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SELECTIVITY IN CYCLOADDITIONS - II.[1] POLAR AND STERIC CONTROL IN THE 1,3-DIPOLAR CYCLOADDITION OF BENZONITRILE OXIDE TO SOME 3-SUBSTITUTED CYCLOPENTENES

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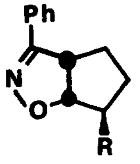
Although 1,3-dipolar and Diels-Alder cycloadditions are mechanistically well understood as $\left[\pi^4_s + \pi^2_s\right]$ concerted processes[2], the perturbation approach[3] has only recently been used to account for the reactivity[4] and regioselectivity[5] patterns of these two reaction types. This theoretical treatment is indeed very promising. Nevertheless, wider application of the theory is prevented, especially for reactions where steric and electronic factors, so far unevaluated, as well as secondary orbital interactions are involved. It is well known that the steric factors very often mask or alter the electronic features of cycloadditions[6].

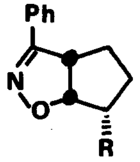
We wish to report here a procedure for the separation and evaluation of the polar and steric effects in the 1,3-dipolar cycloaddition of benzonitrile oxide (BNO)[7] to a suitable dipolarophile. 3-Substituted cyclopentenes were selected as substrates because their envelope conformation ensures the same steric environment for both the regioisomeric attacks *anti* to the substituent. The ratio of the two *anti*-regioisomers should then provide a measure of the polar effect, while *syn*-attack should show both polar and steric dependence.

BNO was generated *in situ* in ether, at 0°, in the presence of 3 equivalents of the 3-substituted cyclopentene. The four isomeric cycloadducts (I-IV) were isolated by column chromatography or fractional crystallization with an overall yield up to 90%. Structural assignments rely on independent stereospecific syntheses and on NMR data. The multiplicity of the isoxazoline ring proton signals allowed regioisomeric identification, while the value of the coupling constant between the cyclopentane proton on the carbon atom bearing the substituent and the adjacent bridgehead proton (J_{cis} 5-9 Hz > J_{trans} 0·5-4 Hz) confirmed the stereochemical assignment. The isomer distribution was measured by glc analysis on a SE-30 column, by comparison with mixtures of known composition.[8]

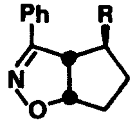
TABLE. Isomer distribution in the reaction mixtures from BNO and 3-substituted cyclopentenes.



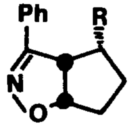
I: 6-anti



II: 6-syn



III: 4-anti



IV: 4-syn

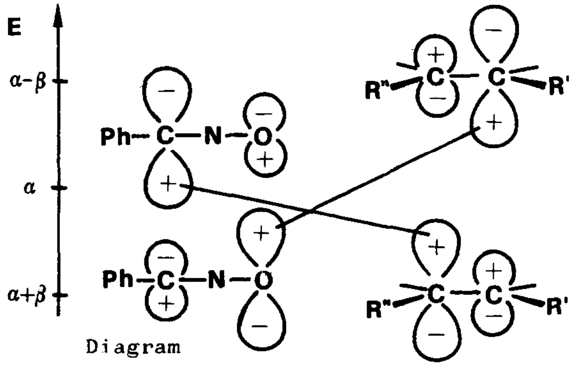
R	Isomer distribution[a]				Ratio	$\Delta\Delta G^{\ddagger}_{p}$	$\Delta\Delta G^{\ddagger}_{St(O)}$	$\Delta\Delta G^{\ddagger}_{St(C)}$	σ^{*b}
	I	II	III	IV	I/III				
iso-Pr	68	13	18	1	3·78	+0·72	0·9	1·6	-0·13
Et	43	20	36	1	1·19	+0·10	0·4	1·9	-0·12
Me	63	3	33	1	1·91	+0·35	1·5	1·9	-0·10
Ph	29	4	66	1	0·44	-0·45	1·1	2·3	+0·22
NMe_2	23	7	70	–[c]	0·33	-0·61	0·7	>2·5	+0·22
OH	12	30	53	5	0·23	-0·82	-0·76	1·3	+0·55
OMe	22	3	71	4	0·31	-0·63	1·1	1·6	+0·66
OAc	15	5	77	3	0·19	-0·88	0·6	1·8	+0·89

[a] Percentage of the total mixture of 4- and 6-substituted tetrahydrocyclopent[d]isoxazoles. [b] P.R. Wells, "Linear Free Energy Relationships", Academic Press, New York, 1968, p. 38. [c] Not detected.

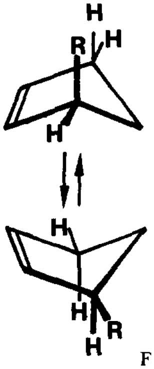
Polar effect. - The ratios for the two anti (I/III) and for the two syn (II/IV) regioisomers can be deduced from the Table. While the values for the syn regioisomeric pair are puzzling, being governed by both polar and steric effects, the values related to anti attack clearly demonstrate, for the first time in 1,3-dipolar cycloadditions, that the regiochemistry of the reaction is considerably and regularly influenced by the electronic effect of the substituent. The regioisomer I is predominant in the case of electron-releasing substituents, whereas the regioisomer III predominates when the cyclopentene is substituted with electron-attracting groups. The free energy difference ($\Delta\Delta G^{\ddagger}_{p}$) between the two regioisomeric pathways shows a change of 1·60 kcal/mole going from 3-isopropyl- to 3-acetoxy-cyclopentene, and correlates qualitatively with the σ^* values of the substituents.[9]

As a general rule it is concluded that the more nucleophilic carbon atom of the polarized double bond interacts preferably with the BNO carbon atom, while the less nucleophilic carbon interacts more easily with the 1,3-dipole oxygen. The observed trend is in line with the well-documented electrophilic and nucleophilic behaviour of the nitrile oxide carbon and oxygen resp. in addition reac tions (e.g. amine addition and protonation).[7]

Our results fit the simple frontier orbital approach[3b] well. The calculated eigenvectors at the interacting centers for the HOMO and LUMO of BNO[10] and of the olefins polarized by the substituent[11] (R' electron-releasing or R'' electron-attracting) are shown in the interaction diagram.



Diagram



Figure

The pair of HOMO/LUMO interactions with the best overlap (indicated by the solid line) work in the same direction, favouring the actually predominant isomer I in the case of the donor R' and isomer III with the acceptor R''.[12]

Steric effect. - The evaluation of the steric effect is more difficult because it largely depends on the unknown pseudoaxial or pseudoequatorial conformational preference of the cyclopentene substituent (see fig.). However, if we assume in the first approximation that the polar effect is the same on the two diastereotopic faces of the 3-substituted cyclopentene, the reactivity decrease for the *syn* attack, deducible from the *syn*/*anti* ratio for each regioisomeric process, should provide a rough estimate of the average steric effect. The free energy differences $\Delta\Delta G^{\ddagger}_{St(O)}$ and $\Delta\Delta G^{\ddagger}_{St(C)}$ for the two stereoisomeric pathways I/II and III/IV resp. are reported in the Table.

The value of the steric barrier $\Delta\Delta G^{\ddagger}_{St(O)}$, which hinders the formation of II compared with I, ranges from 0·4 to 1·6 kcal/mole, whereas the corresponding barrier for the other stereoisomeric pair ranges from 1·6 to 2·5 kcal/mole. This means that the steric sensitivity of the BNO carbon to an α substituent on the olefin is on average about 1 kcal/mole greater than that of the oxygen atom. This approximate value represents the steric control on the regioselectivity and agrees well with qualitative considerations on the steric hindrance of BNO.

The remarkably high amount of the *syn* isomer II in the case of 3-hydroxycyclopentene is also noteworthy. This fact is undoubtedly due to a hydrogen bonding effect between the OH group and the dipole oxygen atom, which stabilizes the transition state leading to the 6-*syn* isomer.

In conclusion, our procedure proves to be successful in recognising and isolating the steric and the hitherto masked polar effect in cycloaddition reactions. A similar treatment regarding the role of the more important resonance effects will be reported in a forthcoming paper.

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References and Footnotes

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8. Experimental details will be reported in a full paper.
9. a) The lack of a linear correlation is, however, not surprising in cyclic molecules because of the dependence of the polar effect on the orientation of the substituent with respect to the reaction centre.[9b] Therefore for each of the two envelope conformations a different polar influence can be expected. We ascribe the unusual order iso-Pr>Me>Et to this fact. b) N.B. Chapman and J. Shorter, "Advances in Linear Free Energy Relationships", Plenum Press, London, 1972, ch. 2.
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12. a) In view of the energy proximity effect,[4b] it is reasonable to assume a predominance of the HOMO(olefin)-LUMO(dipole) interaction. This conclusion is also supported by our results[12b] on the regioselectivity of BNO cycloaddition to cyclopentadiene, taking into account the close value of the HOMO energy of cyclopentene[12c] and the larger HOMO/LUMO distance of olefins with respect to cyclopentadiene. b) G. Bailo, P. Caramella, G. Cellerino, A. Gamba and P. Grünanger, *Gazz.Chim.Ital.* **103**, 47 (1973). c) P. Bishof and E. Heilbronner, *Helv.Chim.Acta* **53**, 1677 (1970).