PMO Calculations for the Regiochemistry of 1,3-Cycloadditions of 3,5-Dichloro-2,4,6-trimethylbenzonitrile Oxide to Thiophen, Furan, Benzothiophen, and Benzofuran

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A perturbational molecular orbital (PMO) treatment has been developed for the title 1,3-cycloaddition reactions. Molecular orbitals were computed by the CNDO/2 method. The results obtained at different levels of approximation of the PMO theory are presented. The regiochemistry is also discussed on the basis of the charge transfer model by using EA's and IP's.
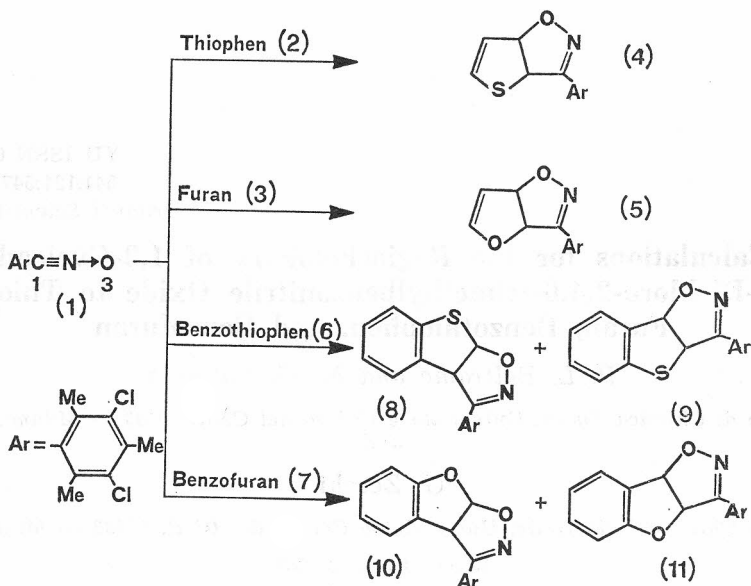
INTRODUCTION

In spite of the extensive literature on 1,3-dipolar cycloadditions, regio-selectivity and reactivity phenomena in these reactions are still worthy of attention. In fact, classical electronic theories of organic chemistry appear to be inadequate to provide satisfactory general rules, and different opinions have been put forward on the nature of 1,3-dipolar cycloadditions[1,2].

In recent years, aiming at the rationalization of the experimental findings in this field, various authors have developed theoretical approaches according to the perturbational molecular orbital theory[3,7]. Because of the usual complexity of the systems which give rise to 1,3-dipolar cycloadditions, more accurate quantum-chemical methods could be adopted only in a few exceptionally simple cases, i. e. the 1,3-cycloaddition of diazomethane to ethylene[8] and that of fulminic acid to acetylene[9,10] and ethylene.[10]

We have recently reported[11] that 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide (**1**) cycloadds to thiophen (**2**) and furan (**3**) in a regiospecific manner, at least within the experimental detection limits, to give the fused 2-isoxazolines (**4**) and (**5**), respectively. On the other hand, 1,3-cycloadditions of **1** to benzothiophen (**6**) and benzofuran (**7**) afford two possible orientational isomers in a similar proportion (**8** : **9** = 70 : 30; **10** : **11** = 60 : 40).

The exceptionality of these dipolarophiles as well as their molecular geometry suitable for a perturbational treatment prompted us to seek a theoretical support to the observed regioselectivities. Although part of the results obtained was communicated in a previous paper[11], a full description of our

Thiophen (2) (4)

Furan (3) (5)

$ArC\equiv N\rightarrow O$
1   3
(1)

Benzothiophen (6) (8) + (9)

$Ar = $ Me, Cl, Me, Me, Cl

Benzofuran (7) (10) + (11)

work seems to be advisable because it involves computations at different levels of approximation of the PMO theory. In the present paper we also discuss the regiochemistry on the basis of the charge-transfer model.

COMPUTATIONS

Within the framework of second-order perturbation theory, the treatment of Salem and Devaquet leads to three components of the interaction energy between two conjugated systems[12]. These are a repulsive term (E_{rep}) and an attractive term (E_{mix}), both of which depend on the overlap of interacting orbitals, as well as a polar term (E_{pol}) representing the electrostatic interaction between net charges on the atoms:

$$E_{rep} = -\sum_{rr'} (q_r + q_{r'}) \eta_{rr'} S_{rr'}$$

$$E_{mix} = -2 \sum_{j}^{occ} \sum_{k'}^{vac} \frac{(\sum_{rr'} c_{jr} c_{k'r'} \eta_{rr'})^2}{E_{k'} - E_j}$$

$$-2 \sum_{j'}^{occ} \sum_{k}^{vac} \frac{(\sum_{rr'} c_{kr} c_{j'r'} \eta_{rr'})^2}{E_k - E_{j'}}$$

$$E_{pol} = \sum_{ss'} \Delta q_s \Delta q_{s'}/R_{ss'}$$

The symbols r and r' indicate interacting atoms on two molecules (each atom contributes a $2p\pi$ orbital) : q_r and $q_{r'}$ are π electron charges, $\eta_{rr'}$ and $S_{rr'}$ are resonance and overlap integrals, respectively; j and k are indices for the molecular orbitals of the first molecule, j' and k' refer analogously to the second molecule; c_{jr} is the coefficient of the $2p\pi$ orbital of the atom r in the

j-th LCAO molecular orbital, the energy of which is E_j. In the polar term, Δq_s and $\Delta q_{s'}$ are net electronic charges on the atoms s and s', which are at a distance $R_{ss'}$ from each other, the summation in this case runs over all pairs of atoms[13].

Resonance integrals were evaluated by the equations[14]

$$\eta_{CC} = -21\,S_{CC}; \quad \eta_{CO} = -26\,S_{CO}$$

where η_{CC} and η_{CO} are in eV.

We assumed that the two molecules remained planar during the approach. Energies were calculated for the reactions giving two regioisomers for several configurations of the approach; in each case, the centre (A) of the $C_1 \ldots O_3$ dipole on the y-axis of **1** and the centre (B) of the $C_\alpha C_\beta$ double bond* on the y'-axis of the dipolarophile were on the z-axis perpendicular to the molecular plane of **1**. The interacting four centres were on a vertical plane perpendicular to both molecular planes. In symmetric configurations, the molecular planes were parallel and both incipient bond lenghts were equal; in unsymmetric configurations, the bond lengths were different. We varied the distances between the interacting atoms independently from 5 to 8 a. u. To take into account the deviations of the overlapping orbitals from the alignment required for pure σ, σ or π, π, overlapping we used equations of the type[15]:

$$S_{rr'} = S_{rr'}\,(\sigma, \sigma)\cos\varphi\cos\vartheta - S_{rr'}\,(\pi, \pi)\sin\varphi\sin\vartheta$$

In this equation we calculated the integrals $S_{rr'}\,(\sigma, \sigma)$ and $S_{rr'}\,(\pi, \pi)$ using the standard formulae[16]; φ and ϑ are the angles between the line joining atoms r and r' and the axes of the $2p\pi$ orbitals centred on r and on r' (see Figure 1). The difference $\vartheta - \varphi = \psi$ represents the angle between the two molecular planes.
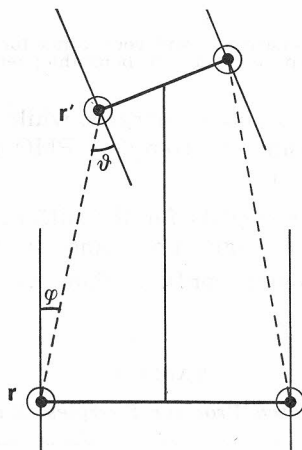

Figure 1. Geometry of a unsymmetric four-centre approach of the reactants.

We named the two possible isomers C_1C_α and C_1C_β, respectively. The molecular geometry for **1** was deduced as described previously.[17] We used the geometries determined by Bak et al. for thiophen[18] and furan[19]. Geometrically,

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* α and β relate to the heteroatom.

we built benzothiophen and benzofuran from a benzene ring and the corresponding five-membered heterocyclic ring in which the appropriate C—C bond was opened to 1.397 Å. To calculate orbital energies, coefficients, and net charges, we employed the CNDO/2 method[20], using an *spd* basis set for chlorine and sulphur atoms. We considered only π-type molecular orbitals. For thiophen and benzothiophen, the highest occupied molecular orbital was centred mostly on the sulphur atom: as HOMO, we chose the next occupied MO below the localized sulphur orbital.

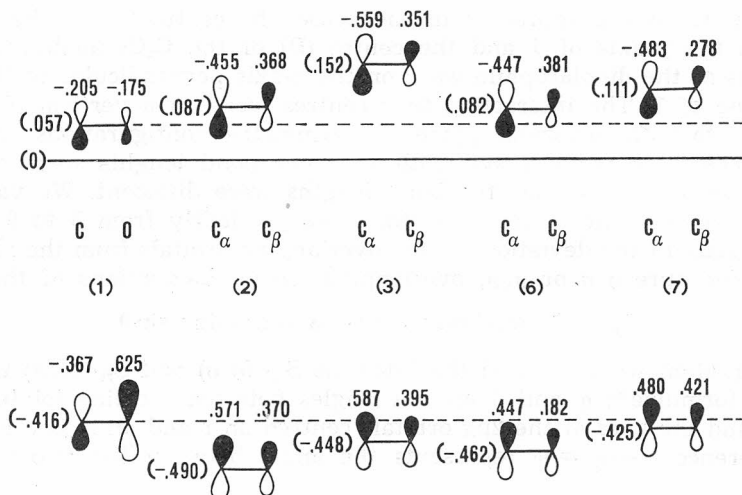Figure 2 shows the energies and coefficients of the frontier orbitals of the five reactants.

Figure 2. Energies (in parentheses/hartrees) and coefficents for the frontier molecular orbitals of nitrile oxide (1), thiophen (2), furan (3), benzothiophen (6), and benzofuran (7).

Table I gives frontier interaction energies, while Table II collects the interaction energies calculated using the complete PMO treatment for symmetrical approaches ($R = R_{C_1C} = R_{O_3C}$).

Figure 3 shows the energy plots for the different approaches in thiophen and furan: for symmetric configurations and, in the case of the favoured orientation, for two unsymmetric configurations with $\psi = +30^0$ ($\overline{C_1C_\alpha} < \overline{O_3C_\beta}$) and $\psi = -30^0$ ($\overline{C_1C_\alpha} > \overline{O_3C_\beta}$).

TABLE I

Calculated Frontier Energies (E/meV)

		2	3	6	7
$R = 7.0$ a.u.	CC_α:	—1.01	—1.17	—0.92	—0.90
	CC_β:	—0.84	—0.88	—0.78	—0.70
$R = 3.3$ a.u.	CC_α:	—705	—748	—666	—570
	CC_β:	—742	—852	—693	—671

TABLE II

Calculated Energies (E/meV) as a Function of Distance R (a.u.) for Symmetrical Approach

| R	E_{mix}	E_{rep}	E_{pol}	E_{tot}	E_{mix}	E_{rep}	E_{pol}	E_{tot}
	Formation of C_1C_α				Formation of C_1C_β			
2								
8	—0.51	1.08	—17.5	—16.9	—0.51	1.06	17.3	17.9
7	—5.01	10.0	—23.9	—18.9	—4.99	9.86	23.5	28.4
6	—42.3	80.9	—33.3	5.3	—42.1	79.5	32.5	69.9
5	—292.2	530.6	—47.7	190.7	—289.7	523.7	46.1	280.1
3								
8	—0.52	1.10	—3.76	—3.18	—0.50	1.10	3.68	4.28
7	—5.02	10.3	—4.40	0.88	—4.90	10.3	4.59	9.99
6	—42.2	82.7	—4.59	35.9	—41.4	82.7	5.60	46.9
5	—289.2	543.3	—3.02	251.1	—285.8	543.6	6.37	264.2
6								
8	—0.52	1.10	—21.2	—20.6	—0.52	1.10	21.0	21.6
7	—5.08	10.0	—28.8	—23.9	—5.07	9.8	28.5	33.2
6	—43.0	80.3	—40.0	—2.7	—42.8	79.4	39.3	75.9
5	—297.3	527.5	—56.9	173.3	—295.3	522.6	55.5	282.8
7								
8	—0.53	1.10	—2.24	—1.67	—0.51	1.11	3.29	3.89
7	—5.10	10.0	—2.83	2.07	—5.00	10.3	4.17	9.47
6	—43.0	81.0	—3.03	35.0	—42.5	83.2	5.12	45.8
5	—294.6	533.6	—1.41	237.6	—294.5	545.3	5.62	256.4
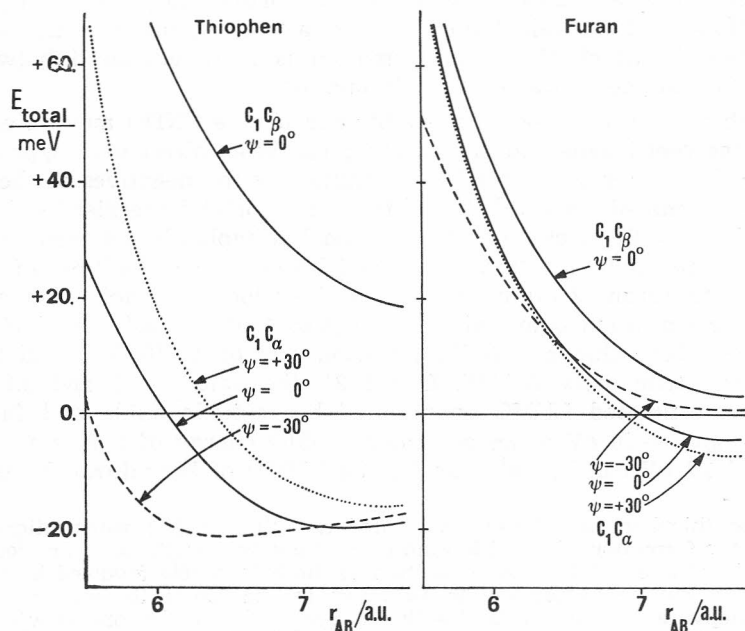
Figure 3. Perturbation energy as a function of distance for different types of approach giving two possible regioisomers in thiophen and furan. (For definition of ψ, see text.)

<center>DISCUSSION</center>

In its simplest frontier-orbital approach, the perturbation theory states that the interaction between the HOMO of one reactant and the LUMO of the other governs the reaction pathway. This interaction occurs in the direction offering the maximum overlapping of the lobes. As shown in Figure 2, the two HOMO/LUMO interactions with the best overlapping give opposite effects: if the dipole LUMO is controlling, the larger coefficients lead to the four C_1C_α isomers, if the dipole HOMO is controlling, the four C_1C_β isomers are predicted. On the other hand, the HOMO/LUMO pair possessing the nearest energy levels, responsible for the most effective interaction, favours the C_1C_β isomers for thiophen and benzothiophen and the C_1C_α isomers for furan and benzofuran.

Furthermore, the frontier-orbital approach, which takes into account both interactions as well as the resonance integrals, predicts for all dipolarophiles the formation of C_1C_α compounds at large distances, and of O_1C_β ones at short distances (Table I). Thus, these different frontier approaches are not able to rationalize the four experimental orientations at the same time.

The results for the symmetric approaches using the complete PMO treatment (see E_{total} in Table II) indicate that the C_1C_α isomers are preferred at various distances for all dipolarophiles. These predictions are in agreement with the experimental findings only for thiophen and furan. This may be accounted for on considering that the model of approach adopted does not consider molecular deformations of the reactants which probably intervene in the case of benzothiophen and benzofuran owing to the size of the molecules.

Figure 3 shows a comparison between symmetrical and unsymmetrical approaches to the formation of the C_1C_α isomers in thiophen and furan, i. e. compounds **4** and **5**, respectively. It is noteworthy that, particularly in the case of thiophen, PMO calculations suggest a non-synchronous mechanism of cycloaddition in which the bond formation is more advanced between the oxygen of **1** and the C_β atom of dipolarophile.*

The above considerations are conditioned by the CNDO method employed to determine coefficients and orbital energies. As an alternative approach, the occupied orbital energies might be substituted by the negatives of the experimentally determined vertical IP's and the vacant orbital energies by the values of the EA's. So, a CI or charge-transfer model is implicitly assumed[5]. This procedure has recently been followed for the 1,3 dipolar cycloadditions of benzonitrile oxide to furan, 2,3-dihydrofuran, and cyclopentadiene[21]. The available data are the ionization potential of furan (8.88 eV)[22], benzofuran (8.66)[23], thiophen (8.87)[24], benzothiophen (8.75)[23], benzonitrile oxide (8.96)[25], and 2,4,6-trimethylbenzonitrile oxide (8.35)[25]. In ref 21, the values — 1 and 2.1 eV are reported as estimated LUMO energies of benzonitrile oxide and furan, respectively, and — 10 eV as an estimated HOMO energy of benzonitrile oxide. A value of 1.2 eV can be obtained for the LUMO of benzofuran by the same

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* Since thiophen and furan easily undergo electrophilic substitutions at the α position, the formation of **4** and **5** could prima facie be thought of as an electrophilic attack of the C atom of **1** to the α position of the heterocycle followed by the cyclization of a zwitterionic intermediate. However, in addition to the previous evidence against a stepwise mechanism for 1,3-dipolar cycloadditions[1,5,21], one should consider that such an intermediate, if formed, is expected to give the corresponding oxime, thus restoring the aromaticity of the heterocyclic ring.

considerations as employed for furan. The experimental values indicate: (a) a small gap between the HOMO energies of furan and benzofuran (and those of thiophen and benzothiophen), (b) a sensible raising of HOMO in going from benzonitrile oxide to 2,4,6-trimethylbenzonitrile oxide that suggests, an analogous displacement even if less marked, in going to 7. The estimated values indicate an energy gap between the LUMO's of furan and benzofuran that more than compensates the gap between the corresponding HOMO's. These observations suggest that, in going from furan to benzofuran, the interaction dipole HOMO-dipolarophile LUMO might become competitive with the other one: as a result, a mixture of C_1C_α and C_1C_β products is obtained.
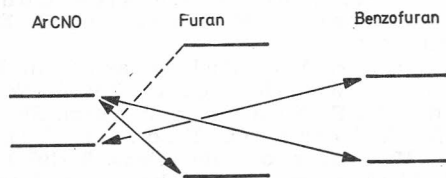
An analogous mixture was found in the cycloaddition of benzonitrile oxide to benzofuran. In this mixture however, the C_1C_α type adduct was prevailing[26]. The lesser extent of the intervention of the interaction dipole HOMO-dipolarophile LUMO can be attributed to the lower HOMO of benzonitrile oxide when compared with 1.

If the absolute estimated values of LUMO energies for furan and benzofuran are also accepted, besides their more significant gap, a value in the range of 1—1.3 eV for LUMO of 1 may be provided. The corresponding reported value for benzonitrile oxide seems to be somewhat low as in the case of the estimated HOMO energy value when compared with the experimental one.

So, the regiochemistry of all reactions under study seems to receive a satisfactory explanation by the above simple qualitative frontier approach, which uses the HO and LU orbital energies derived from experimental data.

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SAŽETAK

PMO-računi regiokemije 1,3-cikloadicija oksida 3,5-diklor-2,4,6-trimetilbenzonitrila i tiofena, furana, benzotiofena i benzofurana

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Razvijen je PMO-formalizam za proučavanje regiokemije 1,3-cikloadicije oksida 3,5-diklor-2,4,6-trimetilbenzonitrila i tiofena, furana, benzotiofena i benzofurana. Molekularne orbitale upotrijebljene u PMO-računima dobivene su s pomoću CNDO/2--aproksimativne SCF MO metode. Regiokemija je također diskutirana na temelju modela prijenosa naboja, za koji su upotrijebljeni elektronski afiniteti i ionizacijski potencijali molekula koje sudjeluju u spomenutim 1,3-cikloadicijskim reakcijama.

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