syn-anti Isomerism in the 1,3-Dipolar Cycloaddition to *cis*-3,4-Disubstituted Cyclobutenes. Part 2.[1] Role of Conformation in Bicyclo[3.2.0]hept-6-enes

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Bicyclo[3.2.0]hept-6-ene (**1a**) and 2,4-dioxabicyclo[3.2.0]hept-6-ene (**1b**) reacted with diazomethane and phenylglyoxylonitrile oxide to give only *anti* adducts. In contrast, a mixture of *syn* and *anti* adducts was isolated from the reactions of the same 1,3-dipoles with bicyclo[3.2.0]hept-6-en-3-one (**1c**), 2,4-dioxabicyclo[3.2.0]hept-6-en-3-one (**1e**), and even with the apparently most crowded, on the *syn* face, 3,3-dimethyl-2,4-dioxabicyclo[3.2.0]hept-6-ene (**1d**). Extensive *ab initio* MO calculations (4-31G) showed that compounds (**1**) prefer a boat-like conformation which, however, becomes flatter and flatter on passing from (**1a**) to (**1e**). As a result there is a progressive lessening of steric hindrance on the *syn* face which neatly parallels the observed increase in *syn* attack along the series (**1a**—**e**). Moreover the energy required to remove steric hindrance on passing from the boat-like to the half-planar conformation is definitively lower for (**1c**—**e**) than for (**1b** and **a**).

A non-intuitive contra-steric dominance of *syn* attack is frequently met in the reactions of 1,3-dipoles with *cis*-3,4-disubstituted cyclobutenes.[1-3] Particularly striking is the behaviour of *cis*-3,4-dimethoxy-, -diacetoxy-, -dichloro-, and -dimesyloxy-cyclobutenes which react with diazomethane to give only *syn*-adducts, and with phenylglyoxylonitrile oxide in highly *syn*-selective reactions.[2d,3]

The preference of the partially formed bonds (in the transition state) to be staggered with respect to the bonds in positions 3 and 4 (Houk's 'staggered model') does not give an unambiguous account of the whole trend of the experimental results.[4]

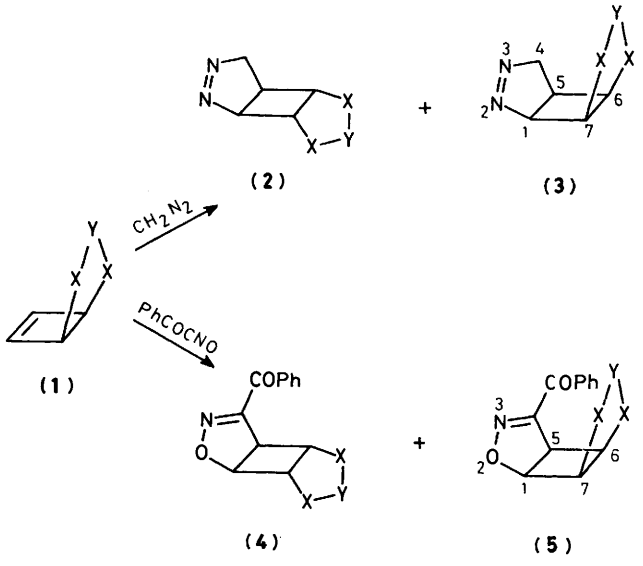
A recent reactivity model by Hehre[5] indicates that nucleophiles (electrophiles) will attack double bonds *anti* (*syn*) to lone-pair-containing allylic substituents; if this general rule is applied to the cycloadditions of diazomethane to the above cited cyclobutenes, predictions follow which are in clear disagreement with experimental data, at least if diazomethane is considered as a nucleophile.

We suggested that the face selectivity-controlling factor might be the energy difference between the opposite out-of-plane distortions of the olefinic hydrogens induced by the concerted *syn* or *anti* attack on the double bond; the sign and extent of such a difference could be anticipated, in the free molecule, by the direction and extent of the π-bond pyramidalization[1] (Figure 1).†

However, we have also shown[7] that high selectivity can be obtained as a consequence of steric and electrostatic repulsions (*anti*-selectivity) or as the effect of hydrogen bonding (*syn*-selectivity) in 5,6-*cis*-*endo*-disubstituted bicyclo[2.2.2]oct-2-enes, which have almost planar double bonds.

In the case of cyclobutenes condensed with a five-membered ring (**1**) the possiblity of conformational equilibria between boat-like and chair-like forms (Figure 2), introduces further variables: the relative abundance of available conformers and the possible different specific reactivity of each of them.

In the present paper we report the reactions of cyclobutenes (**1**) with two classical 1,3-dipoles, the 'electron-rich' diazomethane and the 'electron-poor' phenylglyoxylonitrile oxide (Scheme 1). Structural and conformational information are obtained theoretically by extensive *ab-initio* MO calculations.



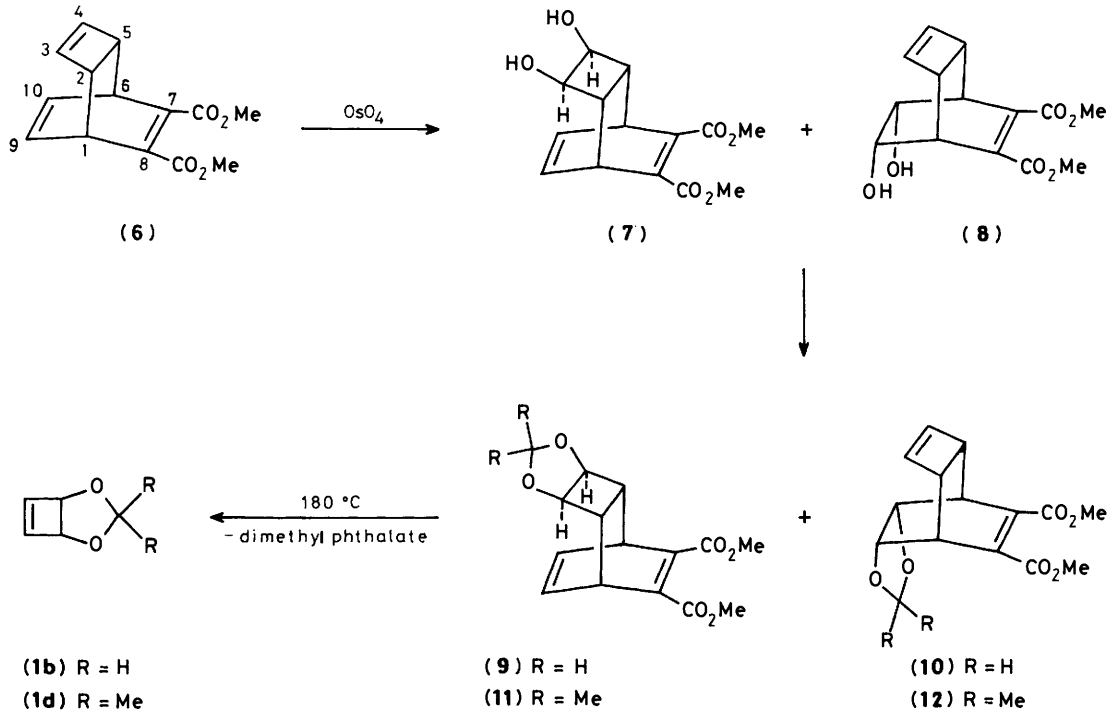
Scheme 1.

Results and Discussion

The synthesis of (**1a**),[8] (**1c**),[9] and (**1e**)[10] has already been reported.

An acetone solution of the unknown (**1d**) could be prepared in good yield from *cis*-3,4-dihydroxycyclobutene[2c] and 2,2-dimethoxypropane. The most successful attempt to prepare (**1b**) from *cis*-3,4-dihydroxycyclobutene, by treatment of this compound with CH_2Br_2 and NaOH under phase-transfer condi-

† A similar explanation was advanced by Houk and co-workers for nitrile oxide cycloadditions to cyclobutenes,[4b] and by Gleiter for nonbornene cycloadditions.[6]



Scheme 2.

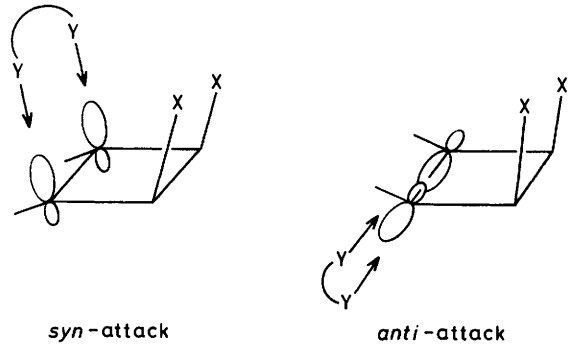


Figure 1.

tions, afforded a dilute solution of (**1b**) in CH_2Br_2, in low yield. Then we undertook an apparently cumbersome route which however led us to obtain pure (**1b** and **d**) (Scheme 2).

Compounds (**1b** and **d**) were synthesized starting from dimethyltricyclo[4.2.2.0^{2,5}]deca-3,7,9-triene-7,8-dicarboxylate (**6**).[11] This compound was *cis*-hydroxylated with OsO_4 and *N*-methylmorpholine *N*-oxide to give a mixture of the two dihydroxy derivatives (**7**) and (**8**) [(**7**):(**8**) 1:2]. The reactivity of the cyclohexadiene double bond, higher than that of the cyclobutene double bond, parallels that previously found in the reaction of (**6**) with nitrile oxides and nitrile imines.[12] The crude (**7**)—(**8**) mixture was transformed into acetal (**9**)—(**10**) mixture from which pure compound (**9**) could be separated by column chromatography. Then pyrolysis (180 °C) of (**9**) at atmospheric pressure under a slow stream of nitrogen afforded pure (**1b**) trapped at −78 °C. Pure (**1b**) was also obtained by carrying out pyrolysis of the crude mixture (**9**)—(**10**).

In a similar way pure (**1d**) was prepared *via* dimethyl acetal (**11**).

Diazomethane reacted with compounds (**1**) in ether at room temperature to give only *anti* adducts in the case of (**1a** and **b**) and a mixture of *syn* and *anti* adducts in the case of (**1d** and **e**); we were not able to characterize the products from the reaction of diazomethane with (**1c**).

Particularly surprising are the results obtained in the reactions of (**1b** and **d**) which were made to react in order to show that steric effects favour *anti* attack. Contrary to our expectations, compound (**1d**), which appeared at first sight the more crowded (on the *syn* face), yielded a 6:4 mixture of *anti* and *syn* adducts whereas (**1b**) underwent a complete *anti* selective attack.

The presence of only one adduct in the case of (**1a** and **b**) was substantiated by careful t.l.c., ^{1}H n.m.r., and g.l.c. analysis of the crude reaction mixture; the ratios between *syn* and *anti* adducts from (**1d** and **e**) were evaluated by ^{1}H n.m.r. analysis and column chromatography.

The structures of compounds rest firmly on ^{1}H n.m.r. data (Table 1). In particular $J_{1,7}$ and $J_{5,6}$ < 2.0 Hz in compounds (**2**) strongly suggest a *trans* relationship between those protons, whereas $J_{1,7}$ and $J_{5,6}$ > 5.0 Hz in compounds (**3**) are in agreement with a *cis* relationship. Moreover the *endo* and *exo* protons at position 4 in the *anti* adducts (**2**) absorbed at the same field in both $CDCl_3$ and C_6D_6 solutions. In contrast the corresponding hydrogens in the *syn* adducts (**3d** and **e**) gave rise to two signals separated by 0.52 p.p.m. in $CDCl_3$ solution, with the *exo* protons resonating at higher field than the *endo* protons. On passing to C_6D_6 the chemical-shift difference increased to 0.81 for (**3d**) and to 0.90 p.p.m. for (**3e**) due to the fact that *exo* protons are more efficiently solvated and consequently their absorptions more shifted to higher fields than the sterically crowded *endo* protons. Finally, in agreement with the expected dipole moments for *syn* adducts, which are higher than those of the corresponding *anti* adducts,[13] the former compounds showed a lower R_F value on t.l.c. than the latter.

To establish the behaviour of compounds (**1**) unequivocally [in particular that of (**1b** and **d**)] towards 1,3-dipoles, we reasoned that it would be necessary to react these compounds with a 1,3-dipole quite different from 'electron rich' diazomethane. Thus we carried out the reaction of (**1**) with the 'electron poor' phenylglyoxylonitrile oxide. The 1,3-dipole was generated *in situ* in ether at room temperature from phenyl-

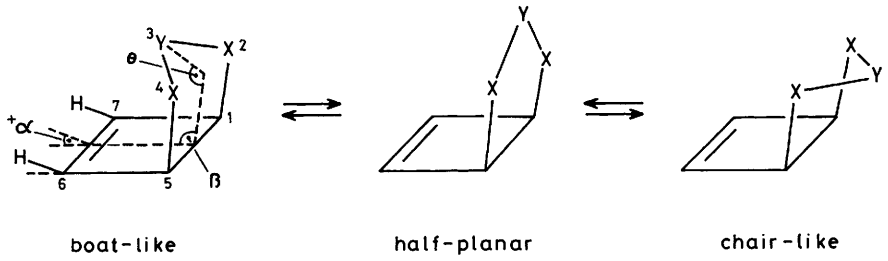


Figure 2.

Table 1. ^{1}H N.m.r. [δ($CDCl_3$)] data for compounds (**2**) and (**3**), and in parentheses Δδ = δ($CDCl_3$) − δ(C_6D_6)[a,b]

Compound	1-H	4-*endo*-H	4-*exo*-H	7-H	6-H	5-H	$J_{1,7}$	$J_{5,6}$
(**2a**)	4.72, dd (0.32)	4.55, m (0.35)		2.62, m (0.30)	1.25—2.25		<2.0	
(**2b**)[c]	5.22, m (0.42)	4.60, m (0.68)		4.42, d (0.20)	4.05, dd (0.55)	2.38, m (0.78)	0.5	2.0
(**2d**)[d]	5.35, m (0.26)	4.55, m (0.63)		4.48, d (0.25)	4.11, dd (0.56)	2.35, m (0.58)	0.5	1.5
(**3d**)[e]	5.39, m (0.59)	4.92, dt (0.13)	4.40, ddd (0.42)	5.05, dt (0.60)	4.60, dt (0.62)	2.61, m (0.91)	5.5	5.5
(**2e**)[f]	5.70, br, d (1.03)	4.82, m (1.28)		4.95, d (1.10)	4.56, dd (1.51)	3.00, m (1.40)	0.5	1.8
(**3e**)[g]	5.75, m (1.30)	5.17, m (1.65)	4.65, dd (1.03)	5.52, dt (1.50)	5.15, dt (1.62)	3.08, m (1.73)	6.0	6.0

[a] *J* in Hz. [b] $J_{5,7}$ and $J_{1,6}$ <0.5 Hz and $J_{1,5}$ *ca.* 6.0 Hz in compounds (**2**). [c] δ($CDCl_3$) 5.08 and 5.32 (br, 2 s, OCH_2O); $J_{6,7}$ 5.0 Hz. [d] δ($CDCl_3$) 1.28 and 1.61 (2 s, Me); $J_{6,7}$ 5.5 Hz. [e] δ($CDCl_3$) 1.20 and 1.38 (2 s, Me); $J_{4\text{-}endo,1}$ 3.0, $J_{4\text{-}exo,1}$ 1.5, $J_{4\text{-}endo,4\text{-}exo}$ 18.0, $J_{4\text{-}exo,5}$ 9.0, $J_{4\text{-}endo,5}$ 3.0, $J_{1,6}$ 2.5, $J_{5,7}$ 2.5, $J_{6,7}$ 5.5 Hz. [f] $J_{6,7}$ 5.8 Hz. [g] $J_{4\text{-}endo,1}$ 3.0, $J_{4\text{-}exo,1}$ 1.0, $J_{4\text{-}endo,4\text{-}exo}$ 19.0, $J_{4\text{-}exo,5}$ 9.0, $J_{4\text{-}endo,5}$ 3.0, $J_{1,6}$ 2.5, $J_{5,7}$ 2.5, $J_{6,7}$ 6.0 Hz.

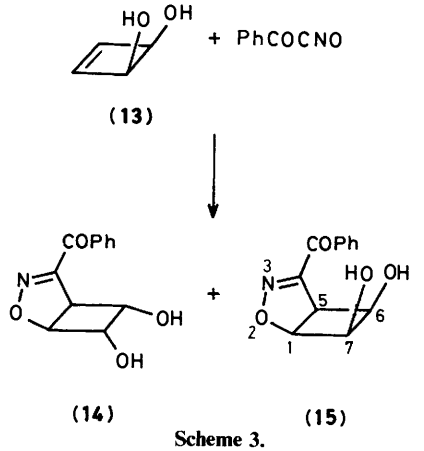
Table 2. ^{1}H N.m.r. data for compounds (**4**), (**5**), (**14**), and (**15**)[a,b]

Compound	Solvent	1-H	6-, 7-H	5-H	$J_{1,7}$	$J_{5,6}$
(**4a**)	C_6D_6	4.18, dd	2.67, br, d	3.25, dd	1.5	1.8
(**4b**)[c]	$CDCl_3$	5.02, d	4.75, m	4.15, br, d	<0.5	0.5
(**4c**)	$CDCl_3$	4.90, dd	3.30, m	4.00, dd	2.0	1.5
(**5c**)	$CDCl_3$	5.35, m	3.43, m	4.45, m	*d*	*d*
(**4d**)[e]	C_6D_6	4.68, dd	4.39, m	3.87, br, d,	1.0	1.0
(**5d**)[f]	$CDCl_3$	5.00, m	4.86, m	4.62, m	*d*	*d*
(**4e**)	$CDCl_3$	5.42, d	5.20, m	4.70, d	<0.5	<0.5
(**5e**)	$CDCl_3$	5.28, m		4.92, m	*d*	*d*
(**14**)[g]	$CDCl_3$	5.20, dd	4.55, m	4.12, br, d	2.5	0.5
(**15**)[h]	$CDCl_3$	5.20, m	4.60, m		*d*	*d*

[a] *J* in Hz. [b] $J_{1,6}$ and $J_{5,7}$ <0.5 Hz and $J_{1,5}$ *ca.* 7.5 Hz in *anti* adducts (**4**). [c] δ($CDCl_3$) 5.10 and 5.35 (2 s, OCH_2O). [d] In the case of *syn* adducts (**5**) and (**15**) strong couplings between cyclobutyl protons give rise to extensive second-order effects. As a result we could not evaluate coupling constants from the very complex signals of these protons. [e] δ(C_6D_6) 1.05 and 1.40 (2 s, Me). [f] δ($CDCl_3$) 1.25 and 1.45 (2 s, Me). [g] δ($CDCl_3$) 1.60 (br, s, OH); $J_{1,5}$ 9.0 Hz. [h] δ($CDCl_3$) 1.60 (br, s, OH).

glyoxylohydroximic acid chloride and triethylamine. Once again we isolated only *anti* adducts from the reactions of (**1a** and **b**) and *syn–anti* mixtures from the reactions of (**1c—e**). The reaction of phenylglyoxylonitrile oxide with (**1c**) was also carried out under different conditions (the 1,3-dipole was generated *in situ* by heating the hydroximic acid chloride in toluene at 110 °C)[14] to give higher yields of adducts with a similar *syn–anti* ratio (*anti:syn* 81:19 *versus* 87:13 at room temperature).

syn and *anti* structures were assigned on the basis of ^{1}H n.m.r. data (Table 2), behaviour on t.l.c. (lower R_F values for *syn* adducts), and chemical correlation. The reaction of phenylglyoxylonitrile oxide with *cis*-3,4-dihydroxycyclobutene[2c] (**13**) afforded a mixture of *anti* (**14**) and *syn* (**15**) adducts (*anti:syn* 13:87 in refluxing toluene) (Scheme 3). Then carbonyldioxy derivatives (**4e**) and (**5e**), respectively, were easily obtained by treating compounds (**14**) and (**15**) with carbonyldi-imidazole.



Scheme 3.

Table 3. Theoretical structural parameters[a] (MO–SCF, 4-31G//4-31G) of bicyclo[3.2.0]hept-6-enes (**1**) and experimental ratios for the cycloadditions of compounds (**1**) with diazomethane and phenylglyoxylonitrile oxide

	β	θ	ΔE[b]	α	*anti*:*syn* CH_2N_2	*anti*:*syn* PhCOCNO
$(\mathbf{1a})_{boat}$	115.8	143.9	5.2	+0.9	100:0[c]	100:0
$(\mathbf{1a})_{chair}$	118.6	213.0		+0.4		
(**1b**)	116.0 .	152.8	2.1	+0.2	100:0	100:0
(**1c**)	115.5	158.3	0.9	+0.8		87:13[d]
(**1d**)	116.7	169.0	0.3	−0.2	60:40	87:13
(**1e**)	114.3	174.3	0.1	+0.5	64:36[c]	66:34

[a] Angles in degrees. [b] Relative energy of the half-planar form (θ 180°) (kcal mol^{-1}). [c] Ref. 1. [d] *anti*:*syn* 81:19 in toluene at 110 °C

Moreover, the *anti* adducts (**4b** and **d**) were hydrolysed to give (**14**), while the *syn* adduct (**5d**) gave (**15**).

The results obtained with phenylglyoxylonitrile oxide neatly parallel those with diazomethane thus clearly showing that the five dipolarophiles tend to impose their own stereochemical demand: *anti* attack for (**1a** and **b**) and mixtures for (**1c—e**) (Table 3).

As far as we know, only the structure of (**1a**) has been experimentally and theoretically investigated. The chair-like structure, given on the grounds of electron diffraction data,[15] has been disproved on the basis of microwave[16] and low-frequency vibrational spectra.[17] Molecular mechanics[18] support the boat form as the highly preferred conformation of (**1a**).

We faced the problem by means of *ab initio* MO-SCF (4-31G) calculations carried out by the use of the Gaussian 82 package.[19] Geometry optimizations were performed with the gradient method (standard convergence criteria, Berny algorithm) implemented in the package and were constrained by C_s symmetry and by fixing C=C, C(sp^3)–H, C(sp^2)–H bond lengths to the standard values, 1.342, 1.094, and 1.083 Å, respectively.

The compounds (**1b—e**) show a single stable conformation which is a boat-like one.* Compound (**1a**) also shows a second stable chair-like conformation at a relative energy of 3.8 kcal mol^{-1}, with an energy barrier of 5.5 kcal mol^{-1} (4-31G//4-31G). Neither higher-level energy calculations (6-31G*//4-31G, 3.6, 5.7 kcal mol^{-1}), nor electron correlation introduced *via* third-order Möller–Plesset perturbation (6-31G*/MP3//4-31G, 3.9, 5.5 kcal mol^{-1}) significantly modify those values. It is worth noting that both the structure of (**1a**) and the above energy difference are fairly well supported by experimental results.[17]

The higher stability of the boat-like conformation is due to the complete staggering of bonds in the penta-atomic ring, whereas in the chair form eclipsing occurs along the C(1)–C(2) and C(4)–C(5) bonds.

The most important structural results are reported in Table 3 together with the experimental ratios of the cycloaddition reactions.

The values of the dihedral angle θ show that the boat-like form becomes flatter and flatter on passing from (**1a**) to (**1e**), which causes a progressive lessening of the steric hindrance to *syn* attack; moreover, as the relative energy of the half-planar form (ΔE) decreases steeply, the residual hindrance on the *syn* face, due to the boat-like conformation, can be overcome with only few tenths of a kcal mol^{-1} for compounds (**1c—e**). Yet, the *endo*-hydrogen atom at C(3) in (**1a** and **b**), and even more the methyl group at the same position in (**1d**) can hinder the *syn* face even in the half-planar form but not in a form with θ 195°. The energy required to reach a form with θ 195° is only 1 kcal mol^{-1} in (**1d**), 3.1 kcal mol^{-1} in (**1b**), and amounts to a barrier energy (θ 185°, 5.5 kcal mol^{-1}) in (**1a**).

The out-of plane bending (α) of the olefinic C–H bonds is small in all cases. The dihedral angle β does not show any important variations within this series of compounds, but the indications are that the smaller this angle, the larger is the *syn* bending of the olefinic hydrogens with respect to the cyclobutene plane;† also oxygen substitution in the X position opposes *syn* bending and can produce sign reversal.

The equilibrium abundance of the chair-like form of (**1a**) ought to be <0.1% at room temperature and the structures of the two forms with quite similar α values do not suggest appreciable differences in the intrinsic reactivity of their double bonds. Accordingly, the selectivity of the cycloaddition to (**1a**) should be discussed on the basis of its boat-like conformation leading to *anti* adducts, mostly for steric reasons. Steric hindrance is also responsible for the *anti* selectivity in the cycloaddition of (**1b**). Compounds (**1c—e**), owing to their boat-like conformation being flat, and even more to the ease with which they relieve hindrance, can undergo detectable *syn* attack.

Conclusions.—According to the results reported, the selectivity of the cycloaddition reactions of compounds (**1**) should be discussed on the basis of boat-like conformations which, however, show highly different hindrance to *syn* attack.

Steric screening appears to be the most important factor dictating *anti* selectivity for (**1a** and **b**), whereas calculations show that the *syn* face is easily accessible to the partner reagent in (**1c—e**). The concomitant feature of low pyramidalizations (small α) legitimates the mixtures of adducts for the latter compounds.

If pyramidalization, and the related out-of-plane distortion asymmetry, were to have a role in favouring the attack at one of the two faces of compounds (**1**) it would be that of reinforcing the *anti* orientation in the reactions of (**1a**) and slightly limiting the equivalence of the two faces, again in favour of the *anti* face, in (**1c** and **e**).

Further experimental and computational data on the factors (out-of-plane bending, steric and electrostatic factors, hydrogen bonding effects, and charge-transfer interactions) which govern face selectivity in cycloadditions will be reported shortly.

Experimental

M.p.s are uncorrected. Elemental analyses were made on a Carlo Erba CNH analyser, model 1106. I.r. spectra were measured on a Perkin-Elmer 157 spectrophotometer. ^1H and ^{13}C n.m.r. spectra were recorded on a Bruker WP80SY spectrometer (operating at 80 and 20.2 MHz) with Me_4Si as internal standard. Mass spectra were measured on a Finnigan MATT 8222 using electron impact and chemical ionization modes. G.l.c. analyses were carried out with a Dani 6500, PTV injector, RSL 200 BP (25 m) capillary column, carrier H_2. Thin-layer chromatography was carried out on plates precoated with Silicagel 60 GF_{254} (Merck). Spots of all of the compounds [with the exception of (**1a**, **b**, and **d**)] could be detected by spraying

* A dominance of boat-like over chair-like conformation in (**1e**) was previously suggested on qualitative grounds.[2b] However, in the light of present results the steric crowding on the *syn* face of the boat-like conformation of (**1e**) was overestimated.

† The experimental geometry of (**1a**) of ref. 15 assumed in our preliminary work[1] led to a large *syn* bending (α 5.13°), and to the conclusion that pyramidalization could explain, *per se*, the *anti* selectivity of (**1a**). The structural feature most responsible for such a high *syn* bending was the very small value of the β dihedral angle (104°) given in the experimental geometry of ref. 15.

Table 4. Physical and analytical data for compounds (**2**)—(**5**), (**14**), and (**15**)

Compound	Yield[a] (%)	Solvent[b]	(M.p./°C)	Elemental analysis (%) Found (Required) C	H	N
(**2a**)[c,d]	70	Oil				
(**2b**)	65	Cyclohexane	45—46	51.3 (51.4)	5.9 (5.8)	20.0 (20.0)
(**2d**)	49	Light petroleum[e]	69—71	57.0 (57.1)	7.2 (7.2)	16.6 (16.6)
(**3d**)	33	Cyclohexane	79—81	57.1 (57.1)	7.2 (7.2)	16.6 (16.6)
(**2e**)	53	Methanol	121—122	46.8 (46.8)	3.9 (3.9)	18.2 (18.2)
(**3e**)	30	Methanol	124—126	47.0 (46.8)	4.0 (3.9)	18.5 (18.2)
(**4a**)	68	Light petroleum[e]	61—62	74.9 (74.7)	6.2 (6.3)	5.9 (5.8)
(**4b**)[d]	58	Cyclohexane	102—103	63.8 (63.7)	4.4 (4.5)	5.7 (5.7)
(**4c**)[d]	29[f]	Cyclohexane	115—116	70.5 (70.6)	5.0 (5.1)	5.6 (5.5)
(**5c**)[d]	4[f]	Cyclohexane	82—84	70.4 (70.6)	5.0 (5.1)	5.7 (5.5)
(**4d**)	59	Light petroleum[e]	87—88	65.6 (65.9)	5.4 (5.5)	5.1 (5.1)
(**5d**)	9	Cyclohexane	139—141	65.7 (65.9)	5.4 (5.5)	5.1 (5.1)
(**4e**)	34	Methanol	165—166	60.4 (60.2)	3.5 (3.5)	5.5 (5.4)
(**5e**)	17	Methanol	144—146	60.4 (60.2)	3.5 (3.5)	5.5 (5.4)
(**14**)	8[g]	Benzene[h]	113—115	62.1 (61.8)	4.8 (4.7)	6.1 (6.0)
(**15**)	51[g]	Benzene	116—118	62.0 (61.8)	4.8 (4.7)	6.1 (6.0)

[a] Yields of isolated products are given. [b] Needles unless specified. [c] (**2a**), $\delta_C(CDCl_3)$ 25.6 (C-8), 31.6, 32.2, 32.5 (C-6, -7, -9), 44.4, 44.7, (C-5, -10), 84.6 (C-4), and 90.9 p.p.m. (C-1). [d] Mass spectra: (**2a**), *m/z* 136 (M^+, 20%), 108 (17, $M - N_2$), 93 (84), 91 (41), 79 (92), 77 (47), 69 (63), and 67 (100); (**4b**), *m/z* 246 ($M + 1^+$, 100), 174 (34), and 105 (17); (**4c**), *m/z* 255 (M^+, 2%), 174 (55), 105 (100), 77 (51); (**5c**), *m/z* 255 (M^+, 1.5%), 174 (30), 105 (100), and 77 (45). [e] Prisms. [f] (**4c**) = 59% and (**5c**) = 14% in toluene at 110 °C. [g] In toluene at 110 °C. [h] Leaflets.

with 3% chromic oxide in sulphuric acid (50%) followed by heating at 120 °C. Compounds (**4**)—(**12**), (**14**), and (**15**) could also be revealed under u.v. light (254 nm). Column chromatography were performed with Silicagel 60 (70—230 mesh) Merck eluting with cyclohexane–ethyl acetate mixtures.

cis-*Hydroxylation of* (**6**).—A mixture of dimethyl tricyclo[4.2.2.0^{2,5}]deca-3,7,9-triene-7,8-dicarboxylate (**6**)[11] (9.7 g, 39 mmol), *N*-methylmorpholine *N*-oxide·2H_2O, OsO_4 (2.1 ml of a 2.5% solution in t-butyl alcohol), water (18 ml), and acetone (24 ml) was stirred at room temperature for seven days. Na_2SO_3 (450 mg) in water (3 ml) was added, the solution was neutralized, and then extracted with ether and ether–ethyl acetate. The extracts were dried and evaporated to dryness. Chromatography on silica gel with cyclohexane–ethyl acetate (70:30) as eluant yielded (**6**) (1.6 g, 16%), and a mixture of (**7**) and (**8**) [oil, 6.0 g, 54%; (**7**):(**8**) 1:2]: (**7**), $\delta(CDCl_3)$ 2.40 (2 H, m, 2-, 5-H), 2.85 (2 H, br, s, OH), 3.54 (2 H, m, 1-, 6-H), 3.78 (6 H, s, CO_2Me), 4.20 (2 H, m, 3-, 4-H), and 6.53 (2 H, m, 9-, 10-H); (**8**), $\delta(CDCl_3)$ 2.78 (2 H, m, 2-, 5-H), 3.05 (2 H, br, s, OH), 3.47 (2 H, m, 1-, 6-H), 3.83 (6 H, s, CO_2Me), 4.20 (2 H, m, 9-, 10-H), and 6.40 (2 H, s, 3-, 4-H).

Preparation of (**9**) *and* (**10**).—A solution of the diol mixture (**7**) + (**8**) (1.5 g, 5.4 mmol) in water (6 ml) was mixed with glacial acetic acid (15 ml); paraformaldehyde (3 g) was then added, followed by cautious addition, with stirring, of sulphuric acid (*d* 1.84; 0.85 ml). The solution was heated at 75 °C for 1 h, was cooled, water (15 ml) was added, and the liquor was extracted with CH_2Cl_2 (3 × 15 ml). The combined methylene dichloride extracts were neutralized with $NaHCO_3$, and then washed with water. The organic solution was dried and evaporated to dryness. Chromatography on silica gel with cyclohexane–ethyl acetate (80:20) as eluant yielded a mixture of (**9**) and (**10**) [oil, 753 mg, 48%; (**9**):(**10**) 1:2]. Pure samples of (**9**) and (**10**) could be isolated by careful chromatography with a less polar eluant: (**9**), glassy solid, $\delta(CDCl_3)$ 2.39 (2 H, m, 2-, 5-H) 3.80 (6 H, s, CO_2Me), 4.00 (2 H, s, 1-, 6-H), 4.25 (2 H, m, 3-, 4-H), 4.92 and 5.27 (2 H, 2 s, OCH_2O), and 6.58 (2 H, m, 9-, 10-H); (**10**), m.p. 84—85 °C (prisms from cyclohexane), $\delta(CDCl_3)$ 2.82 (2 H, m, 2-, 5-H), 3.68 (2 H, m, 1-, 6-H), 3.83 (6 H, s, CO_2Me), 4.40 (2 H, m, 9-, 10-H), 4.55 and 4.97 (2 H, 2 s, OCH_2O), and 6.42 (2 H, s, 3-, 4-H).

Preparation of (**11**) *and* (**12**).—A solution of the diol mixture (**7**) + (**8**) (3 g, 10.8 mmol), toluene-*p*-sulphonic acid (0.18 g), and 2,2-dimethoxypropane (46 ml) in acetone (30 ml) was stirred at room temperature for 3 days. The solution was concentrated under vacuum to 30 ml, then basified with 10% aqueous $NaHCO_3$, the liquor was extracted thrice with CH_2Cl_2, and the extracts were dried and evaporated to dryness. Chromatography on silica gel with cyclohexane–ethyl acetate (80:20) as eluant yielded a mixture of (**11**) and (**12**) [oil, 2.94 g, 85%; (**11**):(**12** 1:2]. Careful column chromatography with a less

polar eluant allowed us to isolate pure samples of (**11**) and (**12**): (**11**), m.p. 65—67 °C (prisms from cyclohexane), δ($CDCl_3$) 1.25 and 1.52 (6 H, 2 s, MeCMe), 2.48 (2 H, m, 2- 5-H), 3.80 (6 H, s, CO_2Me), 4.03 (2 H, br, s, 1-, 6-H), 4.20 (2 H, m, 3-, 4-H), 6.50 (2 H, m, 9-, 10-H); (**12**), m.p. 93—94 °C (prisms from cyclohexane), δ($CDCl_3$) 1.25 and 1.34 (6 H, 2 s, MeCMe), 2.80 (2 H, m, 2- 5-H), 3.60 (2 H, m, 1-, 6-H), 3.85 (6 H, s, CO_2Me), 4.52 (2 H, m, 9-, 10-H), and 6.40 (2 H, s, 3-, 4-H).

Preparation of (**1b** *and* **d**).—Compounds (**9**) and (**11**) [or their mixtures with (**10**) and (**12**), respectively] were heated in a distillation flask at 180 °C under atmospheric pressure for 1 h while the products, (**1b**),[20] oil (32%), δ($CDCl_3$) 5.07 (1 H, m, 3-H), 5.15 (2 H, m, 1-, 5-H), 5.34 (1 H, m, 3-H), 6.25 (2 H, m, 6-, 7-H) and (**1d**), oil (40%), δ($CDCl_3$) 1.40 (3 H, s, 3-Me), 1.55 (3 H, s, 3-Me), 5.25 (2 H, m, 1-, 5-H), and 6.52 (2 H, m, 6-, 7-H), respectively, were removed from the distillation flask with a slow stream of nitrogen and collected in a cold trap at −78 °C free from dimethyl phthalate.

A mixture of *cis*-3,4-dihydroxycyclobutene (**13**) (200 mg, 2.32 mmol), tetraethylammonium bromide (93 mg, 0.44 mmol), methylene dibromide (20 ml), and 50% aqueous sodium hydroxide (20 ml) is vigorously stirred at room temperature for 2 days. Then, the organic phase is separated, dried over magnesium sulphate, and treated with an excess of ethereal solution of diazomethane. After 24 h the solvent was evaporated off; chromatography on silica gel with cyclohexane–ethyl acetate (80:20) as eluant yielded (**2b**) [50 mg, 15% from (**13**)].

A solution of *cis*-3,4-dihydroxycyclobutene (**13**) (100 mg, 1.16 mmol), toluene-*p*-sulphonic acid (12.5 mg), and 2,2-dimethoxypropane (3.3 ml) in acetone (3 ml) was stirred at room temperature for 2 days; then an excess of ethereal solution of diazomethane was added. After 24 h, the solvent was evaporated; chromatography on silica gel with cyclohexane–ethyl acetate (80:20) as eluant yielded (**2d**) [185 mg, 47% from (**13**)] and (**3d**) [122 mg, 31% from (**13**)].

Cycloaddition Reactions.—The cycloaddition reactions of compounds (**1**) (*ca.* 300 mg) with diazomethane were carried out in ether by using a large excess of the 1,3-dipole. The reaction mixtures were kept at room temperature for 48 h in the case of (**1a**) and for ≤5 h in the case of (**1b**, **d**, and **e**). Then the solvent was evaporated off and the residue column chromatographed with cyclohexane–ethyl acetate (90:10—70:30) as eluant. Careful ^{13}C n.m.r. [in the case of (**1a**)], ^1H n.m.r. and g.l.c. analysis of the crude product from the reactions of (**1a** and **b**) showed the presence of only one adduct. The *syn*:*anti* ratio for the reaction of (**1d**) was also evaluated by ^1H n.m.r. analysis.

The cycloaddition reaction of phenylglyoxylonitrile oxide with compounds (**1**) were carried out according to methodology of Huisgen and/or Grunanger.[14]

(i) To a solution of the dipolarophile (*ca.* 300 mg) in anhydrous ether (3 ml) and phenylglyoxylohydroximic acid chloride (10% excess), triethylamine (10% excess) in ether (5 ml) was added dropwise with stirring during 2 h. After a further 10—20 h the mixture was washed with water, the organic solution was dried, evaporated to dryness, and the residue column chromatographed with cyclohexane–ethyl acetate (90:10—60:40) as eluant. Apart from the adducts, minor amounts of products deriving either from decomposition or from dimerization of the nitrile oxide were isolated. Larger amounts of these compounds (*ca.* 40%) were obtained from the reaction of (**1c**).

(ii) A solution of the dipolarophile (*ca.* 300 mg) and phenylglyoxylohydroximic acid chloride (10% excess) in toluene (5 ml) was heated at 110 °C for 2 h. Evaporation of the solvent and column chromatography of the residue allowed the isolation of the adducts and of small amounts (≤5%) of by-products.

Both the pyrazolines and the isoxazolines proved stable under reaction and work-up conditions.

I.r. data are in agreement with the proposed structures. In particular, the N=N stretching absorption (ν 1 530 cm^{-1}) is present in the spectra of compounds (**2**) and (**3**), and the C=O stretching absorption (ν 1 640—1 650 cm^{-1}) in the spectra of compounds (**4**), (**5**), (**14**), and (**15**).

Yields, physical data, and elemental analysis of compounds (**2**)—(**5**), (**14**), and (**15**) are given in Table 4, together with ^{13}C n.m.r. data for compound (**2a**), and mass spectra for compounds (**2a**), (**4b**), (**4c**), and (**5c**).

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