

syn-anti Selectivity in Cycloadditions. Part 4.¹ 1,3-Dipolar Cycloadditions of Nitrones with Polychloronorbornadienes

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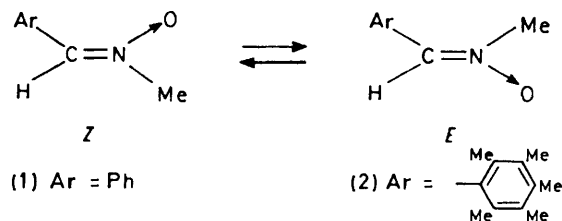
Cyclic and acyclic nitrones reacted smoothly with 1,2,3,4-tetrachloro-, 1,2,3,4,7-pentachloro-, and 1,2,3,4,7,7-hexachloro-norbornadienes to give *syn* and *anti* methylene adducts in varying ratios. The structures of the adducts were assigned on the basis of spectroscopic (¹H n.m.r.) and chemical evidence. The *syn* : *anti* ratios found are interpreted on the basis of steric and stereo-electronic effects in the cycloaddition transition states. Comparison between the results of the reactions of the *E* and *Z* isomers of *C*-pentamethylphenyl-*N*-methylnitronone with those of (*Z*)-*C*-phenyl-*N*-methylnitronone, respectively, suggests that the latter 1,3-dipole might be in equilibrium with the *E* isomer even at room temperature.

THE aim of the present paper was to explore *syn-anti* isomerism in 1,3-dipolar cycloadditions to two diastereotopic faces of dipolarophiles and, meanwhile, to provide evidence for *E* ⇌ *Z* interconversion in acyclic nitrones.²

As regards the former point, it is already known that substituents at position 7 of norbornadiene affect the *syn-anti* selectivity † of both 1,3-dipoles^{3,4} and dienes⁵ in their addition to the double bonds of model compounds. We resumed the study of this problem, choosing polychloronorbornadienes with a chlorine atom at position 7 as the most suitable model for such a study.

It is of interest to note that, although the problem has been the subject of several studies, the *E* ⇌ *Z* conversion of nitrones is still an open question.² It is reported in the literature, for instance, that *C*-phenyl-*N*-methylnitronone (1) is isolable in the most stable *Z* configuration but it was inferred that the *E* isomer, although never detected, is present in solutions at temperatures ≥ 80 °C.⁶ The latter isomer is thought to be much more reactive than the former in 1,3-dipolar cycloadditions.

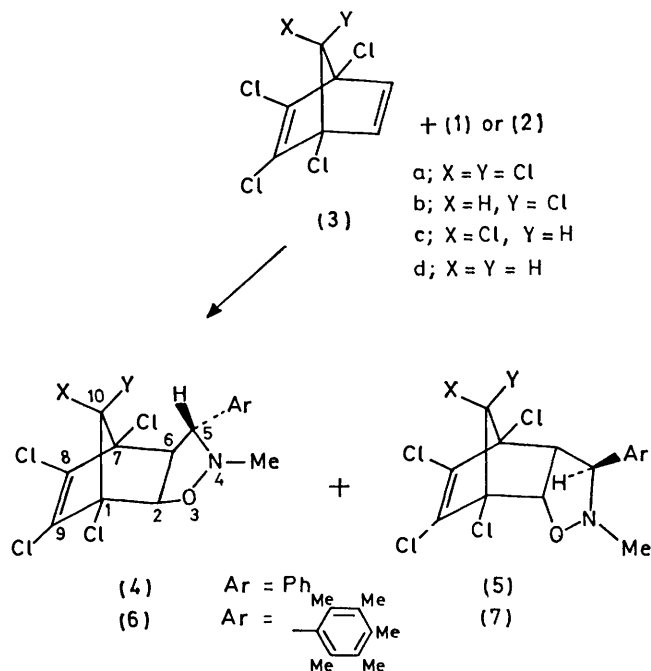
In the case of *C*-pentamethylphenyl-*N*-methylnitronone (2), both the *E* and *Z* isomers were isolated.⁷ Δ*G*[‡] Values for the interconversion *E* ⇌ *Z* of compounds (2*E*) and (2*Z*) were measured (147 °C) and were found to be 33.1 and 34.1 kcal mol⁻¹ respectively. The interconversion is catalysed by benzoic acid, as shown by the Δ*G*[‡] values of 23.9 and 25.4 kcal mol⁻¹ found at 64 °C for the same



process in the presence of a trace of benzoic acid. It is important to note that the energies required by such interconversions are close to the Δ*G*[‡] (25.4 kcal mol⁻¹ at

† In the present paper, the prefixes *syn* and *anti* are utilized instead of *exo* and *endo* according to our recent terminology.² In the *syn* addition the formation of the heterocyclic ring proceeds on the same side of the methylene bridge; conversely *anti* addition develops on the opposite side.

85 °C) found for the cycloaddition of ethyl crotonate and *C*-phenyl-*N*-methylnitronone (1).⁸ Thus, it can be inferred that the energy requirements of cycloadditions of



C-phenyl-*N*-methylnitronone and related compounds are such that they may undergo *Z* ⇌ *E* isomerization in competition with cycloaddition.

We thought we could obtain more information on this problem by comparing the results of the reactions of nitrones (1*Z*), (2*E*), (2*Z*), and cyclic nitrones with dipolarophiles (3).

RESULTS

The reactivity of the nitrone (2*Z*) towards compounds (3a)–(3d)⁹ is low. In ether no reaction occurred either at room temperature or by heating under reflux; furthermore the isomeric nitrone (2*E*) was never detected. Positive results were obtained by heating benzene solutions under reflux for >5 d, to yield the *syn*-adducts (6) and *anti*-adducts (7) (see Table 1). Monitoring the progress of the cycloadditions by t.l.c. allowed the detection of the nitrone

TABLE 1

syn-anti Cycloadduct composition from the reactions of nitrones (1), (2Z), and (8) with polychloronorbornadienes (3)

Nitrone	Olefin	<i>syn</i> -Adduct (%)	<i>anti</i> -Adduct (%)	Total yield (%)
(1)	(3a)	(4a) 0	(5a) 100	92
	(3b)	(4b) 0	(5b) 100	75
	(3c)	(4c) 56	(5c) 44	88
	(3d)	(4d) 100	(5d) 0	90
(2Z)	(3a)	(6a) 0	(7a) 100	90
	(3b)	(6b) 0	(7b) 100	88
	(3c)	(6c) 60	(7c) 40	90
	(3d)	(6d) 100	(7d) 0	92
(8)	(3a)	(9a) 0	(10a) 100	90
	(3c)	(9c) 85	(10c) 15	87
	(3d)	(9d) 100	(10d) 0	87

(2E), its formation in the latter reaction conditions thus being proved. The nitrone (2E) was more reactive than (2Z), and it reacted with (3a) and (3d) in ether at room temperature in the presence of triethylamine. The adducts obtained, after 20 d, were *anti*-(7a) and *syn*-(6d), identical to the same products isolated from the reactions of (2Z). The low yields (*ca.* 20%) found are due to the easy conversion of (2E) to (2Z), the latter isomer being unreactive under the reaction conditions used. The nitrone (2Z) is easily recovered in high yields from the mixture due to its low solubility. The presence of triethylamine causes a reduction in the rate of isomerization.

C-Phenyl-*N*-methylnitrone (1) was treated with the dipolarophiles (3a)–(3d) under two different reaction conditions. In boiling ether, adducts (4) and (5) were formed in very good yields (see Table 1) within 5 d, whereas at room temperature *ca.* 70% yields of (5a) and (4d) [from reaction of (1) with (3a) and (3d) respectively] were reached only after two months.

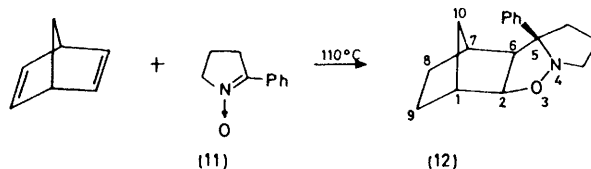
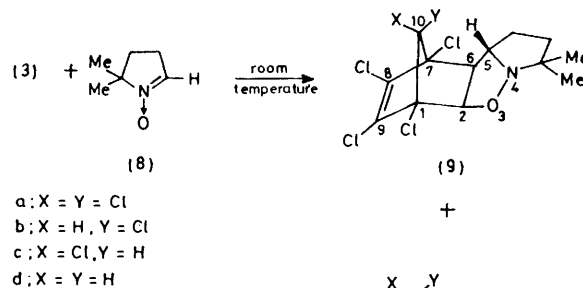
We then proceeded to study the reactivity of cyclic nitrones with this type of dipolarophile. 5,5-Dimethyl- Δ^1 -pyrroline *N*-oxide (8) ¹⁰ reacts easily with the dipolarophiles (3) in anhydrous benzene at room temperature (24 h) to give *syn* and *anti* adducts (9) and (10).

Different behaviour was found for 2-phenyl- Δ^1 -pyrroline *N*-oxide (11) ¹¹ which did not react with the dipolarophiles (3) even in boiling toluene. The 1,3-dipole was found to react with an excess of norbornadiene (110 °C, 4 d, 75% yield) to give the *syn*-methylene adduct (12). The structure of compound (12) was assigned on the basis of ¹H n.m.r. evidence; H-2 shows, in addition to $J_{2,6}$ 6.5 Hz, only coupling constants < 2.5 Hz.¹²

Assignments of *syn* structures for adducts (4d), (6d), and (9d) follow from a coupling constant of *ca.* 2 Hz (*W* coupling path) between the H-2 and 10-X (X = H) protons; conversely the absence of such a coupling in (5b) and (7b) indicates an *anti* relationship of the methylene bridge with respect to the heterocyclic ring. Additional evidence in favour of these structural assignments comes from the aromatic solvent-induced shift found for the H-10 proton of adducts (4d), (6d), and (9d). The shift observed was in fact larger for H-10X (>0.35 p.p.m.) than for H-10Y (Y = H) (<0.25 p.p.m.) (Table 2), as might be expected from the more difficult solvation of the sterically less accessible Y proton. The structures of adducts (5c), (7c), (10c), (4c), (6c), and (9c) were assigned in the same way.

For the first three compounds a shift >0.67 p.p.m. for H-10Y indicates an *anti* relationship between the methylene

bridge and the heterocyclic nucleus while for the others a value < -0.08 p.p.m. was in favour of a *syn* arrangement. The structures of the adducts from (3a) have been assigned by analogy with those of the adducts from (3b).



Configuration at the chiral centre 5 of adducts has been defined by the completely stereoselective synthesis of the

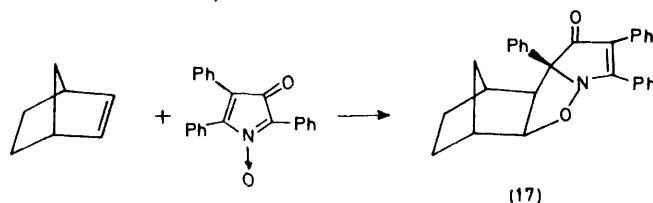
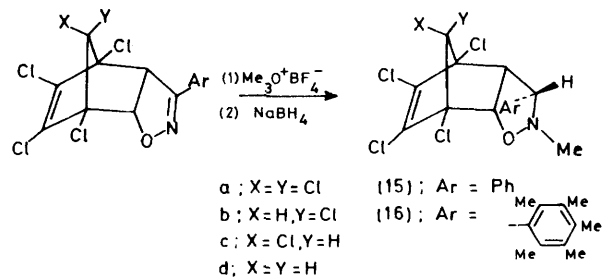
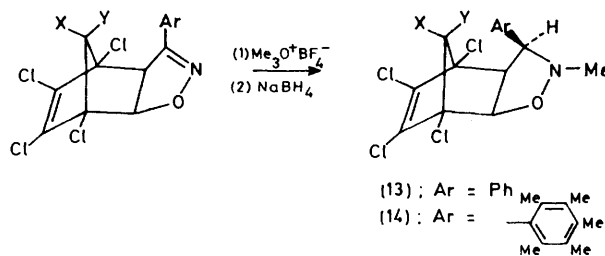


TABLE 2

¹H N.m.r. [$\delta(\text{CDCl}_3)$] data and (in parentheses) $\Delta\delta [= \delta(\text{CDCl}_3) - \delta(\text{C}_6\text{D}_6)]$ for compounds (4)—(16) ^{a,b}

Compounds	H-2	H-5	H-6	H-10Y	H-10X	$J_{2,6}$	$J_{2,10X}$	$J_{5,6}$
(4c)	4.55d (0.32)	3.71d (0.31)	3.25dd (0.34)	5.26s (-0.14)		7.0		6.0
(4d)	4.45dd (0.19)	3.51d (0.18)	3.06dt (0.21)	3.33d (0.22)	2.41dt (0.45)	6.5	2.0	6.5
(5a)	5.06d (0.18)	3.36d (0.03)	3.71t (0.10)			7.0		7.0
(5b)	5.13d (0.05)	3.40d (0.10)	3.80t (0.10)		4.27s (0.87)	7.0		7.0
(5c)	4.87m (0.53)	3.37m (0.10)	3.37m (0.58)	4.30s (0.90)		7.5		7.5
(6c)	4.75d (0.07)	4.30d (0.10)	3.60t (-0.08)	5.32s (-0.08)		7.0		7.0
(6d)	4.60dd (-0.03)	4.21d (0.01)	3.48dt (0.03)	3.45d (0.25)	2.55dt (0.50)	6.0	1.5	6.0
(7a)	5.18m (0.03)	4.08m (-0.05)	4.08m (-0.05)					
(7b)	5.20m (-0.08)	4.10m (-0.10)	4.10m (-0.10)		4.28s (0.88)			
(7c)	5.07d (0.37)	4.03d (0.03)	3.70t (0.30)	4.40s (1.03)		7.5		7.5
(9c)	4.31d (0.53)	3.88m (0.27)	3.08d (0.53)	5.80s (-0.19)		7.0		< 0.5
(9d)	4.28dd (0.40)	3.80m (0.05)	2.95dd (0.42)	3.70d (-0.10)	2.30dt (0.35)	6.0	2.0	< 0.5
(10a)	4.90d (0.42)	3.66m (0.21)	3.60d (0.40)			6.0		< 0.5
(10c)	4.66d (0.60)	3.66m (0.25)	3.15d (0.65)	4.00s (0.67)		7.5		< 0.5
(12)	4.25dt ^c (0.00)					6.0	1.0	
(13c)	4.36d (0.46)	3.85d (0.60)	3.28t (0.68)	5.90s (-0.10)		7.0		7.0
(13d)	4.25dd (0.30)	3.82d (0.49)	3.13dt (0.56)	3.84d (0.09)	2.21dt (0.31)	6.5	2.0	6.5
(14d)	4.30dd (0.20)	4.18d (0.06)	3.23dt (0.21)	4.10d (0.00)	2.20dt (0.10)	6.5	2.0	6.5
(15a)	5.05d (0.32)	3.93d (0.60)	4.16t (0.50)			6.5		6.5
(15b)	5.00d (0.25)	3.95d (0.62)	4.10t (0.45)		3.93s (0.80)	7.5		7.5
(15c)	4.88m (0.55)	3.83m (0.47)	3.83m (0.97)	4.11s (0.66)		7.5		7.5
(16a)	5.16m (-0.24)	4.30m (-0.25)	4.30m (-0.25) ^d					

^a J in Hz. ^b $J_{6,10X} = J_{2,10X}$. ^c $J_{1,2} = J_{2,10X}$. ^d $\delta(\text{CDCl}_3) - \delta(\text{pyridine})$.

epimeric series (13)—(16).¹³ The small aromatic-solvent-induced shift observed for H-5 of adducts (4)—(10) brings further support to the structural assignment. The configuration of C-5 of (12) has been assigned by analogy with the structure of the adduct (17).¹⁴

DISCUSSION

The polychloronorbornadienes (3) studied in the present paper were found to be more reactive dipolarophiles towards the nitron (1) than norbornadiene itself. Molar ratios being equal, C-phenyl-N-methylnitron (1) reacts with (3) at 35 °C in ether in 5 d, whereas with norbornadiene the reaction takes 8 d at 80 °C.⁶

The higher reactivity of compounds (3) can be explained on the basis of the frontier orbital approach. The electron-attracting chlorine atoms of (3) cause a lowering of the frontier orbital energies, with consequently a stronger LUMO(3)-HOMO(nitron) interaction (LUMO = lowest-unoccupied molecular orbital; HOMO = highest-occupied molecular orbital). It seems, therefore, that this effect is not compensated, in the case of norbornadiene, by the otherwise relevant interaction HOMO(3)-LUMO(nitron). Another notice-

able feature of the reactions studied is the effect of chlorine atom at position 7 of (3) on the orientation of the addends. Our results show that the chlorine atom occupying either the X or Y position of compounds (3) favours the approach of the 1,3-dipole on the *anti*-methylene side.

We consider the increased relative reactivity of the *anti* compared with that of the *syn* face on passing from (3d) to (3b) as being due mainly * to steric shielding of the *syn* face of the double bond. However, in the case of (3c) the different reactivity of the two faces can be better rationalized by the stereo-electronic arrangement depicted in (18).⁴ The antibonding orbital σ^* of the chlorine atom would contribute to the dispersion of the negative charge present in the dipolarophilic moiety only for an *anti* transition state (18). It is apparent that both effects are present in (3a).

The configuration of chiral centre 5 [see numbering of adduct (4) and (9)] found for the *syn* adducts may arise from two transition states: the first, as depicted in (19),

* We have evidence that there is also an increased reactivity of the *anti* face of (3b) compared with that of (3d).¹⁵

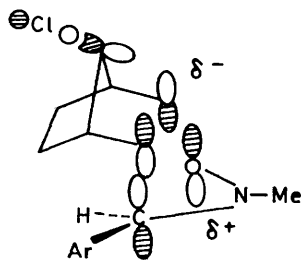
TABLE 3
Physical and analytical data for compounds (4)–(16)

Compound	Crystallization solvent	M.p. ($^{\circ}\text{C}$)	Found (%)			Formula	Required (%)		
			C	H	N		C	H	N
(4c)	Light petroleum ^a	100–102	44.9	3.1	3.6	C ₁₅ H ₁₂ Cl ₅ NO	45.0	3.0	3.5
(5c)	Light petroleum ^b	103–105	45.0	3.1	3.4				
(13c)	Light petroleum ^b	163–164	44.8	2.9	3.5				
(15c)	Light petroleum ^b	160–162	44.6	3.0	3.4				
(5b)	Light petroleum ^b	96–98	45.3	2.9	3.4				
(15b)	Light petroleum ^b	169–171	45.1	3.1	3.6	C ₁₆ H ₁₃ Cl ₄ NO	49.3	3.5	3.8
(4d)	Light petroleum ^b	133–135	49.4	3.4	3.7				
(13d)	Light petroleum ^{c,d}	86–88	49.6	3.6	3.8				
(5a)	Light petroleum ^{b,d}	83–85	41.3	2.4	3.4	C ₁₅ H ₁₁ Cl ₆ NO	41.5	2.5	3.2
(15a)	Viscous yellow oil		41.7	2.3	3.0				
(6c)	Ethyl acetate ^b	223–224	51.0	4.7	3.1	C ₂₀ H ₂₂ Cl ₅ NO	51.1	4.7	3.0
(7b)	Ethyl acetate ^b	205–206	51.4	4.5	2.9				
(7c)	Ethyl acetate ^b	220–222	51.2	4.6	3.1				
(6d)	Light petroleum ^a	207–209	55.4	5.1	3.3	C ₂₀ H ₂₃ Cl ₄ NO	55.2	5.3	3.2
(14d)	Light petroleum ^c	156–158	55.5	5.2	3.3				
(7a)	Light petroleum ^b	162–163	47.3	4.1	2.9	C ₂₀ H ₂₁ Cl ₆ NO	47.6	4.2	2.8
(16a)	Ethyl acetate ^c	205–206	47.2	4.0	2.9				
(9c)	EtOH ^c	180–182	41.0	3.6	3.8	C ₁₃ H ₁₄ Cl ₅ NO	41.4	3.7	3.7
(10c)	Viscous yellow oil		41.1	3.6	3.7				
(9d)	EtOH ^b	85–86	45.1	4.3	4.1				
(10a)	Light petroleum ^b	73–74	37.8	3.1	3.4	C ₁₃ H ₁₆ Cl ₄ NO	45.5	4.4	4.1
						C ₁₃ H ₁₃ Cl ₆ NO	37.9	3.2	3.4
(12)	Light petroleum ^b	77–79	80.3	7.3	5.8	C ₁₇ H ₁₉ NO	80.6	7.6	5.5

^a As needles. ^b As prisms. ^c As leaflets. ^d Yellow.

with an *endo* arrangement of the addends and with the (*Z*)-nitron, the second with the reactants in an *exo* disposition and with the (*E*)-nitron as shown in (20). The formation of the *anti* adducts can be explained analogously.

Clearly the reaction of nitron (2*E*) (reactive at room temperature) goes through the transition state (20). Such a transition state must also suit nitron (2*Z*),



(18)

which at low temperature (boiling ether) is unreactive, but which at higher temperatures (boiling benzene) enters cycloaddition as a consequence of the (*Z*)→(*E*) conversion. Since *C*-phenyl-*N*-methylnitron (1) reacts with compounds (3) at room temperature with the same stereochemical results as found for (2), it can be inferred that in this case (*Z*)→(*E*) conversion takes place at room temperature.

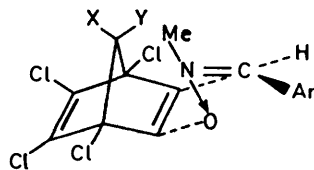
That the alternative arrangement (19) is not easily achieved by the reactants is proved by the reaction of the cyclic nitron (8) with (3), which give rise to the formation of adducts deriving only from transition states of the type (20). An additional point in favour of this thesis is represented by the behaviour of nitron (11), which adds to norbornadiene but is unreactive towards (3). The lack of reactivity of (11) with compounds (3), which are dipolarophiles more reactive than norbornadiene, is evidence of the steric compression present in the two possible arrangements (21) and (22).

In spite of these arguments, transition states such as (19) or (22) cannot be completely ruled out, as they have been described as operating in 1,3-dipolar¹⁶ and Diels-Alder¹⁷ cycloadditions. However, we consider the conversion (*1Z*)→(*1E*) to be the most plausible explanation of the results of the present study.

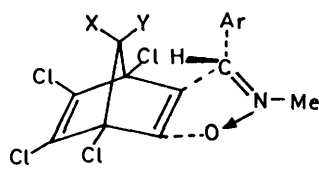
EXPERIMENTAL

N.m.r. spectra were recorded at 36 °C for solutions in CDCl₃ with a Varian A-60 (60 MHz) spectrometer (SiMe₄ as internal standard) by Mr. C. Bugatti. Reaction mixtures were analysed by t.l.c. on silica gel GF₂₅₄ (Merck) and the spots were detected after spraying with a 3% solution of chromic anhydride in sulphuric acid (50%) followed by charring at 120 °C.

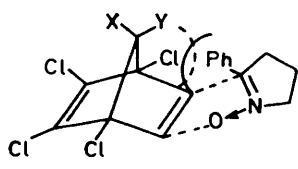
Nitrones (1), (2), and (8) were treated with an excess of the chloronorbornadienes (3) and the end of the reaction was established by the disappearance (t.l.c. analysis) of the 1,3-dipole. The quantitative analysis was carried out by column chromatography with Kieselgel H Merck [elution:



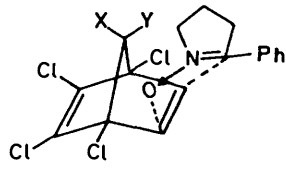
(19)



(20)



(21)



(22)

cyclohexane-ethyl acetate (95 : 5)]. Isomer ratios, reaction yields, and physical data are reported in Table 1 and 3. All adducts were found to be stable under the reaction conditions used.

The synthesis of compounds (13)—(16) was effected in high yield (>85%) starting from the related Δ^2 -isoxazolines¹⁸ by a standard procedure.¹³ T.l.c. and n.m.r. analysis of the crude reaction mixtures did not reveal the presence of the epimers (4)—(7).

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