# 658. *Conjugation in Unsaturated Systems Containing Hetero-atoms. Part I. The Phenylisoxazoles.*

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As a first step in an attempt to examine systematically a number of compounds where $\pi$-systems containing hetero-atoms are conjugated to each other, we have studied semi-theoretically the three phenylisoxazoles.

Isoxazole appears to be scarcely aromatic, resembling the corresponding imine. This helps to explain the similarity of its phenyl derivatives to the phenyl derivatives of its open-chain analogues. A brief analysis of related hydrocarbon systems indicates that, just owing to the low aromaticity of isoxazole, the phenyl group interacts with the isoxazole $\pi$-system slightly more than with another phenyl group, except when attached to position 4 of the isoxazole ring. The interaction, however, is very small, as is also indicated by the small values of the calculated interaction dipole moments, which are in satisfactory agreement with experimental results. Notwithstanding the contrary evidence of charge distributions, the isoxazole ring behaves, with respect to benzene, as an *ortho/para*-directing substituent: this behaviour is predicted correctly by localization energies, and is in agreement with the suggested similarity between isoxazole and an open-chain compound.

This paper is the first of a series to be devoted to interpreting, by semi-theoretical procedures, the interactions of heteroatomic systems conjugated to one another. Here we shall discuss the three phenylisoxazoles (I).[1,2] The experimental evidence about these compounds is fairly extensive, so that we can combine the analysis of an interesting

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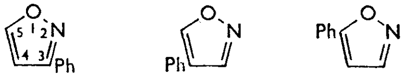
[1] von Auwers and Ottens, *Ber.*, 1925, **58**, 2079; Rupe and Knup, *Helv. Chim. Acta*, 1927, **10**, 305.

[2] Pino and Speroni, *Rend. Ist. Lombardo Sci., Pt. I, Classe sci. mat. nat.*, 1955, **88**, 331.

group of molecules with a test of the method and criteria that will be used for further discussions.



(I)

## METHOD

We have carried out our calculations by the semi-empirical molecular-orbital method, with inclusion of overlap. To ensure the possibility of comparing results and to establish possible theoretical shortcomings we required a single extensive set of parameters for the series of studies. We selected therefore the parameters suggested by Orgel *et al.*,[3] which are satisfactory for isoxazole, have already been used by us in a study of benzisoxazoles,[4] and are defined for most heterocycles. These parameters relate to calculations neglecting the overlap integrals between atomic orbitals, but the results can be transformed into those for calculations including these integrals if it is assumed that the latter are proportional to the corresponding bond integrals through a constant $\lambda$.[5] The transformation required affects only the energies and their derivatives: the atomic charges and hence the dipole mements remain the same as those which would be obtained anyway from the parameter set of ref. 3. All the energies, including the unit $\gamma$ (which is, as usual, the bond integral of the $\pi$-system of benzene) are referred to the Coulomb integral of the $2p\pi$-orbital of carbon in benzene, $\alpha$.* The constant $\lambda$ has been given the value of $0{\cdot}25\ \gamma^{-1}$.

## RESULTS and DISCUSSION

The energies, charges, and dipole moments of the phenylisoxazoles and some other compounds will be discussed here. The only quantity which we define in a way slightly different from the customary is the delocalization energy. It is obtained here by subtracting from the total energy of a molecular $\pi$-system the energies of the electrons assigned to the corresponding atomic orbitals, without allowing for the variations in the atomic parameters introduced as " inductive effects." The interaction energy between two parts (units) of a given compound is defined as the difference between the total energy and the sum of the energies calculated for the isolated units.

*Isoxazole.*—Our calculations indicate that the $\pi$-system of isoxazole is little stabilized by the presence of oxygen: indeed, the difference between the delocalization energy of the ring and that of the corresponding diene system is much lower than in pyrrole and furan ($0{\cdot}229\ \gamma$ for isoxazole, $0{\cdot}634\ \gamma$ and $0{\cdot}604\ \gamma$ for pyrrole and furan, respectively). This result suggests that the main function of oxygen in isoxazole is that of fixing the geometry of the corresponding imine system in a *cis*-form, besides making tautomerism with propionitrile impossible. This suggestion is supported by the fact that the charge distribution already suggested by Speroni and Pino[6] for isoxazole is similar to that of propaldehyde imine: Fig. 1 shows that the charge transfer from the oxygen bridge does not bring about modifications in the relative order of the charges of the three carbon atoms. The importance of an oxygen bridge in stabilizing $\pi$-systems has been discussed extensively for furan,[7] whose aromaticity is low.[8]

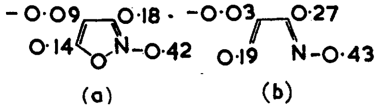


FIG. 1. Charge distributions in isoxazole (a) and propaldehyde imine (b).

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* This means that the integral $\gamma_{xy}$ of an XY bond is equal to $\beta_{xy} - \alpha S_{xy}$, where $\beta_{xy} = \int \chi_x^* \mathscr{H} \chi_y d\tau$, and $S_{xy}$ is the corresponding overlap integral.

[3] Orgel, Cottrell, Dick, and Sutton, *Trans. Faraday Soc.*, 1951, **47**, 113.

[4] Del Re, *Tetrahedron*, 1960, **10**, 81.

[5] Del Re, *Nuovo Cim.*, 1960, X, **17**, 664.

[6] Speroni and Pino, *Rend. Accad. naz. Lincei*, 1949, **4**, 325.

[7] Morris and Pilar, *Chem. and Ind.*, 1960, 469; R. D. Brown and Coller, *Austral. J. Chem.*, 1959, **12**, 152.

[8] See, *e.g.*, Katritzky and Lagowsky, " Heterocyclic Chemistry," Methuen, London, 1960.

The fact that isoxazole can undergo electrophilic aromatic substitution [9] is not in contradiction with the above conclusion, since this particular behaviour does not require stability in the ring.[8,10] The failure of isoxazole to enter the diene reaction [11] can be interpreted in the same way as the failure of cinnamaldehyde imine to undergo the reaction.[12]

*Interactions between Conjugated Systems.*—Since every discussion of conjugation is implicitly referred to conjugated hydrocarbons as " standards," it is important to comment briefly on the interaction energies of some of the latter.

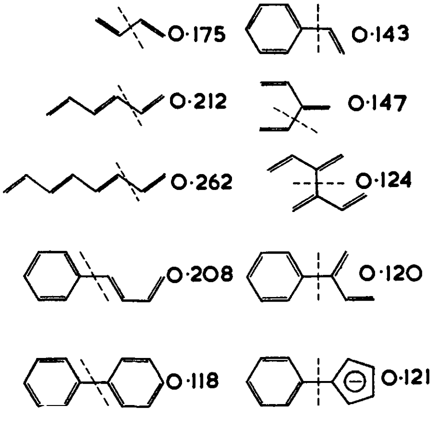
According to resonance theory, stabilization of π-systems by interaction between conjugated rings is relatively low. The molecular-orbital method leads to the same conclusion, but the quantitative results also indicate that the interactions between closed (" aromatic ") conjugated systems connected to each other through one bond are always lower than those between similar open conjugated systems. This phenomenon is related to the possibility of independent internal conjugation within each unit. In fact, even open-chain systems fall into two classes: linear compounds, where the interactions increase when the sizes of the units increase; cross-linked compounds, where the interactions are lower than in the linear ones, and decrease when the individual units increase in size. Table 1 illustrates this point.

We conclude that the interaction energy between two units forming a compound is strictly related to the degree of internal conjugation in these units: in the language of resonance theory, we may say that the interaction energy is lower when the weight of " structures " involving bond and charge shifts in only one unit is higher.

Table 1 also indicates that a double bond cross-linked to a conjugated system does not participate to a large extent in its conjugation: indeed, if ultraviolet absorption spectra are any indication of conjugation, the values of Table 1 can only be too high, since the absorption spectrum of 3-methylenepenta-1,4-diene is practically the same as that of 2-methylbuta-1,3-diene.[13]

TABLE 1.

Interaction energies in some hydrocarbon π-systems (units γ).
Interacting units separated by broken lines.



The above remarks are not invalidated by the recent discussion about conjugation in open-chain hydrocarbons,[14] since here we have compared bonds having essentially the same nature.

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[9] Kochetkov and Khomutova, *Zhur. obshchei Khim.*, 1959, **29**, 535.
[10] Robinson, *Tetrahedron*, 1958, **3**, 323; Tedder, *Ann. Reports*, 1960, **57**, 223.
[11] Grandberg and Kost, *Zhur. obshchei Khim.*, 1959, **29**, 1099.
[12] Snyder and Robinson, *J. Amer. Chem. Soc.*, 1941, **63**, 3279.
[13] Blomquist and Verdol, *J. Amer. Chem. Soc.*, 1955, **77**, 81.
[14] Coulson, *Chem. Soc. Special Publ. No.* 12, 1958, p. 85.

*Phenylisoxazoles.*—(i) *Energies.* The interaction energies between the $\pi$-systems of benzene and isoxazole can now be interpreted.

In 3-phenylisoxazole, we expect an interaction energy close to that of 2-phenylbuta-1,3-diene, but modified by two opposite effects: the presence of nitrogen, which tends to increase the interaction energy (as can be seen from parallel computations for butadiene and propaldehyde imine, which give interaction energies between the two pairs of double bonds of 0·175 and 0·216 $\gamma$); and the presence of an internal conjugation in isoxazole, which, as has been seen, would tend to reduce the interaction. The interplay of these effects gives the result shown in Table 2.

TABLE 2.

Interaction energies (*a*), excitation energies (*b*), and positions of the absorption bands (*c*) of the phenylisoxazoles.

| | (*a*) (in $\gamma$) | (*b*) (in $\gamma$) | (*c*) * (in cm.$^{-1}$) |
|---|---|---|---|
| 3-Phenylisoxazole | 0·127 | 1·332 | 42·0 |
| 4-Phenylisoxazole | 0·110 | 1·307 | 42·2 |
| 5-Phenylisoxazole | 0·152 | 1·220 | 38·5 |

* From Ref. 2.

In 4-phenylisoxazole, the situation is similar to that of the previous isomer, except for the fact that the interaction is now even lower, because there is not a nitrogen atom in the double bond adjacent to the phenyl group: the interaction energy is therefore at a minimum.

5-Phenylisoxazole shows a higher degree of interaction than its two isomers. This is due to the combination of the presence of a diene chain connected head-to-tail to the phenyl group, the low aromaticity of isoxazole, and the presence of the imine nitrogen. The fact that conjugation through oxygen exists, even if it is slight, explains why the interaction energy is smaller than in 1-phenylbuta-1,3-diene.

The interaction energies reported in Table 2 give an idea of the potential energy barrier to internal rotation provided by the conjugation of the two rings. Taking the interaction energy of biphenyl as a reference, we see that we can expect the 3- and the 5-isomer to be practically planar, owing to the higher interaction energy and the much lower hindrance of the only hydrogen of the isoxazole ring that is in a condition to provide such a hindrance. 4-Phenylisoxazole should, on the other hand, show a slight twisting, as does biphenyl.[15]

(ii) *Ultraviolet spectra.* All that can be safely concluded from our calculations is that the bands of the 3- and the 4-isomer are very close to each other, whereas that of 5-phenylisoxazole is shifted towards the red end of the spectrum. As far as it goes, this result is in agreement with the data of ref. 2. As to the discussion of the spectra given in that paper, conclusions almost identical with those given in the preceding section were obtained there by comparing the ultraviolet spectra of the compounds in question with those of the corresponding open compounds (benzaldoxime, styrene, and cinnamaldehyde oxime). We note that the influence of oxygen on the principal absorption band of oximes is negligible: *e.g.*, benzaldehyde *N*-ethyl- and *N*-methyl-imine and oxime have $\lambda_{\text{max.}}$ 245, 247, and 248 m$\mu$, and log $\varepsilon$ $\sim$4·2.[16]

Whereas 3- and 4-phenylisoxazole show a very slight hypsochromic effect with respect to the corresponding open-chain compounds, 5-phenylisoxazole absorbs at a frequency markedly higher than the corresponding oxime. This may be because conjugation of oxygen in the isoxazole ring takes place mainly through the C–O bond. In fact, at least when conjugated to carbonyl groups, oxygen exhibits a strong hypsochromic effect.[17]

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[15] Bastiansen, *Acta Chem. Scand.*, 1948, **3**, 408.

[16] Lang, " Absorption Spectra in the Ultraviolet and Visible Region," Academic Press, New York, 1961.

[17] Bowden, Braude, and Jones, *J.*, 1946, 948.

The effect of its cross-conjugation to polyene chains does not seem to have been studied, so that further experiment is needed to support this suggestion.

(iii) *Charge distributions and electric dipole moments.* Fig. 2 and Table 3 show the charge distributions and the dipole moments calculated for the three phenylisoxazoles.

In the phenylcyclopentadienyl anion, the phenyl group behaves as a weak electron acceptor: its total charge is —0·082. The isoxazole derivative in which the phenyl group occupies the only aromatic position of isoxazole also shows some negative charge on the phenyl group (—0·033). The high electronegativity of oxygen and of nitrogen explains why the phenyl group is instead an electron donor in 3- and 5-phenylisoxazole.

The net charge of the phenyl group in 3-phenylisoxazole is higher than in 5-phenylisoxazole (+0·069 and +0·066, respectively): this is not in contradiction with our previous conclusions. In the former compound, nitrogen acts directly on the benzene ring through one double bond, whereas in the latter it is coupled to benzene through a system of two double bonds. The effect of oxygen in both cases is comparatively unimportant.

An experimental indication of the charge transfer in phenylisoxazoles is provided by the electric dipole moments, also measured by Pino and Speroni.[2] Although they were unable to resolve the total moments in partial contributions of unperturbed isoxazole and of the phenyl groups, these authors gave some interpretations based on rough hypotheses concerning the directions of the interaction moments.

As is shown in Table 3, the parameters we have used lead to values of the moments very close to the experimental ones, and agree with the conclusions obtained by Pino and Speroni as regards the directions of the interaction moments. The only disagreement is for 4-phenylisoxazole. The interaction dipole moment for this compound is predicted by calculations as being directed towards the phenyl group, in accordance with the fact that the phenyl group itself appears to act in this case as an electron acceptor. The experimental data support the idea that the contribution of the phenyl group in this case is very small, but they also indicate that either the interaction dipole moment is still directed towards the isoxazole ring or is negligible. A reason for this may lie in the possible non-coplanarity of the two rings in the ground state of the molecules: an indication that the phenyl group may indeed be out of the plane of the isoxazole ring has been given above.

TABLE 3.

Values of the interaction moment ($\mu_i$), of the angle $\alpha$ formed by it with the moment of the isoxazole ring, and of the total moment calculated ($\mu_{calc}$) and observed ($\mu_{obs}$) (see Fig. 2).

| | $\mu_i$ (D) | $\alpha$ | $\mu_{calc}$ (D) | $\mu_{obs}$ (D) * |
|---|---|---|---|---|
| 3-Phenylisoxazole | 0·9 | 94° | 2·9 | 2·8—3·0 |
| 4-Phenylisoxazole | 0·4 | 116 | 2·6 | 2·9 |
| 5-Phenylisoxazole | 0·8 | 36 | 3·3 | 3·2—3·3 |

The moment $\mu_0$ of isoxazole has been taken as 2·8 D, in the direction shown in Fig. 2.
* From Ref. 2.

As far as the charges on the individual atoms are concerned, we have already seen that the changes with respect to the separate rings are small: the compounds under study do not show anything new from this point of view (Fig. 2). If one were to interpret reactivities on the basis of charges, one should conclude that the only case in which the benzene ring is activated is that of 4-phenylisoxazole: this could be interpreted as meaning that the "aromaticity" of position 4 of isoxazole is transferred to the *ortho/para*-positions of benzene. This conclusion cannot be checked against experimental data because of the lack of information concerning electrophilic substitution on the phenyl group of 4-phenylisoxazole. However, net charges are not as strictly related to reactivities as was once thought, at least when they are very small.[5] In this remark may lie the explanation for experimental evidence indicating that nitration of 5-phenylisoxazole yields the *p*-nitro-derivative.[18] Now, both our calculated charges and the experimental evidence of dipole moments indicate that, in 5-phenylisoxazole, isoxazole behaves as an electron-attracting substituent: so that the contrary experimental evidence of ref. 18 probably means that in this case the electrical effects do not correspond to the actual reactivity. In fact, the calculated localization energies indicate that the *para*-positions in all three compounds are favoured for substitution, the difference with respect to the *meta*-positions being at a minimum for the 3-isomer (Table 4).

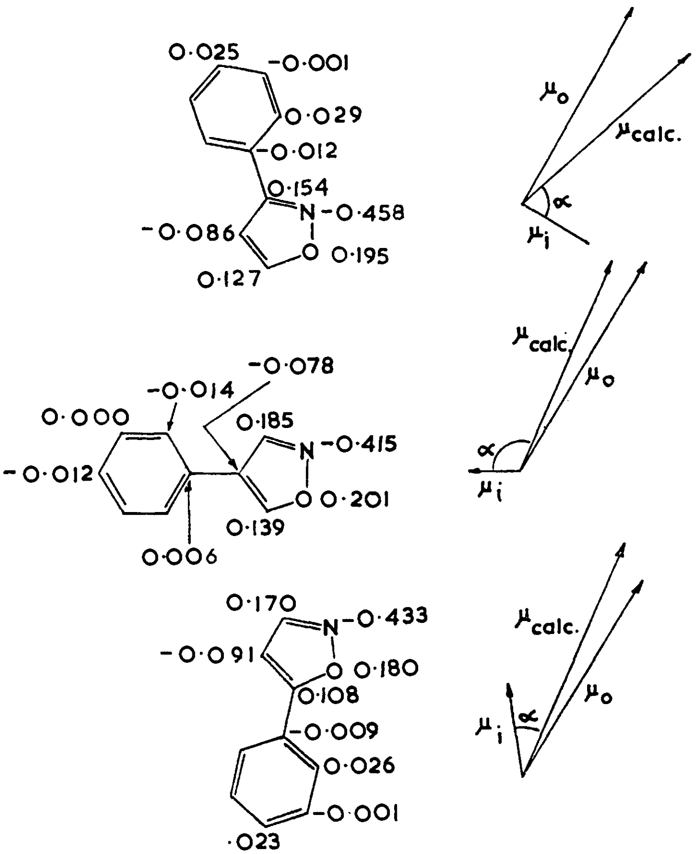

FIG. 2. Charge distributions and dipole moments of the phenylisoxazoles (see Table 3).

TABLE 4.

Localization energies of the *meta*- and *para*-positions of the phenyl groups (units $\gamma$) in phenylisoxazoles.

| | 3-Phenyl | 4-Phenyl | 5-Phenyl |
|---|---|---|---|
| *meta* ................................ | 1·8562 | 1·8552 | 1·8578 |
| *para* ................................ | 1·8554 | 1·7310 | 1·8138 |

The behaviour of isoxazole as an *ortho*/*para*-directing substituent on the phenyl group is in agreement with the picture of isoxazole as an imine given above. In fact, the evidence

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[18] Kochetkov and Khomutova, *Zhur. obshchei Khim.*, 1958, **28**, 359.

concerning derivatives of vinylbenzene points to a strong *ortho/para*-orientation by a $-CH{=}CH-$ group no matter what substituent is attached at the carbon 2 of this double bond.[19] The fact that 5-methoxy-3-phenylisoxazole, which should not differ much from 3-phenylisoxazole itself, gives the *m*-nitro-derivative in concentrated sulphuric acid [20] is not in contradiction with the general conclusion just derived. An unexpected *meta*-nitration takes place in these conditions also with benzaldehyde imines: it has been explained as due to salt formation by the nitrogen atom.[19] This interpretation might very well hold also for 3-phenylisoxazole, where the basicity of nitrogen should be particularly enhanced with respect to isoxazole (see Fig. 2).

*Conclusion.*—It was a purpose of this paper to examine the correlation between theoretical results and experimental evidence in a case where a good analysis of the latter had been already carried out, so as to appraise better the method and the importance of the parameters. As has been seen, the agreement between the interpretations of ref. 2 and the theoretical results is satisfactory.

As far as the theoretical chemistry of isoxazole is concerned, the main conclusions reached here are as follows: (*A*) Isoxazole behaves basically as an imine, the effects of oxygen being mainly to hold the imine chain in a fixed configuration, and to reduce its charge asymmetry by providing an additional negative charge (Fig. 1). (*B*) Interaction of the phenyl with the isoxazole ring is small, close to that with an open $\pi$-system. Isoxazole transfers in part the charge of the position at which it is linked with benzene to the *ortho/para*-position of the latter. (*C*) In accordance with the evidence for unsaturated systems conjugated to benzene and with its similarity to an open-chain imine, isoxazole is expected to behave as an *ortho/para*-directing substituent in all of its phenyl derivatives. The apparent disagreement with respect to the charge distributions seems to be due mainly to the fact that the charges are too small to be significant indices of reactivity. The *meta*-directing effect in 3-phenylisoxazole is possibly due to salt formation.

As to the general question of the interactions between conjugated systems, it appears that they are usually very small, and decrease when the degrees of conjugation within the individual units increase: so that chains of aromatic rings are likely to be very little affected by ring–ring conjugation. A stronger interaction is to be expected whenever open-chain compounds are connected either to each other or to aromatic rings in a head-to-tail arrangement. This conclusion is valid also if the bond integrals are adjusted to the various bond distances, since the latter remain constant anyway in similar compounds.

Therefore, since five-membered rings involving oxygen bridges are to be considered as closer to diene systems fixed in their *cis*-forms than to true aromatic compounds, the properties to be expected of compounds involving them are close to those of compounds containing open-chain dienes in their *cis*-forms. The interactions between the individual units will be higher than if the heterocycles were truly aromatic, but smaller than in polyenes.

This conclusion relates essentially to the ground states of the systems in question. As to their excited states, it must be noted that, although we have found a strict parallelism between our conclusions on the ground states and the ultraviolet spectra, this need not be interpreted as meaning that the excitation energies of polyaryl systems are as little affected by the ring–ring conjugations as are the ground-state energies.

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[19] Ingold, " Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, Ithaca, N.Y., 1953, pp. 241—243.

[20] Gaudiano, Ricca, and Merlini, *Gazzetta*, 1959, **89**, 2466.