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SYN-ANTI SELECTIVITY IN CYCLOADDITIONS. PART II.[1]
REACTION OF CYCLIC NITRONES WITH *CIS*-3,4-DISUBSTITUTED CYCLOBUTENES

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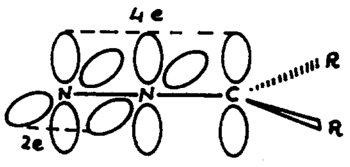
Diazoalkanes **1** and nitrile oxides, 1,3-dipoles both with an orthogonal double bond, are known to react readily with *cis*-3,4-dichlorocyclobutene to give mixtures of *syn* and *anti* adducts, the *syn* cycloadduct being dominant whenever the 1,3-dipole structure is not highly hindered.[1,2] In order to explain the high percentage of the *syn* isomer in the cycloaddition reaction mixtures, the stabilizing interaction (as depicted in **2**) between the empty *p* atomic orbital on the end nitrogen atom of diazoalkanes (or on the carbon atom of nitrile oxides) and the lone pair of the chlorine atom has been put forward.[3] This interaction is operating when the 1,3-dipole is already bent; at an early stage of the reaction an interaction of this type may be supposed between the orthogonal π^* of the linear diazoalkane (or nitrile oxide) and the chlorine lone pairs.

Pursuing our studies on *syn*-*anti* selectivity in 1,3-dipolar cycloadditions, we now report that even in the reaction of cyclic nitrones, i.e. 1,3-dipoles without an orthogonal double bond, with *cis*-3,4-dichlorocyclobutene the *syn* adduct is the major constituent in the mixture of the two adducts. It appears, therefore, that the secondary orbital interaction model above described for 1,3-dipoles possessing an orthogonal double bond does not represent the main factor controlling the *syn*/*anti* ratio in 1,3-dipolar cycloadditions.

Both 3,4-dihydroisoquinoline-N-oxide and 5,5-dimethyl- Δ^1-pyrroline-N-oxide, heated under reflux in benzene with *cis*-3,4-dichlorocyclobutene (**3a**), yielded a mixture of two 1:1 adducts, which were separated by column chromatography (Kieselgel H Merck; eluant cyclohexane/AcOEt 4:1).[4]

Structures **4a** and **6** were attributed to the major components, which in both cases possess the higher m.p.'s and the smaller R_F values,[5] whereas structures **5a** and **7** were assigned to the minor components.

Following ^{1}HNMR data are relevant for structural assignments: (i) the values of $J_{45}<3{\cdot}0$ Hz, showing a *trans*-relationship between H-4 and H-5 protons,[6] infer an *exo*-transition state, e.g. **8**, for the formation of all four adducts **4a**, **5a**, **6** and **7**; (ii) the variations of chemical shifts values of protons H-4 compared



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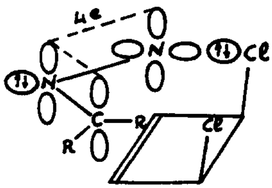

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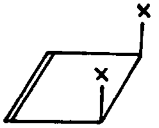

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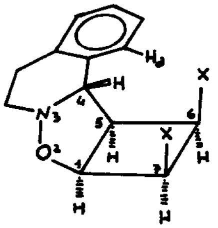

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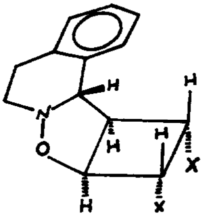

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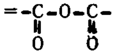
a:X = Cl ; b:X = CO_2CH_3 ; c:X-X = 
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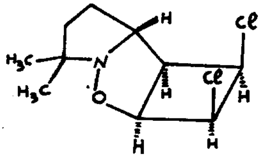

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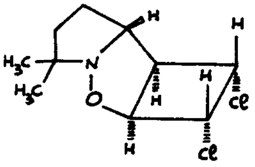

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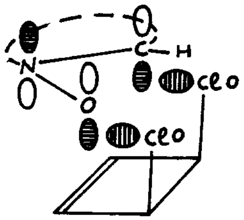

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TABLE. Yields, ^{1}HNMR data of compounds 4-7 for deutero-benzene solutions and $\Delta\delta=\delta(CDCl_3) - \delta$ (deutero-benzene) values (in brackets).[a]

Comp.	Mp(°C)	Yield (%)	H-1	H-4	H-5	J_{45}(Hz)
4a	161	71	3·90-4·20m[b](≥0·50)	4·78d(≤0·25)	3·09m(0·67)	2·5
5a	102	26	4·55m(≤0·30)	3·77bs(≥0·67)	3·40m(0·35)	<0·5
4b	141-3	12	4·38m(0·50)	5·80d(-0·23)	3·38(0·44)	2·7
5b	97-99	85	4·70m(0·05)	4·00bs(0·35)	c	<0·5
6	157	68	4·13m(0·60)	3·77m(0·19)	2·73m(0·85)	<0·5
7	91	29	4·51m(0·19)	3·02m(0·69)	3·02m(0·38)	<0·5

[a] $\Delta\delta$ of H-6 and H-7 protons for _syn_ adducts are higher than the $\Delta\delta$ relative to H-4 proton; the opposite was observed for _anti_-adducts. [b] Overlapped by signals of H-6 and H-7 protons [c] Signal could not be identified with certainty

with those of other protons by passing from $CDCl_3$ to C_6D_6 point toward a *syn*-structure for compounds **4a** and **6** and toward an *anti*-structure for compounds **5a** and **7**.

The significantly smaller variation observed for proton H-4 in adducts **4a** and **6** is due to the face of the molecule bearing the H-4 proton possessing a lower degree of solvation because of the steric hindrance by the chlorine atoms.[8]

Comparison of the *syn*/*anti* ratios for adducts obtained in boiling EtOH (overall yield 96%; ratio **4a**/**5a** = 3·45), acetonitrile (94%; ratio **4a**/**5a** = 3·05) and benzene (ratio **4a**/**5a** = 2·73) respectively, showed that the higher the solvent polarity, the larger is the amount of the *syn* isomer.

3,4-Dihydroisoquinoline-N-oxide has been also reacted with *cis*-3,4-dicarbomethoxy cyclobutene (**3b**) and the anhydride (**3c**) in benzene at room temperature. In the former case the *anti*-isomer **5b** (having a lower m.p. and a higher R_F than the *syn*-adduct **4b**) was largely dominant; with **3c** the *anti* adduct **5c** was exclusively formed.[9]

Structural assignements of **4b** and **5b** follow from their ^{1}HNMR data (see Table). Significantly H-4 proton of compound **4b** absorbed at very low fields being deshielded by the carbomethoxy group at position 6. Owing to the same deshielding effect, the aromatic proton H-a (ortho to C-4) was found to absorb at lower field than the other aromatic protons both in benzene and in $CDCl_3$ (H-a proton δ 7·95 m and 7·67 m; other three aromatic protons δ 6·80-7·20 and 6·97-7·40 in benzene and $CDCl_3$, respectively).

The above results allow us to draw the following conclusion: simple steric interaction and dipole-dipole repulsive interactions favour formation of *anti*-adducts in 1,3-dipolar cycloadditions of cyclic nitrones with cyclobutenes **3b** and **3c**. This is in sharp contrast with the behaviour of the same 1,3-dipoles reacting with dichlorocyclobutene to give *syn*-adducts as a result of positive electronic effects.

Since the stereochemistry of final adducts in the latter cycloadditions implies only *exo*-transition states, the terminal ends and not the central atom of the 1,3-dipole must be taken into account.

Whether these electronic effects involve a $\sigma-\pi^*$ interaction in the dichlorocyclobutene[10] or a stabilizing interaction between the LUMO 1,3-dipole and the chlorine lone pairs e.g. **8**[1] or even Van der Waals-London forces,[11] will be the object of further studies.

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References and Footnotes

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3. N. El-Ghandour, O. Henri-Rousseau and J. Soulier, Bull.Soc.Chim.France, 2817 (1972)
4. All compounds gave satisfactory C,H,N (±0·3%) analyses.
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6. As found for similar systems, a cis-relationship would require a $J_{45} \geq 6{\cdot}0$Hz.[7]
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8. A definitive proof for the correct attributions of structures to adducts **5a** and **6** is represented by the preliminary results of an X ray study on such compounds: A. Coda Corsico Piccolini and S. Coda, private communication.
9. Compound **5c** was not isolated as such but was transformed into **5b** (overall yield 69%) on CH_3OH/H_2SO_4 treatment.
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