Extension of a Perturbation Molecular Orbitals Model to the Study of Regioselectivity in 1,3-Dipolar Cycloadditions: Reactions of 3,5-Dichloro-2,4,6-trimethylbenzonitrile Oxide with Heteroaromatic Systems

Laura Bonati, Tiziana Benincori, Gaetano Zecchi and Demetrio Pitea *
Dipartimento di Chimica Fisica ed Elettrochimica, Università degli Studi di Milano, Via Golgi 19, 20133 Milano, Italy

A model which makes use of the complete perturbation treatment of Salem and Devaquet has already been applied to Diels–Alder reactions and is now proposed for the interpretation of regioselectivity in the 1,3-dipolar cycloadditions of 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide with some heteroaromatic systems. The van der Waals minima relevant to the hypothesized alternative reaction paths have been suggested as model structures (perturbed states) for the corresponding weakly interacting complexes in the early stages of the reaction. To evaluate the atom–atom non-bonded interactions between polar partners an explicit Coulombic term is added to the Lennard-Jones (6–12) function previously used. Moreover, because of the dominant contribution of non-interacting atoms in determining the van der Waals minima, the minimization procedure is constrained to the region of the non-bonding energy hypersurface where the $2p_\pi$-orbitals involved in the new bond formation overlap significantly. The obtained regioselectivities are in good agreement with experimental ones.

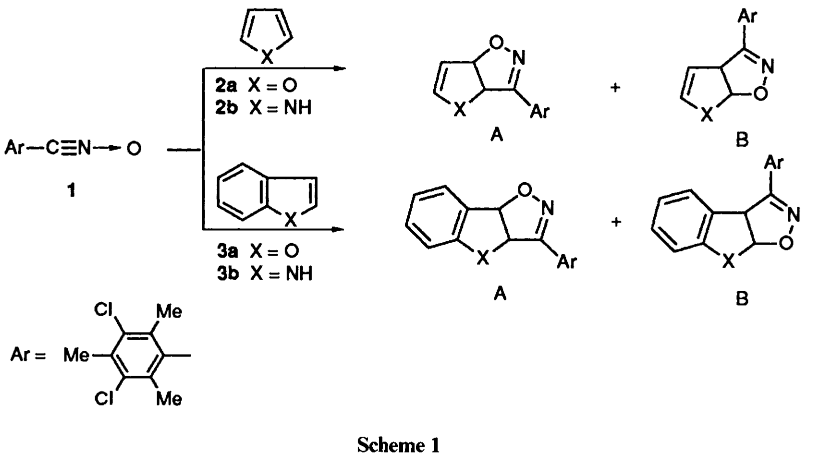
In this paper we examine the 1,3-dipolar cycloadditions of 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide **1** with some simple heteroaromatic systems and their benzo-condensed derivatives (see Scheme 1). For these reactions two different reaction paths can be envisaged, leading to the regioisomers A and B. Owing to the synthetic importance of these reactions (in particular, the reaction with furan **2a**[1]), the rationalization of their regioselectivity has attracted renewed interest.

The study of these reaction mechanisms could be dealt with by computing the potential-energy surface (PES) to locate and characterize all relevant stationary points. However, we suggested[2] that the perturbation treatment of the interaction is a better approach when molecular dimensions do not allow calculations of the PES to be made at an adequate computational level.

Within the framework of the perturbation molecular orbital (PMO) method, patterns of reactivities and selectivities in 1,3-dipolar cycloadditions of nitrile oxides have been generally studied by using the Frontier Molecular Orbital (FMO) approximation.[3] However, in many cases FMO energies and coefficients turned out to be unsuitable for the rationalization of experimental results.

More comprehensive theories of reactivity, which take into account contributions other than orbital interactions (*i.e.*, closed-shell repulsions and polar effects) have been developed[4,5] within the framework of the PMO theory and have been applied to some nitrile oxide cycloadditions.[6,7] In particular, a detailed analysis by Beltrame *et al.*[6] on the reactions of the nitrile oxide **1** with heterocycles **2a** and **3a** has shown that results obtained by FMO approximation are in disagreement with the experimental orientations and have shed light on the role of the polar contributions in long-range interactions. Moreover, these authors have indicated steric factors as being liable for the failure of the PMO treatment in rationalizing regioselectivities of the benzo-condensed dipolarophiles.

The PMO model we deal with in this paper should be particularly suitable in overcoming this problem because of the unbiased definition of the structure of the weakly interacting complexes in the early stages of the reaction (the perturbed states). The model, which we previously applied to Diels–Alder reactions,[2,8] has been improved to take into account the different nature of the long-range interactions involved in 1,3-dipolar cycloadditions, and is employed to rationalize the regioselectivity of the examined reactions.[6,9]



Scheme 1

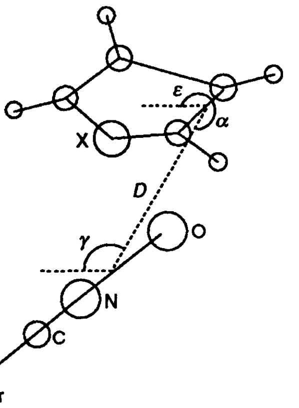


Fig. 1 Geometrical parameters which describe the reagents' approach (A adduct)

After the theoretical investigation we examined the predictive ability of our procedure by studying the reaction of compound **1** with pyrrole **2b**. The results are discussed.

Computational Procedure.—The interaction energies for the different reaction paths leading to the A and B regio adducts were obtained within the framework of the second-order perturbation theory by the Intermolecular Orbital (IMO) treatment of Salem and Devaquet.[4]

The interaction energy (E_{int}) expression [eqn. (1)] includes a

$$E_{int} = E_{ovr} + E_{pol} \qquad (1)$$

term (E_{ovr}), which depends on the overlap between the interacting orbitals [E_{ovr} is the sum of E_{rep} and E_{mix} in eqns. (2) and (3) of ref. 8(*c*)], and a Coulombic term (E_{pol}) which takes into account polar effects [see eqn. (4) in ref. 8(*c*)]. Preliminary calculations have indicated that the examined 1,3-dipolar cycloadditions are essentially charge controlled. As a consequence, molecular geometries and electronic properties of the isolated reagents were estimated by the AM1 method,[10] which shows a very real improvement over other semiempirical methods, particularly in the description of molecular charge distribution.[11]

In order to investigate the influence of the adopted computational method on the evaluated molecular properties, *ab initio* calculations[12] were also carried out on furan and 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide AM1 geometries with both STO-3G and 6-31G basis sets.

The van der Waals minima relevant to the hypothesized alternative reaction paths have been suggested[2,8] as model structures (perturbed states) for the corresponding weakly interacting complexes in the early stages of the reaction. In treating the non-bonded interactions between all the pairs of atoms of the two molecules a Lennard-Jones (6–12) potential function, parametrized for H, C, N and O atoms by Scott and Scheraga[13] was used.

In order to extend the model to the examined class of reactions, parameters for Cl atoms were calculated by employing the same procedure adopted by the above mentioned authors.* Moreover, to improve the description of the electrostatic contributions which have a considerable weight in the long-range interactions between polar partners, an explicit Coulombic term was added to the (6–12) function. The resulting potential, usually[14] referred to as (6–12–1), is given by eqn. (2),

$$U_{ij} = d_{ij}\cdot r_{ij}^{-12} - e_{ij}\cdot r_{ij}^{-6} + Q_i\cdot Q_j\cdot r_{ij}^{-1} \qquad (2)$$

where Q_i and Q_j are net atomic charges determined by the AM1 method.

Finally, because of the dominant contributions of non-interacting atoms in determining the van der Waals minima, the adduct conformations were constrained in the region of the non-bonding hypersurface where $2p_\pi$-orbitals involved in the new bond formation overlap significantly. By assuming that this condition is satisfied whenever the overlap energy between the interacting π-orbitals has a negative value, such a constraint was always imposed during the non-bonding energy (E_{nb}) minimization procedure.

In Fig. 1 are reported geometrical parameters employed[2] to describe the reagents' approach during the E_{nb} minimization.

Experimental

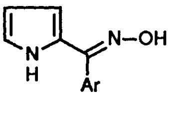
General.—M.p.s were taken on a Büchi apparatus and are uncorrected. IR spectra were run on a Perkin-Elmer 1725X FT-IR spectrometer. NMR spectra were recorded on a Varian XL-200 instrument; chemical shifts are given in ppm from $SiMe_4$. Mass spectra were determined on a VG-70EQ apparatus.

Reaction of Nitrile Oxide **1** *with Pyrrole* **2b**.—A solution of the nitrile oxide **1** (2.0 g) in freshly distilled pyrrole (48 cm^3) was stirred at room temperature for 24 h. The excess of pyrrole was removed under reduced pressure and the residue was submitted to flash chromatography on silica gel. Elution with toluene–ethyl acetate (9:1) gave 2-(3,5-dichloro-2,4,6-trimethylbenzoyl)-pyrrole oxime **4** (58%), m.p. 180–182 °C (from benzene); ν_{max}(Nujol)/cm^{-1} 3430 and 3180; δ_H(CDCl$_3$) 2.25 (6 H, s), 2.60 (3 H, s), 5.90 (1 H, m), 6.15 (1 H, m), 6.98 (1 H, m) and 10.3 (2 H, br s); δ_C(CDCl$_3$) 18.1 (q), 18.9 (q), 109.0 (d), 115.7 (d), 122.1 (d), 125.1 (s), 133.0 (s), 133.3 (s), 134.5 (s), 134.8 (s) and 147.7 (s); *m*/*z* 296 (M$^+$) and 279 (M$^+$ − OH, 100%) (Found: C, 56.45; H, 4.9; N, 9.5. $C_{14}H_{14}Cl_2N_2O$ requires: C, 56.57; H, 4.75; N, 9.43%).

Further elution gave 3-(3,5-dichloro-2,4,6-trimethylbenzoyl)-pyrrole oxime **5** (14%), m.p. 153–157 °C (decomp.) (from benzene); ν_{max}(Nujol)/cm^{-1} 3410 and 3290; δ_H(CDCl$_3$) 2.20 (6 H, s), 2.58 (3 H, s), 6.10 (1 H, m), 6.69 (1 H, m), 7.51 (1 H, m) and 8.5 (2 H, br s); δ_C(CDCl$_3$) 18.8 (q), 19.6 (q), 111.2 (d), 116.7 (s), 118.4 (d), 124.5 (d), 133.8 (s), 134.8 (s), 134.9 (s), 136.4 (s) and 152.3 (s); *m*/*z* 296 (M$^+$) and 279 (M$^+$ − OH, 100%) (Found: C, 56.8; H, 4.75: N, 9.3%).

For diagnostic purposes, the above ^{1}H and ^{13}C NMR data were compared with those available for pyrrole derivatives.[15]

Attempts to isolate primary cycloadducts were unsuccessful; however, their intermediacy was assumed on the basis of the fact that, in the reaction of nitrile oxides with indole,[15,16] the primary cycloadducts were labile compounds, easily rearranging to oximes.



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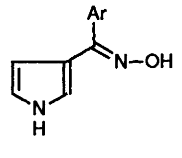

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Results and Discussion

Experimental results on the examined 1,3-dipolar cycloadditions are summarized in Table 1. The first step of our analysis was the evaluation of geometrical and electronic properties of the isolated interacting molecules, necessary for the intermolecular

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* The calculated parameters d_{ij} and e_{ij} in the 6–12 potential (ref. 13) for the Cl ··· Cl interaction are: d = 2 316 000 Å^{12} kcal mol^{-1} Å^{12}, e = 2520 Å^6 kcal mol^{-1} (1 cal = 4.184 J). For the mixed interactions, parameters have been determined by means of the combining rules commonly used for this purpose (ref. 14).

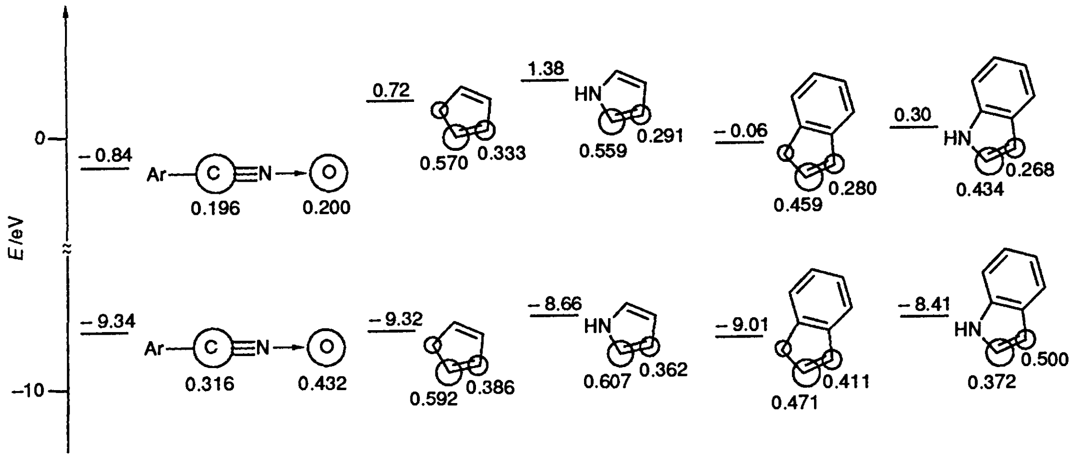

Fig. 2 FMO analysis from AM1 calculations

Table 1 Experimental results

Dipolarophile	Yield (%)	Regioisomer ratio A:B
2a[a]	78	100:0
2b[b]	72	80:20
3a[a]	80	40:60
3b[c]	80	0:100

[a] See ref. 6. [b] See the Experimental section. [c] See ref. 9.

Table 2 FMO energies and p_π-coefficients estimated by different computational methods

Reagent	Method	HOMO			LUMO		
		E/ (eV)	C	O	E/ (eV)	C	O
1	AM1	−9.34	0.316	0.432	−0.84	0.196	0.200
	STO-3G	−0.24	0.440	0.647	0.18	0.241	0.308
	6-31G	−0.33	0.202	0.329	0.07	0.142	0.164
			0.182	0.297		0.191	0.203
		E/ (eV)	C_α	C_β	E/ (eV)	C_α	C_β
2a	AM1	−9.32	0.592	0.386	0.72	0.570	0.333
	STO-3G	−0.24	0.586	0.353	0.26	0.633	0.356
	6-31G	−0.31	0.350	0.211	0.14	0.329	0.178
			0.309	0.205		0.525	0.305

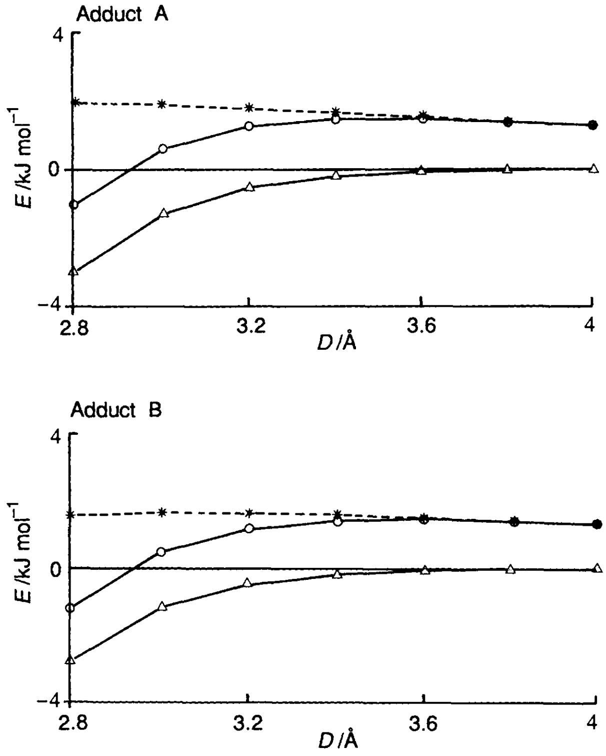

Fig. 3 Energy contributions along the concerted synchronous pathway for the reaction of the nitrile oxide **1** with furan **2a**:*, E_{pol}; ○, E_{int}; △, E_{ovr}

calculations. Conformational analysis, performed by the AM1 method, furnished molecular geometries in good agreement with experimental results; in particular, the 3,5-dichloro-2,4,6-trimethylbenzonitrile oxide molecule turned out to be planar, with an almost linear arrangement of CCNO atoms ($\widehat{CCN}$ 179.75° and $\widehat{CNO}$ 179.72°) and bond-length values (CN 1.171 Å and NO 1.179 Å) close to those of a triple CN bond and a single NO bond, respectively. Such features indicate, as expected on the basis of experimental and theoretical evaluations on the parent fulminic acid,[3a] that the nitrilium betaine formula (*a*) gives the most important contribution to the resonance hybrid:

$$\underset{(a)}{\mathrm{R{-}C{\equiv}\overset{+}{N}{-}\overset{-}{O}}} \Longleftrightarrow \underset{(b)}{\mathrm{R{-}\overset{-}{C}{=}\overset{+}{N}{=}O}} \Longleftrightarrow \underset{(c)}{\mathrm{R{-}\overset{+}{C}{=}N{-}\overset{-}{O}}} \Longleftrightarrow \underset{(d)}{\mathrm{R{-}\overset{-}{C}{=}N{-}\overset{+}{O}}}$$

$$\Longleftrightarrow \underset{(e)}{\mathrm{R{-}\ddot{C}{-}N{=}O}} \Longleftrightarrow \underset{(f)}{\mathrm{R{-}\dot{C}{=}N{=}\dot{O}}}$$

The FMO analysis (Fig. 2), which indicates a $\mathrm{LUMO_{dipole}}$–$\mathrm{HOMO_{dipolarophile}}$ control for all the examined reactions, predicts the formation of products different from those observed for reactions of heterocycles **2a**, **2b** and **3b**. A reason for the failure of the FMO approximation can be envisaged in the small difference in the size of the terminal LUMO coefficients of the dipole. As shown for example in Table 2 for substrates **1** and **2a**, the relative magnitude of FMO coefficients on the reaction centres is quite independent of the adopted computational method.

Moreover, a more detailed analysis has shown that none of the examined reactions is frontier controlled; as is reported in Table 3, contributions to the stabilization energy [E_{mix} in eqn. (3), ref. 8(*c*)] of many other orbital interactions are of comparable importance with respect to the $\mathrm{LUMO_{dipole}}$–$\mathrm{HOMO_{dipolarophile}}$. Once more[2,8,17–19] a reliable prediction of regioselectivity using only the sizes of the coefficients of an FMO pair cannot be obtained and the use of a more complete and general PMO theory becomes necessary.

Table 3 Percentage contributions to the attractive term of E_{ovr}[a,b]

Reagent	Adduct	Interacting MOs (dipole–dipolarophile)						
		3OMO–LU	3OMO–2UMO	3OMO–3UMO	HO–LU	HO–3UMO	LU–HO	3UMO–HO
2a	A	—	10.9	—	9.2	—	4.1	17.0
	B	—	14.3	—	7.1	—	3.0	10.0
2b	A	8.0	14.3	—	5.9	—	3.1	10.0
	B	12.0	10.3	—	8.1	—	4.6	19.0
3a	A	—	—	15.4	6.4	10.9	3.0	11.8
	B	—	—	16.3	5.1	11.4	2.6	9.9
3b	A	—	—	15.0	5.7	10.5	2.8	9.4
	B	—	—	15.4	4.5	10.7	3.0	13.6

[a] In addition to FMO contributions, only those greater than 10% are reported. [b] Values refer to concerted synchronous pathways.

Table 4 Energy values for some distances (D) between molecular planes along the concerted synchronous pathway

			E_{pol}	E_{ovr}	E_{int}
Reagent	D/Å	Adduct	kJ mol^{-1}		
2a	4.0	A	1.29	−0.01	1.28
		B	1.34	−0.00	1.34
	3.5	A	1.60	−0.13	1.47
		B	1.56	−0.10	1.45
	3.0	A	1.89	−1.32	0.57
		B	1.64	−1.17	0.47
	2.5	A	2.00	−9.36	−7.36
		B	1.27	−8.88	−7.61
2b	4.0	A	2.13	0.00	2.13
		B	0.45	0.00	0.45
	3.5	A	2.58	−0.04	2.54
		B	0.42	−0.05	0.37
	3.0	A	2.99	−0.62	2.37
		B	0.17	−0.72	−0.55
	2.5	A	3.14	−5.32	−2.17
		B	−0.63	−5.73	−6.36
3a	4.0	A	1.37	−0.02	1.35
		B	0.07	−0.01	0.06
	3.5	A	1.65	−0.19	1.46
		B	−0.50	−0.14	−0.64
	3.0	A	1.93	−1.76	0.17
		B	−1.65	−1.52	−3.17
	2.5	A	2.04	−11.88	−9.84
		B	−3.95	−11.19	−15.13
3b	4.0	A	1.43	−0.01	1.42
		B	−2.14	0.00	−2.14
	3.5	A	1.75	−0.12	1.63
		B	−3.49	−0.10	−3.59
	3.0	A	2.17	−1.20	0.97
		B	−5.74	−1.14	−6.89
	2.5	A	2.68	−8.51	−5.84
		B	−9.58	−8.65	−18.23

Table 5 Geometrical parameters[a] in the absolute E_{nb} minima evaluated by (6-12) and (6-12-1) potential functions

				α	γ	ε
Reagent	Function	Adduct	D/Å	deg		
2a	(6-12)	A	3.51	56.7	91.8	179.9
		B	3.95	131.9	88.0	0.1
	(6-12-1)	A	4.76	38.5	91.4	10.3
		B	3.54	122.7	95.7	24.2
	(6-12-1)[b]	A	3.91	47.7	83.7	28.4
		B	3.06	105.3	76.2	4.1
2b	(6-12)	A	4.00	47.7	92.6	179.9
		B	4.66	140.4	95.7	26.4
	(6-12-1)	A	3.44	59.5	94.0	136.5
		B	5.09	137.1	120.1	51.6
3a	(6-12)	A	6.14	34.1	119.5	61.9
		B	3.35	115.1	99.2	28.1
	(6-12-1)	A	3.14	85.9	108.0	180.0
		B	3.27	111.5	98.7	27.8
3b	(6-12)	A	6.13	34.1	119.7	63.0
		B	3.35	115.7	98.6	28.2
	(6-12-1)	A	5.57	36.3	115.2	45.1
		B	3.49	109.8	113.5	37.5

[a] See Fig. 1. [b] Q_i and Q_j in the (6-12-1) potential function are *ab initio* 6-31G Mulliken atomic charges.

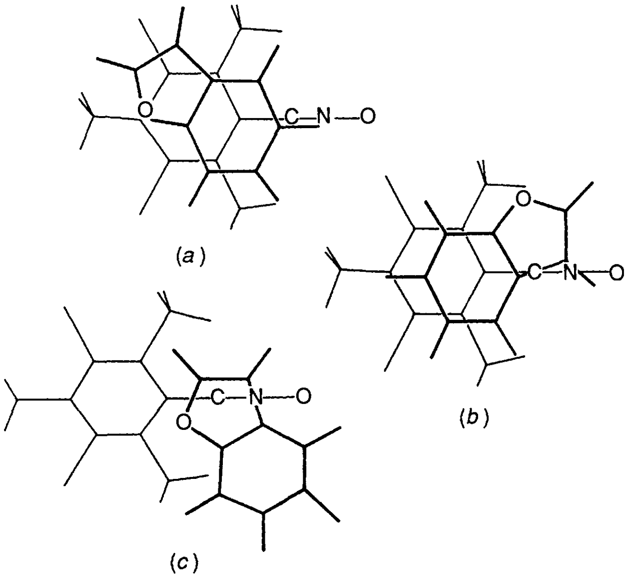

Fig. 4 Absolute E_{nb} minima for the reaction of the nitrile oxide **1** with benzofuran **3a**. E_{nb} has been calculated by means of: (*a*) the (6-12) potential function; (*b*) the (6-12-1) potential function; (*c*) the (6-12-1) potential function with the constraint $E_{ovr} < 0$.

Results obtained with the Intermolecular Orbital method[4] on the concerted synchronous path (Table 4) have shown that polar energy contributions have a considerable weight with respect to the overlap energy between π-MOs in determining the interaction energy. This trend is particularly evident in the long-range region (3–4 Å), as shown in Fig. 3 for the reaction between compounds **1** and **2a**. It is clear that an expression for E_{int} lacking in the polar term cannot be used to rationalize the behaviour of 1,3-dipolar cycloadditions.

Moreover, as we have previously pointed out,[2,8] E_{int} is also strongly dependent on the position of one reacting molecule with respect to the other; we cannot rationalize all the experimental orientations by supposing a synchronous path (see Table 4). The model we proposed, which suggests the van

Table 6 Geometrical parameters[a] and energy values in the E_{nb} minima evaluated by the (6-12-1) potential function with the constraint $E_{ovr} < 0$

Reagent	Adduct	D/Å	α	γ	ε	E_{pol}	E_{ovr}	E_{int}
			deg			kJ mol^{-1}		
2a	A	3.00	84.3	70.2	102.4	−1.39	−0.23	−1.62
	B	2.98	102.0	91.6	78.5	1.31	−0.01	1.30
2b	A	2.91	84.3	92.5	151.4	1.29	−0.05	1.24
	B	3.49	109.8	115.6	35.9	1.42	−0.00	1.42
3a	A	3.13	72.0	101.7	90.7	2.62	−0.01	2.61
	B	3.18	101.5	90.8	71.5	−1.38	−0.00	−1.38
3b	A	3.64	75.5	122.2	114.5	2.06	−0.02	2.04
	B	3.14	100.9	93.7	82.4	−4.57	−0.00	−4.57

[a] See Fig. 1.

der Waals minima as model structures for the perturbed states of Diels–Alder reactions, should also be suitable for the description of the reactivity of the examined substrates.

Contrary to what we found for Diels–Alder reactions, a van der Waals surface description performed with the (6-12) potential function provided non-bonded minima well away from the probable reaction route. As shown in Table 5 the values of the α and ε angles were found to be very different from those predicted for the synchronous path ($\alpha = \varepsilon = 90°$) and the distance D between the molecular planes was too large. These minima are not acceptable due to the low values of overlap integrals between $2p_\pi$-interacting orbitals.

Since these results could be a consequence of an inadequate description of the van der Waals interactions between polar partners, minima were recalculated with a potential which explicitly takes into account Coulombic interactions between charge distributions, *i.e.* the (6-12-1) function. Comparison between E_{nb} minima obtained with both the potentials (Table 5) showed that the (6-12-1) function improves the previous results only slightly. To investigate whether this behaviour is due to the use of unsuitable atomic charges, E_{nb} minimization was also performed by using *ab initio* 6-31G Mulliken atomic charges. The inclusion of *ab initio* charges resulted in a marked decrease in the distance D (Table 5) but adduct conformations remained too distorted to allow a significant overlap between the interacting orbitals.

From an inspection of all the obtained E_{nb} minima conformations [see, for example, Fig. 4(*a*) and Fig. 4(*b*) for compound **3a**] it is clear that they are mostly determined by the π-stacked arrangement of the aromatic rings. To favour the interactions between atoms directly involved in the new bond formation, the minimization procedure was constrained in the region characterized by negative values of the overlap energy between the interacting orbitals. The minima so obtained [see, for example, Fig. 4(*c*)] describe more closely the approach of the two reagent molecules in the early stages of the reaction.

The energy values in the E_{nb} minima, obtained for all the examined reactions with the constrained procedure (Table 6), allowed the rationalization of the product distribution experimentally observed,[6,9] *i.e.* a regioselectivity for product A for furan **2a** and a regioselectivity for product B for benzofuran **3a** and indole **3b**. Moreover, the formation of oxime **4** in the reaction of nitrile oxide **1** and pyrrole **2b** (see Experimental section) was correctly predicted on the basis of this improved model.

Conclusions.—In this paper we have confirmed that proper application of the PMO approach must avoid any kind of approximation (in particular the FMO one) and must not introduce any arbitrariness into the choice of the perturbed state. We also demonstrated that the perturbed state model we previously proposed for the Diels–Alder reaction is also suitable for the rationalization of the selectivity in 1,3-dipolar cycloadditions if polar contributions are included in evaluating the van der Waals interactions. Moreover, the results we obtained indicate that whenever E_{nb} is dominated by the interaction of atoms which are not directly involved in the reaction, a negative E_{ovr} constraint must be introduced in the search of the perturbed-state structure. In this way, regions of the van der Waals hypersurface which are far from viable reaction paths are excluded and the perturbed states so obtained actually foreshadow the transition states of the reaction.

The constrained procedure, which rationalizes the experimental regioselectivities of the title reactions, can be considered as a generalization of the model we previously proposed and certainly has a wider range of applicability.

The results obtained for the reaction of pyrrole **2b** are very encouraging with regard to the predictive ability of our model.

Acknowledgements

We wish to thank Dr. C. Gatti for helpful discussions. Financial support by the Italian CNR is gratefully acknowledged (Grant No. CT88.00201.03).

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Paper 1/00076D
Received 7*th January* 1991
Accepted 2*nd April* 1991