Stereochemistry of the Diels–Alder Reaction: Effect of Diene Structure on *endo*-Selectivity

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Structures are assigned to adducts of cyclohexa-1,3-diene and spiro[2.4]hepta-1,3-diene with a number of dienophiles. Product ratios are determined, results are compared with reactions of cyclopentadiene, and it is concluded that the major steric interaction which controls *endo*-selectivity is that between substituents of the dienophile and the methylene hydrogens of cyclopentadiene and of cyclohexa-1,3-diene, and the methylene group of spiro[2.4]hepta-1,3-diene.

In the preceding paper [1] the importance of repulsive non-bonding interactions in controlling *endo*-selectivity in the Diels–Alder reaction was recognised. With cyclopentadienes the major interaction has been attributed [2] to be that between substituents of the dienophile and a hydrogen of the methylene group of the cyclopentadiene. This conclusion was derived by study of the selectivity in additions to cyclopentadiene (1) and to 2,5-dimethyl-3,4-diphenylcyclopentadienone (2). The conclusion is based on the relative unimportance of dipolar interactions between diene and dienophile and the supposition that substitution of a diene will not markedly influence *endo*-selectivity. To avoid these complications, shown in the following paper [3] to be not unimportant, we have investigated the influence of diene structure upon *endo*-selectivity choosing the simpler dienes (3) and (4).

To avoid unnecessary conformational complications dienophiles (5a—d) were chosen. Adducts of cyclopentadiene (1) were not isolated as structures have been assigned earlier.[4-7] The stability of the adducts (10d) and (11d) in benzene at 90° was established; the stability of other adducts of cyclopentadiene was assumed. Adducts of spiro[2,4]hepta-1,3-diene (3) were prepared, separated by preparative g.l.c., and structures were assigned by consideration of their n.m.r. spectra (fully discussed in the Experimental section). The stability of adducts of diene (3) was established. Cyclohexa-1,3-diene (4) gave known [7-10] adducts with dienophiles (5a—c), and the stability of these adducts was assumed.

The reaction of cyclohexa-1,3-diene (4) with 2-chloroacrylonitrile (5d) gave two adducts (8d) and (9d), partially separable by preparative g.l.c. Recently the same adducts have been prepared by Krieger and Nakajima [11] and structures were assigned by a consideration of their n.m.r. spectra. The similarity of the two spectra and our reservations concerning an assignment based on chemical shift differences led us to attempt to assign structures to adducts (8d) and (9d) based on other evidence.

Hydrolysis of the major adduct (9d) or the minor adduct (8d) with aqueous potassium hydroxide gave in addition to small amounts of bicyclo[2.2.2]oct-5-en-2-one (12) a mixture of hydroxy-acids. Methylation with diazomethane gave mixtures of hydroxy-esters, which were analysed by g.l.c., and separated by chromatography over silica gel. The isomeric esters, characterised as their 3,5-dinitrobenzoates, were distinguished by their n.m.r. spectra. Resonances attributable to olefinic protons at τ 3·66 and 4·40 in ester (14) and at τ 3·87 and 4·43 in ester (15) indicated that (14) and (15) were bicyclic. The absence of such resonances showed the third ester (13) was tricyclic. In accordance with the hydrolysis of adducts (10d) and (11d) to give the hydroxy-acid (16),[12] the tricyclic acid is formed by participation of the double bond and structure (13) is assigned to the ester of this acid. The assignment of configuration to the hydroxy-group accords with similar examples of double bond participation in bicyclo[2.2.2]octenes.[13,14]

Oxidation by manganese dioxide of esters (14) and

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[2] K. N. Houk and L. J. Luskus, *J. Amer. Chem. Soc.*, 1971, **93**, 4606.
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[12] J. Paasivirta and H. Krieger, *Suomen Kem.*, 1965, **38B**, 182.
[13] H. L. Goering and M. F. Sloan, *J. Amer. Chem.*, 1961, **83**, 1992.
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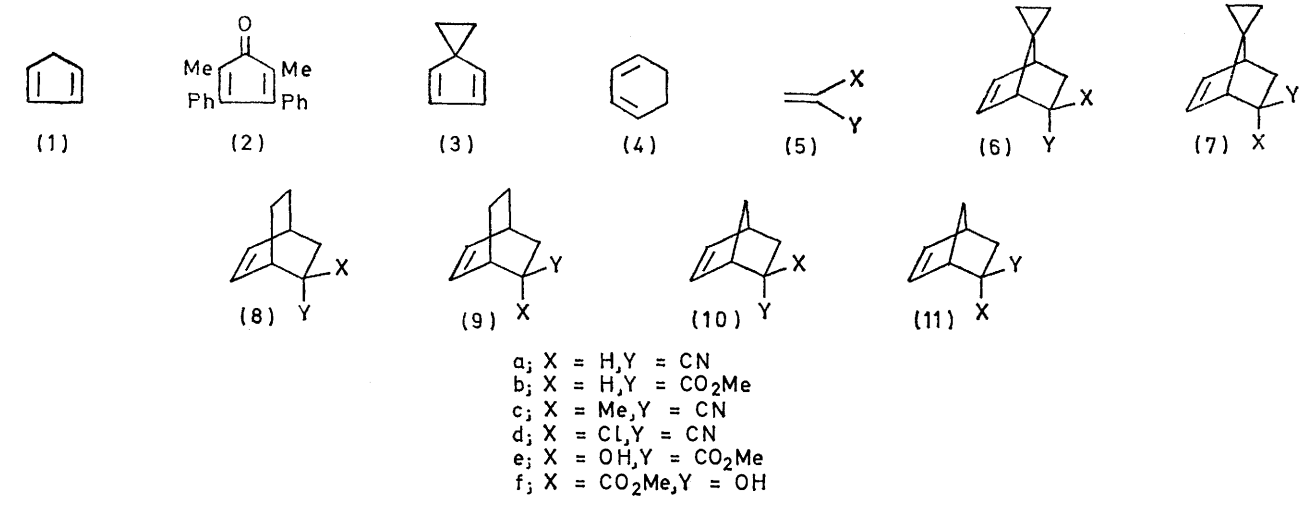
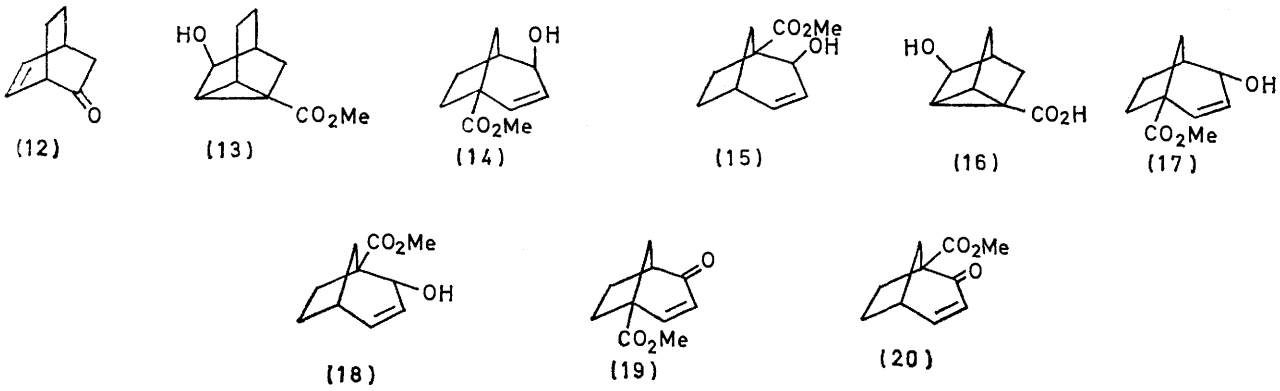
(15) to give αβ-unsaturated ketones, $\nu_{max.}$ 1680 cm^{-1}, $\lambda_{max.}$ 240 nm, suggested the bicyclic esters were substituted bicyclo[3.2.1]octenes and could not be the bicyclo[2.2.2]octenes (8f) and (9f). Esters (14) and (15) gave different ketones and were thus not epimers.





Their allylic nature indicated possible structures (14), (15), (17), and (18). Structures were assigned by consideration of the resonances of the olefinic and allylic protons. The relative position of the ester group was indicated by the more deshielded vinyl resonance, a doublet at τ 2·45 in ketone (19) and a quartet at τ 2·94 in ketone (20). The configuration of the hydroxy-groups in esters (14) and (15) were given by $J_{3,4}$ 4·1 and $J_{4,5}$ 2·5 Hz for ester (14) and $J_{2,3}$ 4·1 Hz for ester (15). These values agree with others obtained [15,16] with substituted bicyclo[3.2.1]octenes and bicyclo-[3.2.1]octadienes and contrast with expected values $J_{3,4}$ 2·0 and $J_{4,5}$ 4·7 Hz for ester (17) and $J_{2,3}$ 2·0 Hz for ester (18).

The adduct (8d) gave largely the tricyclic acid but adduct (9d) mainly bicyclic acids. This difference in behaviour is accounted for by the favourable orientation for double bond participation in the hydrolysis of adduct (8d) only. The instability of the expected carbonium ion intermediates indicates that hydrolysis is concerted. This difference in behaviour of adducts (8d) and (9d) enables their structures to be assigned and our view that the major adduct is (9d) accords with the earlier assignment [11] based on spectral data.

TABLE 1

endo-Selectivity in Diels–Alder reactions in benzene at 80°

Diene	Dienophile	Adducts (%)			
(1)	(5a)	(10a)	54·9	(11a)	45·1
(1)	(5b)	(10b)	74·7	(11b)	25·3
(1)	(5c)	(10c)	17·1	(11c)	82·9
(1) [a]	(5d)	(10d)	19·5	(11d)	80·5
(3)	(5a)	(6a)	65·0	(7a)	35·0
(3)	(5b)	(6b)	95·8	(7b)	4·2
(3)	(5c)	(6c)	10·0	(7c)	90·0
(3)	(5d)	(6d)	6·0	(7d)	94·0
(4)	(5a)	(8a)	55·4	(9a)	44·6
(4)	(5b)	(8b)	82·6	(9b)	17·4
(4)	(5c)	(8c)	9·1	(9c)	90·9
(4)	(5d)	(8d)	18·0	(9d)	82·0

[a] Result at 40°.

Table 1 gives product ratios, obtained by g.l.c. analysis of crude reaction mixtures. With the same

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dienophile, cyclopentadiene (1) and cyclohexa-1,3-diene (4) show similar *endo*-selectivity. Spiro[2,4]hepta-1,3-diene (3) shows enhanced selectivity with dienophiles (5a—d). With acrylonitrile (5a) additional selectivity relative to cyclopentadiene (1) is small but methyl acrylate (5b) is considerably more selective. With methacrylonitrile (5c) and 2-chloroacrylonitrile (5d) the selectivity of the methyl and chloro-groups respectively for the *endo*-position is increased relative to cyclopentadiene (1).

Acrylonitrile (5a) which is planar has little selectivity in adding to either cyclopentadiene (1) or spiro[2,4]-hepta-1,3-diene (3) because secondary orbital overlap is unimportant and because steric interactions in all the modes of addition are small. With methacrylonitrile (5c) the increased stereoselectivity with the dienes (3) and (4) which are more hindered to *exo*-attack supports the view that the *exo*-transition state is destabilised by non-bonding repulsive interactions.[2] If attractive interactions in the *endo*-transition state were the determining influence enhanced stereoselectivity in reaction of (5c) with (3) and (4) would not be expected. In the dienophiles (5a, c, and d) no conformational problems need be considered. Yet comparison of the selectivity of addition of (5c and d) shows that an analysis based simply on non-bonding interactions is inadequate. Methacrylonitrile (5c) shows greater selectivity in addition to cyclohexa-1,3-diene (4) but 2-chloroacrylonitrile (5d) greater selectivity with spiro-[2,4]hepta-1,3-diene (3).

A further complication is illustrated in the additions of methyl acrylate (5b). *endo*-Selectivity with (3) is large, in contrast to additions to (1) or (4). This high specificity is attributed to the conformational mobility associated with the ester. In addition to the effect of secondary orbital interactions stabilising the *endo*-transition state, severe non-bonded interactions may be introduced. The magnitude of these interactions will vary from one diene to another.

Little [17] has examined the applicability of linear free energy relationships to the addition of mono- and di-substituted dienophiles to cyclopentadiene, and observed poor correlations. Such correlations might also be applied to different dienes, but our results suggest that steric interactions partly explain the poor correlations observed by Little and make the applications of linear free energy relationships to either dienes or dienophiles of doubtful value.

We conclude from these results that attack to give *exo*-adducts is particularly hindered with spiro[2,4]-hepta-1,3-diene. These observations accord with the postulate [2] of non-bonding repulsive interactions in the transition state leading to *exo*-products. The results suggest this interaction is particularly important with the methylene groups of (3). However as we show more fully in the following paper [3] *endo*-selectivity with different dienes is modified not only by the steric requirements of the diene but also by dipolar interactions.

EXPERIMENTAL

For general details see the preceding paper.[1]

Spiro[2,4]hepta-1,3-diene (3).—The diene (3), b.p. 56—57° at 95 mmHg (lit.,[8] b.p. 57° at 100 mmHg) was obtained in 80% yield and contained <2% 1,2-dibromoethane.

Reaction of Acrylonitrile with Spiro[2,4]hepta-1,3-diene (3).—The diene (3) (0·92 g) and acrylonitrile (0·53 g) were heated under reflux in benzene (15 ml) for 5 h. Removal of the solvent under reduced pressure afforded an oil, which on distillation gave the epimeric adducts (6a) and (7a), b.p. 130—132° at 20 mmHg, in 71% yield. G.l.c. analysis of the crude reaction mixture showed 64·8% (6a), R_t 22·2 min, and 35·2% (7a), R_t 16·8 min (column G; 170°). The adducts were separated by preparative g.l.c. on a 15 ft 10% CDMA on Chromosorb W column at 152°. Adduct (6a), *m/e* 145 (M^+) and 92 ($M - C_3H_3N$), had R_t 26·0 min and adduct (7a), *m/e* 145 (M^+) and 92 ($M - C_3H_3N$), had R_t 20·0 min.

Reaction of Methyl Acrylate with Spiro[2,4]hepta-1,3-diene (3).—The diene (3) (2·00 g) and methyl acrylate (1·88 g) were heated under reflux in benzene (50 ml) for 12 h. Removal of the solvent under reduced pressure afforded an oil, which on distillation gave the epimeric adducts (6b) and (7b), b.p. 108—112° at 16 mmHg, in 77% yield. G.l.c. analysis of the crude reaction mixture showed 95·8% (6b), R_t 21·6 min, and 4·2% (7b), R_t 17·6 min (column G; 138°). The adducts were separated by preparative g.l.c. on a 15 ft 10% TCEP on Chromosorb W column at 125°. Adduct (6b), *m/e* 178 (M^+), 147 ($M - CH_3O$), 119 ($M - CO_2Me$), and 92 ($M - C_3H_5O_2$), was obtained pure but adduct (7b) was only characterised by mass spectroscopy–g.l.c. with M^+ 178. Equilibration of adduct (6b) by sodium methoxide in methanol gave a mixture of epimers [73·9% (6b) and 26·1% (7b)]. The composition of this mixture was unchanged by heating under reflux in benzene.

Reaction of Methacrylonitrile with Spiro[2,4]hepta-1,3-diene (3).—The diene (3) (0·9 g) and methacrylonitrile (0·67 g) were heated under reflux in benzene (15 ml) for 12 h. Removal of the solvent under reduced pressure gave two products, separated by preparative g.l.c. on a 15 ft 10% CDMA on Chromosorb W column at 170°. Adduct (7c), *m/e* 159 (M^+) and 92 ($M - C_4H_5N$), had R_t 13·0 min and adduct (6c), *m/e* 159 (M^+) and 92 ($M - C_4H_5N$), had R_t 17·5 min. G.l.c. analysis of the crude reaction mixture showed 90% (7c), R_t 25·6 min, and 10% (6c), R_t 32·8 min (column E; 140°). In *p*-xylene at 138° methacrylonitrile gave 86·6% (7c) and 13·4% (6c).

Reaction of 2-Chloroacrylonitrile with Spiro[2,4]hepta-1,3-diene (3).—The diene (3) (0·92 g) and 2-chloroacrylonitrile (5d) (0·87 g) in benzene (15 ml) at 20° for 18 h gave adducts (6d) and (7d). Separation by preparative g.l.c. on a 15 ft 10% CDMA on Chromosorb W column at 160° gave adduct (7d), *m/e* 181 (M^+), 179 (M^+), and 92 ($M - C_3H_2ClN$), R_t 11·0 min, and adduct (6d), *m/e* 181 (M^+), 179 (M^+), and 92 ($M - C_3H_2ClN$), R_t 14·5 min. G.l.c. analysis of the crude reaction mixture showed 94% (7d), R_t 28·2 min, and 6% (6d), R_t 32·3 min (column G; 158°).

Reaction of 2-Chloroacrylonitrile with Cyclohexa-1,3-diene.—Cyclohexa-1,3-diene (84·5 g) and 2-chloroacrylonitrile (123·5 g) were heated in benzene (45 ml) containing hydroquinone (3 g) at 75° for 165 h. Removal of material of

[17] W. L. Dilling, R. D. Kroening, and J. C. Little, *J. Amer. Chem. Soc.*, 1970, **92**, 928.

low b.p. under reduced pressure gave a dark brown solid. Distillation afforded adducts (8d) and (9d), b.p. 60—100° at 0·2—5·0 mmHg, m.p. 60—70°, in 32% yield. Partial separation by preparative g.l.c. on a 15 ft 15% PPG on Chromosorb W column at 130° gave adduct (8d), m.p. 74—89°, containing 11·5% (9d) and 1% of a further impurity of unknown structure, and adduct (9d) m.p. 61—71°, containing 11·5% (8d) and 7·5% of a further impurity of unknown structure. G.l.c. analysis of crude reaction mixtures showed at 80° 82% (9d) and 18% (8d), at 142° 80% (9d) and 20% (8d) (column C; 165°).

Reaction of 2-Chloroacrylonitrile with Cyclopentadiene.—Cyclopentadiene and 2-chloroacrylonitrile were reacted as described [12] to give adducts (10d) and (11d), b.p. 95—98° at 15 mmHg, m.p. 36—38°, in 90% yield. G.l.c. analysis of the crude reaction mixture showed 80·5% (11d) and 19·5% (10d) (column A; 120°). Partial separation by chromatography on silica gel impregnated with silver nitrate (10%) afforded initial fractions containing 62% (11d) and 38% (10d) and final fractions containing 93% (11d) and 7% (10d).

Hydrolysis of 2-Chloro-2-cyanobicyclo[2.2.2]oct-5-ene.—2-*endo*-Chloro-2-*exo*-cyanobicyclo[2.2.2]oct-5-ene (9d), containing 19% of the epimer (8d) was heated under reflux in aqueous potassium hydroxide (6·5N) for 4 h. Extraction of the cold solution with ether afforded, from the ether solution, bicyclo[2.2.2]oct-5-en-2-one (12) (7%) and unchanged starting materials (8%). Acidification of the aqueous phase afforded, by extraction with ether, a mixture of acids (85%) which slowly solidified. The solid had m.p. 132·5—144°, raised to 166·5—168° by recrystallisation from acetone. Methylation of the crude acids with diazomethane in ether afforded esters, $\nu_{max.}$ 3400 and 1725 cm^{-1}, which were chromatographed on silica gel. Elution with benzene–ether (9 : 1) gave methyl *exo*-2-hydroxybicyclo[3.2.1]oct-3-ene-1-carboxylate (15), $\nu_{max.}$ 3400 and 1725 cm^{-1}, τ 3·87 (1H, q, J 9·7 and 6·6 Hz), 4·43 (1H, q, J 9·7 and 4·1 Hz), 5·80 (1H, t, J *ca* 4 Hz), 6·27 (3H, s), and 7·15—8·80 (8H, complex). The 3,5-*dinitrobenzoate* had m.p. 107·5—110° (from ether) (Found: C, 54·35; H, 4·45; N, 7·5. $C_{17}H_{16}N_2O_8$ requires C, 54·25; H, 4·3; N, 7·45%). Elution with benzene–ether (17 : 3) gave methyl *exo*-4-hydroxybicyclo[3.2.1]oct-2-ene-1-carboxylate (14), $\nu_{max.}$ 3400 and 1725 cm^{-1}, τ 3·66 (1H, q, J 10·0 and 1·4 Hz), 4·40 (1H, octet, J 10·0, 4·1, and 1·8 Hz), 6·20 (1H, m), 6·32 (3H, s), and 7·32—8·90 (8H, complex). The 3,5-*dinitrobenzoate* had m.p. 140·5—141° (from ether) (Found: C, 54·45; H, 4·4; N, 7·85. $C_{17}H_{16}N_2O_8$ requires C, 54·25; H, 4·3; N, 7·45%). Elution with further benzene–ether (17 : 3) gave methyl 5-hydroxytricyclo[2.2.2.$0^{2,6}$]octane-2-carboxylate (13), $\nu_{max.}$ 3400 and 1720 cm^{-1}, τ 6·08 (1H, m), 6·35 (3H, s), and 7·40—8·85 (10H, complex). The 3,5-*dinitrobenzoate* had m.p. 157·5—158° (from ether) (Found: C, 54·40; H, 4·1; N, 7·75. $C_{17}H_{16}N_2O_8$ requires C, 54·25; H, 4·3; N, 7·45%).

Hydrolysis of adduct (9d) gave (15) (21%), (14) (50%), and (13) (29%), and adduct (8d) gave (15) (3·5%), (14) (7·0%), and (13) (89·5%).

Oxidation of alcohol (15) (73 mg) by manganese dioxide (582 mg) in dry ether (10 ml) gave after 24 h methyl 2-oxobicyclo[3.2.1]oct-3-ene-1-carboxylate (20) (72 mg), as a yellow oil, $\nu_{max.}$ 1730, 1675, and 1605 cm^{-1}, $\lambda_{max.}$ 240 nm, τ 2·94 (1H, octet, J 9·8, 6·9, and 1·7 Hz), 4·20 (1H, d, J 9·8 Hz), 6·30 (3H, s), and 7·0—9·0 (7H, complex).

Oxidation of alcohol (14) similarly gave methyl 4-oxobicyclo[3.2.1]oct-2-ene-1-carboxylate (19) (69%) as a yellow oil, $\nu_{max.}$ 1730, 1680, and 1605 cm^{-1}, $\lambda_{max.}$ 240 nm, τ 2·45 (1H, d, J 9·9 Hz), 4·10 (1H, q, J 9·9 and 1·9 Hz), 6·23 (3H, s), and 6·8—8·8 (7H, complex). Ketones (19) and (20) had different R_f values (Ucon 15%; 145°).

N.m.r. of Adducts of Spiro[2,4]hepta-1,3-diene.—Structures were assigned to adducts by considering the following features of their spectra (see Table 2); the relative chemical shifts of 2_{ex}-H and 2_{en}-H and the relative chemical shifts of protons of an *endo*- and of an *exo*-substituent. In view of the unusually large difference (17 Hz) between the position of the methyl resonances of adducts (6b) and (7b) supplementary evidence for their assignment was sought. Coupling between the protons at C-1, -2, -3, and -4 could not be considered on a simple first-order basis in the major reaction product, a situation also found with methyl 1,4,5,6,7,7-hexadeuteriobicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylate.[18] However, using a LAOCOON IV program computer analysis gave $J_{1.2ex}$ 4·7, $J_{1,6}$ 3·0, $J_{2ex,3ex}$ 9·5, and $J_{2ex,3en}$ 4·4 Hz which establishes that the major reaction product has an *endo*-substituent and is (6b). Only the major adduct of spiro[2,4]hepta-1,3-diene with 2-chloroacrylonitrile was obtained and therefore the assignment of structure is less certain. However, comparison of the chemical shifts of the bridgehead and olefinic protons with those [4] of the adducts (10d) and (11d) leads to our tentative assignment. Separation of the bridgehead protons in (7d) is 45 Hz and in (11d) is 40 Hz. Separation of the olefinic protons in (7d) is 25 Hz and in (11d) is 25 Hz. For both sets of protons smaller separations are observed in (10d).

TABLE 2

N.m.r. data for adducts of spiro[2,4]hepta-1,3-diene

	τ Values									
Compound	1-H	4-H	2_{ex}-H	2_{en}-H	3_{ex}-H	3_{en}-H	5-H	6-H	Me	Cyclopropane protons
(6a)	7·44	7·69	7·02		7·70	8·59	3·73	3·58		9·3—9·7
(7a)	7·42	7·65		7·72	7·85	8·38	3·85	3·73		9·0—9·6
(6c)	7·73	7·73			8·13	8·78	3·61	3·61	8·39	9·3—9·7
(7c)	7·58	7·73			7·53	8·83	3·64	3·86	8·76	9·0—9·6
(7d)	7·11	7·56			7·15	8·10	3·79	3·52		9·0—9·5
(6b)	7·46	7·79	6·91		7·96	8·46	3·73	3·42	6·42	9·4—9·75
(7b)	*a*	*a*		*a*	*a*	*a*	3·78	3·78	6·25	9·35—9·65

[a] Signal not identified.

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