syn–anti-Isomerism in the Cycloaddition of Nitrile Oxides to *cis*-3,4-Dichlorocyclobutene

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1,3-Dipolar cycloaddition reactions of *cis*-3,4-dichlorocyclobutene with several nitrile oxides yield mixtures of *syn*- and *anti*- 4-substituted 6,7-dichloro-2-oxa-3-azabicyclo[3.2.0]hept-3-enes. The structures of the cycloadducts are deduced from n.m.r. and dipole moment data and a possible explanation for the abnormally high proportion of the sterically disfavoured *syn*-isomer is presented.

WHEREAS the stereospecificity of 1,3-dipolar cycloadditions has long been well-established and many examples of their regioselectivity have been collected,[1] only recently have studies of some other aspects of these reactions, such as perispecificity[2] and *exo–endo* isomerism,[3] been initiated.

Data available on *syn–anti* isomerism are scarce,[4] and

[1] R. Huisgen, *Angew. Chem.*, 1963, **75**, 741.

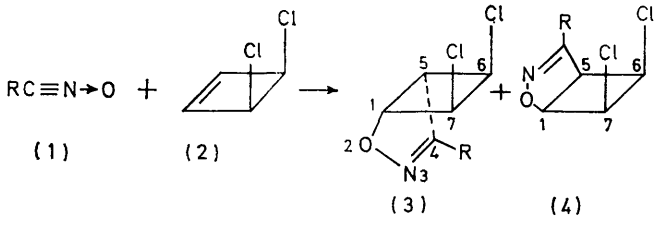
[2] K. N. Houk and C. R. Watts, *Tetrahedron Letters*, 1970, 4025; K. N. Houk and L. J. Luskus, *ibid.*, 1970, 4029; P. Caramella, P. Frattini, and P. Grünanger, *ibid.*, 1971, 3817.

[3] W. C. Agosta and A. B. Smith tert., *Chem. Comm.*, 1970, 685; D. R. Arnold and L. A. Karnischky, *J. Amer. Chem. Soc.*, 1970, **92**, 1404; P. B. Woller and N. H. Cromwell, *J. Org. Chem.*, 1970, **35**, 888; R. Huisgen and M. Mader, *Angew. Chem.*, 1969, **81**, 621; J. W. Lown and K. Matsumoto, *Canad. J. Chem.*, 1971, **49**, 3443; M. Joucla and J. Hamelin, *Compt. rend.*, 1971, **273***C*, 769, R. Greé and R. Carrié, *Tetrahedron Letters*, 1971, 4117; R. Huisgen, R. Grashey, H. Hauck, and H. Seidl, *Chem. Ber.*, 1968, **101**, 2548.

[4] This term refers to the attack of a 1,3-dipole on the two diastereotopic faces of a double bond: see *e.g.* K. L. Williamson, Y.-F. Li Hsu, R. Lacko and C. He Youn, *J. Amer. Chem. Soc.*, 1969, **91**, 6129.

in most known cases [5] the formation of the major or of the exclusive cycloadduct obtained can be attributed to steric approach control in the transition state. However the discovery that diazoalkanes react with *cis*-3,4-disubstituted cyclobutenes to yield only the sterically less favoured *syn*-cycloadduct [6] or a mixture of the two possible isomers [7] reveals that other factors must also be at work.

We have begun a systematic study of *syn–anti* isomerism in 1,3-dipolar cycloadditions, and now report the results obtained with nitrile oxides (1) and *cis*-3,4-dichlorocyclobutene (2). A mixture of the 1,3-dipole and an excess of dipolarophile in diethyl ether or in acetonitrile at room temperature always yielded a



mixture of the two isomeric *cis,anti,cis*- (3) and *cis,syn,cis*- (4) cycloadducts. Yields and isomer ratios are reported in Table 1.

TABLE 1

syn–anti-Cycloadducts (3) and (4) from nitrile oxides and *cis*-3,4-dichlorocyclobutene

R	Method [a]	Total yield (%)	Ratio (3) : (4)
a; EtO_2C	A	29	26 : 74
b; MeCO	A	49·5	27 : 73
c; Me	A	69	31 : 69
d; *p*-NO_2·C_6H_4	A	84	31 : 69
	C	78	19 : 81
e; *m*-NO_2·C_6H_4	A	86·5	31 : 69
f; *o*-NO_2·C_6H_4	A	66	37·5 : 62·5
g; *p*-ClC_6H_4	A	82	44 : 56
h; Ph	A	82	52 : 48
	C	79	29 : 71
i; *p*-MeC_6H_4	A	95	58 : 42
j; *p*-MeO·C_6H_4	A	90	59 : 41
	C	78·5	34 : 66
k; 2,4,6-Me_3-3,5-Cl_2C_6	B	88	58 : 42
l; 2,4,6-$Me_3C_6H_2$	B	80	72·5 : 27·5
m; 2,6-$Cl_2C_6H_3$	B	88	73·5 : 26·5
	C	47·6	51 : 49
n; 2,4,6-$(MeO)_3C_6H_2$	B	90	93 : 7
	C	60	76 : 24
o; F_5C_6	b	59	28 : 72

[a] A: solvent ether, nitrile oxide prepared *in situ* from hydroximic acid chloride; B: solvent ether, stable nitrile oxide; C: solvent acetonitrile. [b] Reaction run in CH_2Cl_2, with nitrile oxide generated *in situ* from the oxime and $Pb(OAc)_4$.

Structural assignments for the adducts (3h) and (4h) were made on the basis of n.m.r. analysis [8] and comparison with products obtained by independent synthesis,[9] as well as through dipole moment measurements [2·94 for (3h) and 4·71 D for (4h)].* All the other structures were assigned from comparison of their n.m.r. and t.l.c. data with those of (3h) and (4h).

In the n.m.r. spectrum of (3h) the cyclobutane protons had significantly different chemical shifts: the 5-proton showed a multiplet centered at δ 4·46, the 1-proton a multiplet centered at δ 5·33, and the 6- and 7-protons overlapping multiplets at δ 4·74. The signals for the cyclobutane protons of compound (4h) were not distinguishable, and the spectrum showed a complex multiplet in the range of δ 4·87—5·55.

The n.m.r. spectra of the other adducts can be divided into three pattern types: (i) when R is *para*-substituted phenyl, the spectra of the two isomers are almost identical with the respective spectra of the parent compounds, *viz.* (3h) or (4h); (ii) when R is *o,o'*-disubstituted phenyl (3 or 4k—o), the spectra of the *syn*-adducts show the same general pattern as that of (4h), whereas the spectra of the *anti*-adducts are somewhat different from that of (3h), showing a higher separation of the chemical shifts in the central region [*e.g.* compound (3l) gave four groups of lines: δ 4·31 (m, 5-proton), 4·62 (m) and 4·89 (m) (6- and 7-protons), and 5·36 (m, 1-proton)]; (iii) when R is alkyl (3 or 4a—c), the reverse phenomenon is observed, *i.e.* the spectral patterns of the *anti*-adducts are very similar to that of (3 h), whereas the signals of the *syn*-adducts are more spread out [*e.g.* for compound (4b) the 5-proton signal fell at higher field, showing a multiplet centered at δ 4·70; the other three protons showed a multiplet in the range δ 5·12—5·58].† Despite these slight differences, however, the similarities of the general spectral patterns within the two series of adducts (*syn* and *anti*) allowed assignment of stereochemistry to all products with reasonable certainty.

From the ratios of the isomers formed from reactions in ether (see Table 1) small values of $\Delta\Delta G^{\ddagger}$ can be inferred; they vary from 0·65 kcal mol^{-1} in favour of the *syn*-transition state for (1a) to about 1·5 kcal mol^{-1} in favour of the *anti*-transition state for (1n). In all other cases

* We thank Professor M. Sanesi, Institute of Physical Chemistry, Pavia, for these measurements.

† The n.m.r. spectra of the *anti*-adducts are for solutions in $CDCl_3$, whereas those of the *syn*-adducts are for solutions in $(CD_3)_2CO$. A change of solvent [$CDCl_3$ for $(CD_3)_2CO$ and *vice versa*] brought about some minor alterations (see ref. 8) in the spectra, but the patterns of the compounds of the two series were still very different. Diagrams of spectra of compounds (3 and 4b), (3 and 4h), and (3 and 4l) are available as Supplementary Publication No. SUP 20807 (8 pp.) [see Notice to Authors No. 7 in *J. Chem. Soc.* (*A*), 1970, Issue No. 20].

[5] See *e.g.* K. Alder and G. Stein, *Annalen*, 1931, **485**, 211, 223; 1935, **515**, 165, 185; R. Huisgen, R. Grashey, P. Laur, and H. Leitermann, *Angew. Chem.*, 1960, **72**, 416; R. Huisgen, L. Möbius, H. Stangl, G. Szeimies, and J. M. Vernon, *Chem. Ber.*, 1965, **98**, 3992; R. Huisgen, W. Scheer, G. Szeimies and H. Huber, *Tetrahedron Letters*, 1966, 397; R. Huisgen, H. Knupfer, R. Sustmann, G. Wallbillich and V. Weberndorfer, *Chem. Ber.*, 1967, **100**, 1580; R. Huisgen, R. Grashey, H. Hauck, and H. Seidl, *ibid.*, 1968, **101**, 2043; R. R. Fraser and Y. S. Lin, *Canad. J. Chem.*, 1968, **46**, 801; R. Lazar, G. G. Cocu, and N. Barbulescu, *Rev. Chim.* (*Roumania*), 1969, **20**, 1; J. F. Stephen and E. Marcus, *J. Heterocyclic Chem.*, 1969, **6**, 969; S. McLean and D. M. Findlay, *Tetrahedron Letters*, 1969, 2219; M. G. Barlow, R. N. Haszeldine, and W. D. Morton, *Chem. Comm.*, 1969, 931; R. S. Bly, F. B. Culp, and R. K. Bly, *J. Org. Chem.*, 1970, **35**, 2235; N. El Ghandour and J. Soulier, *Comp. rend.*, 1970, **271***C*, 766.

[6] M. Franck-Neumann, *Angew. Chem.*, 1969, **81**, 189.

[7] M. Franck-Neumann, *Tetrahedron Letters*, 1968, 2979; R. A. Keppel and R. B. Bergmann, *J. Amer. Chem. Soc.*, 1972, **94**, 1350.

[8] R. Mondelli and A. Gamba, *Org. Magnetic Resonance*, 1973, **5**, 101.

[9] G. Bianchi, R. Gandolfi, and P. Grünanger, *Tetrahedron*, 1970, **26**, 5113.

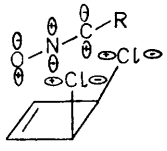
the value does not exceed 0·65 kcal mol^{-1}. The proportion of *syn*-adduct is markedly increased if the reaction is carried out in acetonitrile instead of ether.

The following conclusions can be deduced from our results:

(i) Steric effects should favour formation of the *anti*-isomer. The decrease in proportion of the *syn*-isomer going from aceto- to benzo- to mesito-nitrile oxide (especially when *ortho*-disubstituted benzonitrile oxides are involved) has to be mainly ascribed to this factor. Nevertheless the *syn*-isomer is largely predominant in the cycloaddition reactions involving the sterically less demanding aliphatic nitrile oxides and the benzonitrile oxides carrying electron-attracting *para*-substituents. Even with the crowded *ortho*-disubstituted benzonitrile oxides the proportion of *syn*-isomer is remarkably high and does not correspond to expectations based on steric factors alone.

(ii) The higher dipole moment of (4h) in comparison with (3h) suggests that in a concerted process the transition state leading to the *syn*-isomer is more polar than the one leading to the *anti*-isomer. This is consistent with the already mentioned increased formation of the former isomer in a more polar solvent. Moreover, although the lack of complete dipole moment data for the nitrile oxides [10] does not allow general conclusions to be drawn, it should be noted that along the series (1d), (1g), (1h), (1i) and (1k), (1l) the amount of the *anti*-isomer increases with increasing dipole moment of the starting nitrile oxide. This suggests that the *syn*-adduct is disfavoured by electrostatic interactions.*

(iii) If we assume a frontier-orbital controlled [12] mechanism, a symmetry-allowed stabilizing interaction between the non-bonding atomic orbitals (NBAOs) of the two chlorine atoms of structure (2) and the lowest unoccupied molecular orbital (LUMO) of the nitrile oxide seems to account for the abnormally predominant *syn*-attack of the dipole on the double bond. As molecular models show, this interaction is favoured by the mutual spatial arrangement of the two chlorine atoms and the nitrile oxide molecule approaching the dipolarophile on parallel planes.[13] This interaction is already effective at distances where the dipole–double bond



(5)

interaction is still not significant, and can be represented as in formula (5). The different values of the *syn–anti* ratio obtained with various nitrile oxides are therefore attributable, in addition to steric and electrostatic factors, to the different energy levels of the LUMO of the dipole. A lower value of the LUMO energy level (favoured, for example by electron-attracting substituents) would enhance the LUMO(dipole)–NBAO(chlorine atoms) interaction and therefore increase the proportion of the *syn*-isomer.

A less attractive explanation is a possible through-space interaction between the NBAOs of the chlorine atoms and the π and π^* MOs of the cyclobutene double bond, schematically represented in the Figure. If we assume, for instance, a prevalent LUMO(dipole)–HOMO (dipolarophile) interaction, in this case the π' MO of dichlorocyclobutene derives from an antibonding mixture of π and n_1 MOs and should interact with the dipole LUMO most favourably from the *anti*-side.†

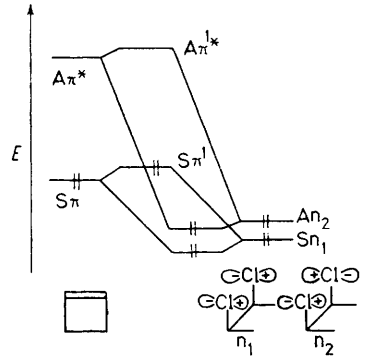


FIGURE Schematic diagram of the symmetry-allowed through-space interactions of the π and π^* MOs of the cyclobutene double bond with n_1 and n_2 NBAOs of the chlorine atoms in *cis*-3,4-dichlorocyclobutene. The energy levels of these orbitals have only a qualitative significance and their relative positions are based on the values of the ionization potentials of the cyclobutene (9·43 eV) and methyl chloride (11·28 eV)[14]

In order to verify the validity of our conclusions and to study the preferred (*exo* or *endo*) spatial disposition of the dipole in the transition state, the cycloadditions of *cis*-3,4-dichlorocyclobutene and analogous compounds to other 1,3-dipoles are under investigation.

EXPERIMENTAL

N.m.r. spectra were recorded at 36 °C on a Perkin-Elmer R12A (60 MHz) spectrometer with Me_4Si as internal standard, with $CDCl_3$ as solvent for the *anti*-adducts and $(CD_3)_2CO$ for the *syn*-adducts (which are sparingly soluble in chloroform). The calculations [8] on the reference compounds (3h) and (4h) refer to solutions in both these solvents and in other solvents too.

The compositions of reaction mixtures were determined

* This relationship excludes the hypothesis that the primary factor governing *syn–anti* isomerism in our system is an attractive interaction of the van der Waals–London type, recently invoked in an analogous problem.[11]

† A HOMO(dipole)–LUMO(dipolarophile) interaction would lead to the same conclusions. For a similar treatment of through-space orbital interaction see ref. 14.

[10] See C. Grundmann and P. Grünanger, ' The Nitrile Oxides,' Springer Verlag, Heidelberg, 1971, p. 21; P. Beltrame, C. Veglio, and M. Simonetta, *J. Chem. Soc.* (*B*), 1967, 867.

[11] K. L. Williamson, Y.-F. Li Hsu, R. Lacko, and C. H. Youn, *J. Amer. Chem. Soc.*, 1969, **91**, 6129; K. L. Williamson and Y.-F. Li Hsu, *ibid.*, 1970, **92**, 7385.

[12] K. Fukui, *Accounts Chem. Res.*, 1971, **4**, 57; R. Sustmann, *Tetrahedron Letters*, 1971, 2717, 2721; R. Sustmann and H. Trill, *Angew. Chem.*, 1972, **84**, 887.

[13] R. Huisgen, *Angew. Chem.*, 1963, **75**, 741; *J. Org. Chem.*, 1968, **33**, 2291.

[14] M. N. Paddon-Row, *Tetrahedron Letters*, 1972, 1409.

by t.l.c. on silica gel GF254 (Merck). The products could be detected on t.l.c. plates by spraying with a 3% solution of chromic oxide in sulphuric acid (50%) followed by heating at 120° in an air-bath.

Elemental analyses were performed by Dr. L. Maggi Dacrema.

Reaction of Nitrile Oxides (1) *with* cis-3,4-*Dichlorocyclobutene* (2).—A mixture of the appropriate nitrile oxide and a three-fold excess of dichlorocyclobutene in ether was set aside (at 18—20° for the unstable and at 25° for the stable nitrile oxides) until total disappearance of the dipole was shown by t.l.c. If unstable, nitrile oxides were generated *in situ* from the hydroximic acid chloride and triethylamine (Method A); if stable, they were used directly (Method B). Some reactions were also run in acetonitrile (Method C). The pentafluorobenzonitrile oxide was generated *in situ* from the oxime and lead tetra-acetate in dichloromethane as solvent. The mixture was separated by column chromatography [silica gel H (Merck); eluant cyclohexane–ethyl acetate in various proportions]. The *cis,syn,cis*-4-substituted 6,7-dichloro-2-oxa-3-azabicyclo[3.2.0]hept-3-ene (4) was always eluted more slowly than the *cis,anti,cis*-isomer (3). The adducts are stable; no decomposition occurs during the isolation procedure. Yields and isomers ratios (based on column chromatography separation) are reported in Table 1. Physical and analytical data of the isomers (3) and (4) are given in Table 2.

Minor amounts (*ca.* 5%) of the corresponding furoxans were isolated from the cycloaddition reactions of unstable nitrile oxides; larger amounts were obtained only in the cases of (1c) (13·5%) and (1a) (50%; main product).

When the reaction was carried out in acetonitrile (Method C), as well as the cycloadducts and small amounts of furoxans, we isolated in some cases the corresponding 3-aryl-5-methyl-1,2,4-oxadiazoles and nitriles. The nitrile oxides (1m) and (1n) gave 2,6-dichlorobenzonitrile (35%) and 2,4,6-trimethoxybenzonitrile (4%), respectively, and the nitrile oxides (1d), (1h), (1j), and (1n) gave the corresponding 5-methyloxadiazoles (yields 11, 11·5, 15·5, and 8·1%, respectively). The following compounds are new: 5-*methyl*-3-p-*nitrophenyl*-1,2,4-*oxadiazole*, yellow plates (from EtOH), m.p. 143—145° (Found: C, 53·0; H, 3·6; N, 20·6. $C_9H_7N_3O_3$ requires C, 52·7; H, 3·4; N, 20·5%), δ ($CDCl_3$) 2·66 (3H, s, Me); 3-p-*methoxyphenyl*-5-*methyl*-1,2,4-*oxadiazole*, needles (from cyclohexane), m.p. 58—60° (Found: C, 63·3; H, 5·5; N, 14·8. $C_{10}H_{10}N_2O_2$ requires C, 63·2; H, 5·3; N, 14·7%), δ (CCl_4) 2·58 (3H, s, Me); and 5-*methyl*-3-(2,4,6-*trimethoxyphenyl*)-1,2,4-*oxadiazole*, plates (from cyclohexane–benzene), m.p. 147—148° (Found: C, 57·7; H, 5·7; N, 11·4. $C_{12}H_{14}N_2O_4$ requires C, 57·6; H, 5·6; N, 11·2%), δ ($CDCl_3$) 2·61 (3H, s, Me).

TABLE 2

Physical and analytical data

Compound	Cryst. solvent*	M.p. (T/°C)	Found (%) C	H	N	Formula	Required (%) C	H	N
(3a)	EtOH–Ch [a]	84—85	40·1	3·9	6·1	$C_6H_7Cl_2NO$	40·4	3·8	5·9
(4a)	EtOH–Ch [b]	115—116	40·5	3·9	6·1				
(3b)	EtOH [c]	105—107	40·5	3·7	6·9	$C_7H_7Cl_2NO_2$	40·4	3·4	6·7
(4b)	EtOH [c]	84—86	40·6	3·6	6·8				
(3c)	Ch [b]	100—101	40·3	4·1	7·9	$C_6H_7Cl_2NO$	40·0	3·9	7·8
(4c)	Ch [a]	101—102	40·1	4·2	7·6				
(3d)	$(CH_2Cl)_2$ [b,d]	191—192	45·8	3·1	9·8	$C_{11}H_8Cl_2N_2O_3$	46·1	2·8	9·8
(4d)	$(CH_2Cl)_2$ [b,d]	212—213	45·7	3·1	9·9				
(3e)	EtOH [b]	167—168	46·3	2·9	10·1				
(4e)	EtOH [b]	175—176	46·1	2·9	10·0				
(3f)	EtOH [b]	130—132	46·4	2·9	9·9				
(4f)	EtOH [c,d]	198—200	45·9	2·8	10·0				
(3g)	EtOH [b]	159—160	47·9	3·0	5·2	$C_{11}H_8Cl_3NO$	47·8	2·9	5·1
(4g)	EtOH [b]	221—222	47·9	3·0	5·3				
(3h)	MeOH [c]	112—113	54·3	3·8	5·8	$C_{11}H_9Cl_2NO$	54·6	3·7	5·8
(4h)	MeOH [c]	163—164	55·0	3·8	6·0				
(3i)	EtOH [b]	120—122	56·4	4·5	5·7	$C_{12}H_{11}Cl_2NO$	56·3	4·3	5·5
(4i)	EtOH [c]	189—190	56·1	4·4	5·6				
(3j)	EtOH [b]	144—145	53·0	4·3	5·2	$C_{12}H_{11}Cl_2NO_2$	53·0	4·0	5·1
(4j)	EtOH [b]	184—185	53·6	4·3	5·2				
(3k)	EtOH [b]	223—224	47·9	3·8	3·8	$C_{14}H_{13}Cl_4NO$	47·6	3·7	4·0
(4k)	MeOH [b]	249—251	47·5	3·9	4·1				
(3l)	EtOH [b]	150—151	59·1	5·3	5·0	$C_{14}H_{15}Cl_2NO$	59·1	5·3	4·9
(4l)	EtOH [b]	196—197	59·4	5·3	5·1				
(3m)	EtOH [a]	167—168	42·4	2·3	4·7	$C_{11}H_7Cl_4NO$	42·4	2·3	4·5
(4m)	EtOH [a]	182—183	42·9	2·3	4·8				
(3n)	EtOH [b]	184—185	50·4	4·5	4·4	$C_{14}H_{15}Cl_2NO_4$	50·6	4·5	4·2
(4n)	EtOH [b]	171—172	51·0	4·6	4·3				
(3o)	Ch	122—123			4·5	$C_{11}H_4Cl_2F_5NO$			4·2
(4o)	Ch	124—125			4·2				

* Ch = cyclohexane.
[a] Prisms. [b] Needles. [c] Leaflets. [d] Yellow. [e] Plates.

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