoid structure which is apparently the consequence of the conjugation through oxygen to the isoxazole system. It is remarkable that there appears to be a very well localized CN bond, more localized, indeed, than the corresponding one in isoxazole. This may very well correspond to the fact that the mesomeric effect of oxygen influences the benzene ring mainly through the CN bond, instead than directly, so that the conjugated system is substantially that of benzaldoxime, whose U.V. spectrum is indeed very similar to that of indoxazene.[20] This conclusion is supported by the remark that the effect of oxygen when conjugated to a phenyl group through a NC bond is to increase the bond order of the CN bond: this was shown in a study of benzonitriloxide as compared to benzonitrile[21] by simple Hückel calculations and supported by the experimental results of an infra-red study of the same compounds.[22]



(a) (b) (c)

FIG. 2. Bond-orders of (a) isoxazole,[18] (b) indoxazene, (c) anthranil.

In anthranil, as we have said, the quinoid structure appears to be favoured in our molecular diagram. Substantially, a comparison with isoxazole shows that two effects are superimposed in this compound: (a) the typical delocalization of an isolated benzene ring, (b) the delocalization along the perimeter of the molecule, leading to an increase of the NO and CO bond orders, and a decrease of the CN bond order. The latter effect corresponds to the fact that no aromaticity and practically no stability as a ring compound could be expected for anthranil if the quinoid structure were not accompanied by a closure of the conjugation through the oxygen atom. This also means that, since there appears to be such a conjugation, the present treatment agrees perfectly with the now established structure II for the anthranil molecule. It is also interesting to remember here that in anthranil the partial localization energy of the benzene ring is much higher than in indoxazene. This is apparently due to the great amount of conjugation which is needed to stabilize the CON unit. For the same reason a smaller partial delocalization energy corresponds to the isoxazole unit of anthranil, as compared to that of indoxazene.

VI. REACTIONS OF INDOXAZENE AND ANTHRANIL

Even if many objections can be made to the use of charges, as calculated by the naïve Hückel method, in discussing reactivities,[23] the intuitive electrostatic model of

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[20] P. Grammaticakis, *Bull. Soc. Chim. Fr.* V8, 101 (1941).

[21] G. Del Re, *Atti Accad. Lincei* 22, 491 (1957).

[22] S. Califano, R. Moccia, R. Scarpati and G. Speroni, *J. Chem. Phys.* 26, 1777(L) (1957).

[23] R. D. Brown, *Quart. Rev.* 6, 62 (1952).

reactions appears to be rather consistent with experimental facts (as far as ionic reactions are concerned), when they are used only to predict the direction of a certain reaction will take where large differences in atomic charges are found, as it happens in compounds containing heteroatoms. Therefore, with some reservations, we shall use them to discuss a few reactions of the two compounds under study.

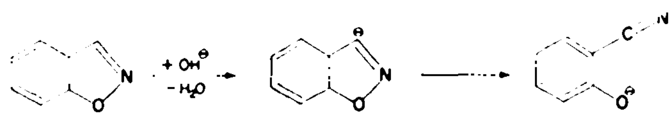
The preceding discussion of charge- and bond-orders has shown a few general points. In both compounds the reactivity is practically localized in the isoxazole ring, the CNO unit of indoxazene being just a little less stable than that of isoxazole, while the CON unit of anthranil is markedly less stable than that of isoxazole. Therefore, the comparatively high reactivity of both compounds and the particular sensitivity to many reagents of the part of anthranil are indicated by our previous results. As to the benzene units, if an electrophilic substitution can be carried out without destroying the isoxazole ring, our molecular diagrams predict that substituents will enter *ortho-para* to the CO bond in indoxazene, *ortho-para* to the CN bond in anthranil: the substitution itself should be comparatively more selective in anthranil than in indoxazene, according to charges—though, as far as Table 3 goes, indoxazene should undergo substitutions somewhat more easily, since its benzene unit is less deactivated than that of anthranil.

The fact that the benzene rings of both compounds act as an electron donor (section VD) suggests that an electron attracting group on the benzene ring should cause a destabilization of both compounds. One instance at least is known:[24] 6-nitro-indoxazene cannot be isolated when obtained from the appropriate oxime, because it undergoes immediately transformation to a salicylo derivative (see following subsection).

Apart from the above general remarks, we will now consider a few examples of reactions of the compound under study in more detail.

A. *Indoxazene*

The reactions of indoxazene are those typical of an isoxazole derivative, in agreement with all our preceding results. The most interesting one is the formation, with alkali, of a nitrile derivative. The following mechanism has been proposed for this



I V VI (A)

reaction[25] in the case of isoxazole. Such a mechanism implies the loss of a hydrogen atom by indoxazene, followed by a cleavage of the N–O bond. There is some support for this mechanism from the semi-theoretical point of view. The high positive charge of the carbon atom adjacent to nitrogen can serve as a justification for the easy cleavage of the C_3-H bond, and, while ion V in itself cannot be expected to be more stable than I, it certainly has a smaller proton affinity than the OH^- ion, thus making the reaction I → V very plausible.

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[24] J. Meisenheimer, P. Zimmermann and U. V. Kummer, *Liebigs Ann.* **446**, 205 (1926).

[25] G. Speroni and P. Pino, *Atti Accad. Lincei* VIII, 6, 325 (1949).

One can also predict that, given the higher positive charge of carbon 3 in indoxazene with respect to isoxazole, the stage in question should occur more easily in the former compound, i.e., for instance, at a lower pH.

The second stage of the reaction (A) involves only a rearrangement of the ion V, and therefore should be a rather fast step, with little, if any, activation energy involved. Although this stage is entirely justified by chemical experience, because ion VI is known to be a very stable one, whereas ions of a type like V are in general only short-lived intermediates, it is interesting to examine this point in the light of semi-empirical calculations. If the effect of negative charges on coulomb integrals is neglected, the energies of the π-systems of V and VI are $10\alpha + 12{\cdot}237\beta$ and $10\alpha + 12{\cdot}180\beta$ respectively, so that the difference is in favour of ion V for $0{\cdot}057\beta$. If, just for the sake of a better interpretation of this figure, we give β a value of -33 kcal/mole[26] we have that the π-system of ion V should be more stable by about 2 kcal/mole than that of ion V. Even if one considers the fact that in ion VI the N–O bond of V is replaced by a π'-C-N bond, one finds that the energies of the two ions are practically the same, since the energies of the two bonds just mentioned are of the same order of magnitude.[27] Therefore, if one does not consider explicitly the negative charge, neither of the two ions is actually favoured. However, the negative charge actually plays an important role in this reaction, since in the salicylonitrile ion the repulsion between the phenate oxygen and the nitrile nitrogen, both highly negative, makes a ring closure improbable, while a similar reason should favour very much the opening of the ring in ion V.

As we have already pointed out, the reaction so far discussed, as well as the others indoxazene undergoes, is substantially similar to the corresponding reactions of the isoxazole with no substituents in position 3, as a comparison between the charges of isoxazole and indoxazene (Fig. 1) immediately shows.

B. Anthranil

The case of anthranil is much different. First of all, isoxazoles having substituents in their 3-positions usually show a high stability towards alkali,[28] which is not the case of anthranil[1] as has also been deduced from Table 3. This remark, together with the fact that the charge of carbon 5 of the isoxazole ring in the latter compound is even higher than the charge of carbon 3 in isoxazole and indoxazene, supports the suggestion, originally due to Schmidt,[29] that in anthranil the hydrogen belonging to the isoxazole unit is labile. One should therefore suggest a tautomerism—at least potential- of the type (B):

II VII (B)

This kind of tautomerism implies the formation of an ion similar to ion V [see (A)] which, in strong alkaline media, might rearrange to another ion IX which should then

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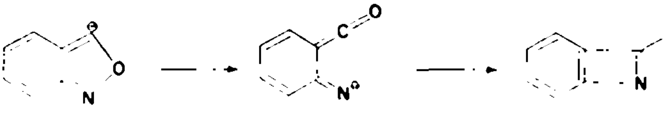
[26] G. W. Wheland, *Resonance in Organic Chemistry* p. 669. John Wiley, New York (1955).

[27] T. L. Cottrell, *The Strengths of Chemical Bonds.* Butterworths, London (1954).

[28] L. Claisen, *Ber. Dtsch. Chem. Ges.* **24**, 3904 (1891); more recent work on isoxazoles is to be found in the work of A. Quilico *et al.* mainly in *Gazz. Chim. Ital.*[19]

[29] O. Schmidt, *Ber. Dtsch. Chem. Ges.* **36**, 2459, (1903).

behave as a ketene derivative; this could even undergo a further rearrangement (C) leading to the formation of a four-membered ring of the lactam type. Such a rearrangement would just give the ion corresponding to the structure III proposed for anthranil for its discoverers.[1] The reason for suggesting the existence of X, as a short lived intermediate, is that ions with a negative charge localized on a nitrogen atom are not very likely. However, it must be noted that from an experimental point of view it is doubtful whether it would be possible to distinguish between IX and X,



VIII IX X (C)

since both are to be considered as short lived intermediates: the question is only interesting in connection with the formulation of reaction mechanisms. From the semi-theoretical point of view, if, as usual, we neglect the effect of negative charges on coulomb integrals, the energies of the π-systems of VIII, IX and X are found to be respectively: $10\alpha - 12{\cdot}237\beta$, $10\alpha + 11{\cdot}938\beta$, $10\alpha - 12{\cdot}057\beta$. If we evaluate the total energy differences in (C) by use of bond energies[27] and of the preceding figures (β being taken again as 33 kcal/mole[28]), we find:

$$E\,(\mathrm{VIII} \rightarrow \mathrm{IX}):\ -31\ \text{kcal/mole};$$

$$E\,(\mathrm{IX} \rightarrow \mathrm{IX}):\ +25\ \text{kcal/mole};$$

$$E\,(\mathrm{VIII} \rightarrow \mathrm{X}):\ -6\ \text{kcal/mole}.$$

Therefore, all reservations made about the validity of these figures, we are led to assume that the most probable form of the ion in discussion here is the form IX. Here again, however, we must remark that it is extremely probable that ion X, once formed, is extremely more stable than IX for a reason our calculations have not taken into account, i.e. the possibility the negative charge of X has to spread over the whole molecule, which should make X much less reactive than IX. Curiously enough, even this consideration leads us to consider IX as the most appropriate intermediate for the reactions in alkaline media, since we can assume that the unimolecular step leading to the formation of a strained ring such as the lactam ring is slower than other reactions which IX should undergo more readily than X, especially those involving either the nitrogen atom or the ketene group. Therefore, the following scheme for the formation of anthranilic acid (XI) from indoxazene in strong alkaline media seems to be quite plausible.

Among the many other reactions of anthranil, we shall discuss here only one, which has been a very important point in the dispute about its structure.[2] This is the addition of hydroxylamine to anthranil, which obliged even those who supported the isoxazole formula to agree that "the aldehydic character, although not typical of anthranil as such, is to some extent latent" in it.[30]

From the point of view of the semi-theoretical treatment, what is really important in this connection is not whether anthranil contains a carbonyl group, but whether it

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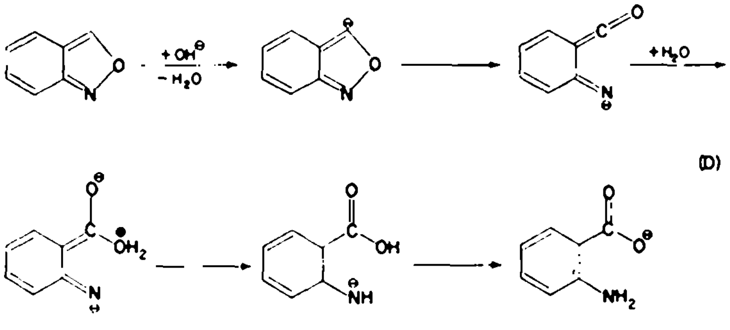
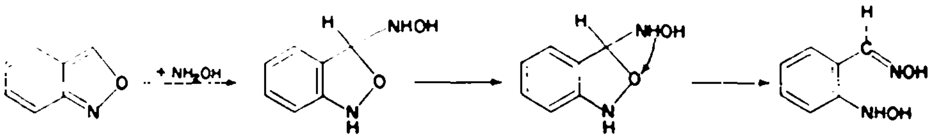
[30] E. Bamberger and E. Demuth, *Ber. Dtsch. Chem. Ges.* 34, 4015 (1901).



(D)

XI

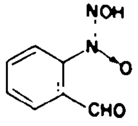
can undergo reactions typical of this group. It is not probable that, in the environment in which addition of hydroxylamine is usually carried out, any importance should be attributed to the formation of negative ions by anthranil. Therefore, the static diagram of Fig. 1 should be considered. Here again, the high positive charge of carbon 5 appears to give an explanation for this peculiar reaction. By analogy with the typical reactions of formation of oximes,[31] a mechanism can be formulated roughly as follows:



(E)

The only difference between mechanism (E) and that of the usual oxime forming reactions is the attack of a proton to nitrogen. This is justified by the fact that nitrogen, according to Fig. 1, is very negative in the ground state of anthranil and that steps (a) and (b) are probably simultaneous. Therefore, we can say that the 'latent aldehydic character' of anthranil is a result of both the high positive charge of its carbon atom and of the negative charge of nitrogen: the latter is probably essential in order that the attack of hydroxylamine may be followed by the actual formation of an oxime.

The high negative charge of nitrogen in anthranil suggests also that this compound should be basic. This is quite possible, since isoxazole itself is slightly basic:[25] however, there is no information, at least as far as we know, about this property of anthranil. The only reaction that can be correlated with the basic properties of anthranil is its ability to give a diazonium salt with $NaNO_2$ and strong sulphuric acid.[32] However, it is impossible here to give a mechanism for this reaction, since it proceeds through the formation of a nitrosophenylhydroxylamine derivative, XIII.



XIII

which corresponds to the product of a simultaneous nitrosation and oxidation

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[31] H. Meerwein, O. Fuchs, H. J. Sasse, H. Schrodt and J. Spille, *Ber. Dtsch. Chem. Ges.* **89**, 2060 (1956); see also ref. 16.

[32] E. Bamberger and J. Lublin, *Ber. Dtsch. Chem. Ges.* **42**, 1723 (1909); see also A. A. Morton, *The Chemistry of Heterocyclic Compounds* p. 426. McGraw-Hill, New York (1946).

VII. CONCLUSION

As we have already mentioned, the naïve Hückel method is not only open to very serious theoretical objections, but is far from having reached a well determined status as an interpolation procedure inspired by the formalism of quantum mechanics. Therefore, in a research like the one we have presented, two aspects are bound to be present: the particular application of the method as a scheme for correlating properties of certain compounds to each other and to those of other compounds, and a critical analysis of the "theoretical" quantities used to get such a correlation.

In our particular case, we have tried to reach our main purpose—that of interpreting in terms of a general scheme the properties of indoxazene and anthranil—by using only a limited amount of numerical data, in order to avoid the risk of introducing too many definitions.

The conclusions we have reached are as follows:

(a). The comparatively good stability of indoxazene and anthranil is predicted in our results and is to be attributed to the stabilizing effect of the benzene ring condensed to the isoxazole unit;

(b). The peculiar properties of anthranil, as compared to similar isoxazole derivatives, are correctly interpreted in the frame of the method used, under the assumption that anthranil is actually an isoxazole derivative;

(c). The reactivities of both benzisoxazoles appear to agree with the charges found for their π-electron systems.

These conclusions are mainly of a semi-qualitative nature, and this is not surprising, since it is probable that the semi-empirical MO–LCAO approach cannot give more than this sort of information. However, within such a limitation, it appears to work: and we can reasonably expect that many of its conclusions are reliable.

In our particular case, one is especially interesting, namely the existence and stability of the positive and negative ions derived from the two benzisoxazoles. A careful investigation of this problem from the experimental point of view would be very appropriate.

Also the effect of electron attracting or electron releasing substituents in various positions would be of great interest; in particular the variation of the dipole moments and of the reactivity of these two compounds after substitution might probably lead to very interesting advances in the chemistry of heterocyclics.

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