Stereoelectronic Control in Organic Chemistry: Addition Reactions of Some 1,4-Benzoquinone 4-(*O*-Methyloximes)

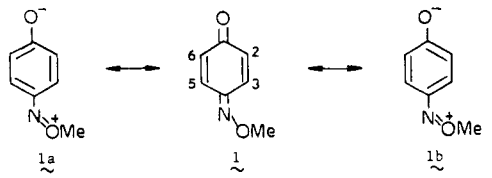
Jack E. Baldwin* and Robert K. Norris[1]

Dyson Perrins Laboratory, Oxford OX1 3QY, United Kingdom

Received July 8, 1980

The addition of bromine and chlorine to 1,4-benzoquinone 4-(*O*-methyloxime) (**1**) under kinetic control and of cyclopentadiene to **1** or the 2-methyl derivative (**3**) under conditions where isomerization about the C=N bond can occur gives rise to products in which those having the unreacted double bond anti to the methyloxime group (configuration **31**) greatly predominate over the alternative syn configuration (**32**). An n → σ^* interaction of the nonbonding electrons on the oxime nitrogen with the antiperiplanar (app) bond in the six-membered ring is invoked. This interaction which lengthens the app bond and consequently reduces π overlap across the app bond in **32** is believed to account for the difference in stability between **31** and **32**. This interaction is also believed to produce differential delocalization in 1,4-quinone 4-oxime derivatives, wherein the quinonoid double bond syn to the oxime substituent is delocalized to a lower extent than the anti double bond.

During an ^{1}H NMR study of tautomerism in the *p*-nitrosophenol–*p*-benzoquinone oxime system,[2] it was found that syn–anti isomerism occurred in the quinonoid forms, not only in the oximes themselves[3] but also in their acetate esters[4] and methyl ethers.[5] Substituents at the 2-position strongly influenced the proportions of syn and anti forms; electron-donating substituents favored the syn isomers, and electron-withdrawing substituents favored the anti isomers. An explanation for these results was advanced[3-5] which involved, in essence, greater contribution from the canonical structure **1a** than **1b**, for example, in the methyloxime **1**. This tentative proposal has not been challenged, nor have theoretical calculations appeared on this system. In addition to allowing rationalization of the syn–anti equilibria, this proposal also derived support from coupling constant data in the 1,4-benzoquinone 4-oxime system, namely, that the vicinal (or allylic) coupling constant across the quinonoid double bond was *always* larger when the bond was syn to the oxime group than when it was anti, for any given pair of isomers. For example, in the methyloxime **1**, $J_{2,3} > J_{5,6}$.

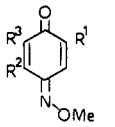


1a **1** **1b**

An interest in the effect of orientation of lone pairs on the reactivity of molecules caused us to seek tests for a difference in chemical reactivity of the two quinonoid double bonds. The methyloximes were chosen, since they, unlike the oximes,[2,3] less readily lose stereochemical integrity about the C=N bond and also, unlike the *O*-acyl derivatives, e.g., acetates,[4] do not readily hydrolyze. The addition of halogens (principally bromine) and Diels–Alder cycloadditions were chosen as possible probes into differential reactivity of the 2,3 and 5,6 double bonds.

The addition of halogens to benzoquinones is well established[6] and has been shown to result in *trans*-dihalides in which the two halogen atoms adopt *quasi*-axial positions.[7] Some very early work reports the addition of bromine and chlorine to the methyloximes **1**[8] and **2**;[9] however, the stereochemical ramifications were not recognized. The only recent report,[10] which utilizes ^{1}H NMR spectroscopy, on halogen addition to quinone oxime derivatives does not attempt to assign stereochemistry around the C=N bond, and the authors "deliberately neglect the problem of syn–anti isomerism".

The Diels–Alder reaction of quinones with dienes is one of the classic reactions of organic chemistry;[11] however, addition of dienes to methyloximes such as **1**, **2**, or **3** has not been reported.



	R^1	R^2	R^3
1	H	H	H
2	H	Me	H
3a	Me	H	H
3b	H	H	Me
13	Br	H	H
14	H	H	Br
15	Cl	H	H
16	H	H	Cl
17	H	Cl	H
18	Me	H	Br
19	Br	H	Me
20	Br	Me	H

Results

Halogen Addition Reactions. The halogen addition products from the methyloximes **1–3** were prepared by addition of bromine (or chlorine) to an equimolar amount of the appropriate methyloxime in carbon tetrachloride, chloroform, or dichloromethane, followed by removal of the solvent. The ^{1}H NMR spectra of the resulting product mixtures were recorded and the resonances assigned to the

(1) On study leave from the Department of Organic Chemistry, The University of Sydney, N.S.W., 2006 Australia.
(2) Norris, R. K.; Sternhell, S. *Aust. J. Chem.* **1966**, *19*, 841.
(3) Norris, R. K.; Sternhell, S. *Aust. J. Chem.* **1969**, *22*, 935.
(4) Norris, R. K.; Sternhell, S. *Aust. J. Chem.* **1971**, *24*, 1449.
(5) Norris, R. K.; Sternhell, S. *Aust. J. Chem.* **1972**, *25*, 1907.
(6) One of the earlier reports: Clark, T. H. *Am. Chem. J.* **1892**, *14*, 555. A more recent study: Savoie, J. Y.; Brassard, P. *Can. J. Chem.* **1966**, *44*, 2867.
(7) Norris, R. K.; Sternhell, S. *Aust. J. Chem.* **1966**, *19*, 617.
(8) Bridge, J. L. *Justus Liebigs Ann. Chem.* **1894**, *277*, 79.
(9) Bridge, J. L.; Morgan, W. C. *Am. Chem. J.* **1898**, *20*, 761.
(10) Savoie, J. Y.; Brassard, P. *Can. J. Chem.* **1971**, *49*, 3515.
(11) For reviews: Butz, L. W. *Org. React.* **1949**, *5*, 136; Huisgen, R.; Grashey, R.; Sauer, J. In "The Chemistry of Alkenes"; Patai, S., Ed.; Interscience: London, 1964; pp 878–929; Finley, K. T. In "Chemistry of Quinonoid Compounds"; Patai, S., Ed.; Interscience: London, 1974; pp 986–1011.

0022-3263/81/1946-0697$01.00/0

Table I. ^{1}H NMR Data for Halogen Addition Products with 1-3

entry	compd	chemical shifts, ppm (from Me_4Si) H2	H3	H5	H6	OMe	coupling constants, Hz $J_{2,3}$	$J_{2,6}$	$J_{3,5}$	$J_{5,6}$
1	4	6.22 dd	6.99 dd	5.55 dd	4.54 dd	4.14 s	10.40	1.30	1.85	2.75
2	5	6.18 dd	7.46 dd	5.18 dd	4.68 dd	4.06 s	10.65	1.45	1.85	2.95
3	6	6.20 dd	7.52 d	2.17[a] s	4.70 d	4.08 s	10.60	1.55		
4	7	6.09 dq	2.16[a] d	5.61 d	4.52 dd	4.14 s	1.30	1.40		2.70
5	8	6.27 d	6.96 dd	5.70 d	2.04[a] s	4.16 s	10.3		1.85	
6	9	2.03[a] d	7.31 dq	5.16 dd	4.72 d	4.05 s	1.50		1.85	2.75
7	10	2.03[a] d	6.81 dq	5.54 dd	4.58 d	4.11 s	1.50		1.85	2.60
8	11	6.26 dd	7.05 dd	5.48 dd	4.35 dd	4.15 s	10.30	1.30	1.65	2.75
9	12	6.22 dd	7.52 dd	5.00 dd	4.47 dd	4.09 s	10.60	1.30	1.85	2.95

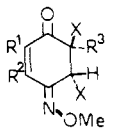
[a] Methyl group.

Table II. Product Distributions from Monohalogenation[a] of Methyloximes 1-3

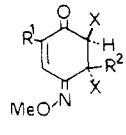
entry	methyloxime	halogen	solvent	products (yield, %)
1	1	Br_2	CCl_4	4 (79), 5 (21)
2	1	Cl_2	CCl_4	11 (72), 12 (28)
3	2	Br_2	CCl_4[b]	6 (9), 7 (91)
4	3[c]	Br_2	$CHCl_3$	8 (22), 9 (68), 10 (10)
5	3[c]	Br_2	CH_2Cl_2	8 (35), 9 (54), 10 (11)

[a] Reactions were performed at 20 ± 2 °C, with a reproducibility of ±4%. [b] Identical result (within experimental error) in $CHCl_3$ and CH_2Cl_2. [c] 3a/3b ratio of 9:1.

products 4–12 (see Table I). The proportions of products formed are collected in Table II.



	R^1	R^2	R^3	X
4	H	H	H	Br
7	H	Me	H	Br
8	H	H	Me	Br
10	Me	H	H	Br
11	H	H	H	Cl



	R^1	R^2	X
5	H	H	Br
6	H	Me	Br
9	Me	H	Br
12	H	H	Cl

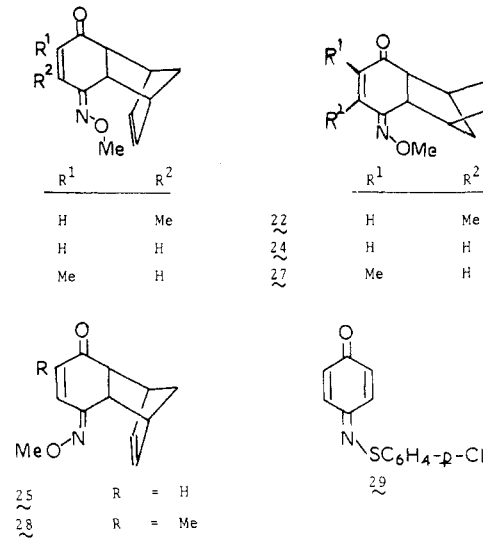
The assignments in Table I, which show an exceptional degree of self-consistency, were made originally on the expectation[2-5] that H3 (or H5) syn to the oxime group will occur at lower field than H3 (or H5) in the anti arrangement. For example, H3 in 4 (δ 6.99) is assigned upfield of H3 in 5 (δ 7.46) whereas the situation is reversed for H5, downfield in 4 (δ 5.55) relative to 5 (δ 5.18). The trans diaxial arrangement of the halogens in the adducts 4–12 follows from the magnitude of the coupling constants $J_{5,6}$ (2.6–2.95 Hz, $J_{eq,eq}$)[7] and the long-range couplings $J_{2,6}$ and $J_{3,5}$. The "model" adduct 7, in which steric restraints will ensure[12] that the methyloxime group is syn to the halogenated bond, gives an "absolute" shift for H5 (syn to OMe) of 5.61 ppm which is similar to the shift for H5 in 4 (δ 5.55), 8 (δ 5.70) and 10 (δ 5.54) but quite different from the shifts for H5 (anti to OMe) in 5 (δ 5.18) and 9 (δ 5.16). A further (one of many) consistent observation is the small but readily measurable deshielding of the methoxy group when syn to the halogenated side of the molecule, e.g., δ 4.14 in 4 and 7 relative to δ 4.06 in 5.

The adducts 4, 5, 7 and 9–12 were found to readily eliminate hydrogen halide when treated with triethylamine (in CH_2Cl_2 or in $CDCl_3$). The adduct 8, which does not have a proton α to a carbonyl group, was stable to this treatment, thus allowing its separation from 9 and 10. ^{1}H NMR experiments showed that treatment of pure 4 with triethylamine in deuteriochloroform gave initially the (*Z*)-methyloxime 13, which subsequently equilibrated with the *E* isomer (14).[13] Similarly, the chlorine adduct 11 (and 12) gave 15 (and 16) without formation of the 3-chloro compound 17,[14] mixtures of 8–10 gave unchanged 8 and mixtures of 18 and 19, and 7 gave only 20.

The proportions of halogen adducts (Table II) represent kinetic products. This is clearly shown in entries 4 and 5 where the proportion of 10 is the same as the proportion of 3b in the mixture of 3a and 3b used. Equilibration of 9 and 10 using hydrogen bromide in chloroform[16] gave a mixture in which 10 predominated (>75%).

Diels-Alder Reactions with Cyclopentadiene. The methyloxime 2, with fixed stereochemistry around the C=N bond,[12] reacted readily with refluxing cyclopentadiene (4–5 h) to give a near quantitative yield of 1:1 adducts. A reasonable (70%) isolated yield of the adduct 21 (Chart I) was obtained. As expected, by analogy with

Chart I



	R^1	R^2
21	H	Me
23	H	H
26	Me	H

	R^1	R^2
22	H	Me
24	H	H
27	Me	H

25 R = H
28 R = Me

29

(13) The percentage of the *Z* isomer (13) at equilibrium, presumably catalyzed by the triethylammonium ion, was 63 ± 4%.

(14) The original claim[8] that 11, on elimination of hydrogen chloride, gave 17 in addition to 15 (and 16), although later qualified,[9] has not been corrected in the primary literature; however, the Beilstein abstract[15] of the original work[8] omits mention of the formation of 17.

(15) "Beilstein's Handbuch der organischen Chemie"; Springer-Verlag: Berlin, 1925; Vol. 7, p 574.

(16) This isomerization presumably takes place via the O-protonated species,[5] whose formation in concentrated sulfuric acid has been demonstrated in the case of quinone methyloximes.[17]

(17) Belyaev, E. Y.; Skvortsov, N. K.; Tovbis, M. S.; El'tsov, A. V. *Zh. Org.* Khim. 1976, *12*, 1467; *Chem. Abstr.* 1976, *84*, 176504.

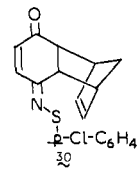
(12) Norris, R. K.; Sternhell, S. *Aust. J. Chem.* 1972, *25*, 2621.

the behavior of substituted *p*-benzoquinones, this adduct was found to be the result of addition to the unsubstituted double bond in an endo fashion.[11] The ^{1}H NMR data (see Table III) are entirely consistent with this structural assignment. The values for $J_{2,7}$ ($J_{exo,exo}$) and $J_{1,2}$ and $J_{7,8}$ ($J_{bridgehead,exo}$) are in the ranges normally found in bicyclo[2.2.1]heptene derivatives.[18] Furthermore, inspection of the ^{1}H NMR spectra of the total reaction product (and also later fractions from recrystallizations) showed the presence of the exo adduct **22** (ca. 7%). The ^{1}H NMR data for **22** (entry 2, Table III) are quite consistent with this assignment. In particular, the reduced values for $J_{2,7}$, $J_{1,2}$, and $J_{7,8}$,[18] and the change in chemical shifts for H2 and H7 (0.69 and 0.63 ppm, respectively, in going from the exo to the endo adduct), which compares most strikingly with the corresponding change in bicyclo[2.2.1]heptene (0.62 ppm),[19b] are excellent proof of stereochemistry. In addition, the slight downfield shift of the vinyl protons (and methyl group) on the 4,5 and 9,10 double bonds on going from the endo (mutual through-space shielding of double bonds) to the exo adduct is apparent.

The unsubstituted methyloxime **1** also readily reacted with cyclopentadiene to give a nearly quantitative recovery of 1:1 adducts. The major product (ca. 90%) was assigned to the (*Z*)-endo configuration **23**, whose ^{1}H NMR data are nearly identical with the model **21** (see Table III, entries 1 and 3). In addition, the (*Z*)-exo isomer **24** (ca. 8%) whose ^{1}H NMR data are comparable with those from **22** (Table III, entries 2 and 4) was readily detected. On further close examination, another compound could be seen, in ca. 2% yield, whose ^{1}H NMR data are consistent with the (*E*)-endo configuration, **25** (see entry 5). The assignments to the endo adducts **23** and **25** of *Z* and *E* stereochemistry, respectively, is confirmed by the agreement of the chemical shifts of H5 in **23** (6.82 ppm) with those of the similar vinyl protons, H3, in **4**, **8**, and **11** (6.96–7.05 ppm) and of H5 in **25** (7.49 ppm) with that of H3 in **5**, **6**, and **12** (7.46–7.52 ppm).

The methyloxime **3** under the same conditions as those used for **1** and **2** reacted more slowly, and starting material still remained after reaction times of 4 h (21%) and 8 h (15%). The product distribution, however, was identical after these times and was also independent of the **3a**/**3b** ratio which was initially 9:1 and ca. 1:1 in parallel experiments. The products were identified by ^{1}H NMR and their proportions estimated as (*E*)-*endo*-**26** (87 ± 2%), (*E*)-*exo*-**27** (6 ± 1%), and (*Z*)-*endo*-**28** (7 ± 1%). Their ^{1}H NMR data agree with the analogous compounds formed from **1** and **2** with cyclopentadiene (compare entry 6 with 1 and 3, entry 7 with 2 and 4, and entry 8 with 5 in Table III). The chemical shifts of the vinyl quartets for H5 in **26** (δ 6.68) and **27** (δ 6.88) (anti to the methyloxime group) compare favorably with the corresponding shift for H3 in **10** (δ 6.81), and the resonance for H5 in **28** (δ 7.34) occurs quite close to the resonance for H3 in **9** (δ 7.31).

The *S*-(*p*-chlorophenyl) thiooxime **29** was prepared in the hope that the larger *p*-chlorophenyl group would sterically destabilize the *E* configuration in the cyclopentadiene adduct. The reaction of **29** with cyclopentadiene was complete in 1.5 h and gave a 1:1 adduct which was greater than 93% pure. The minor component(s) were not identified, but the major product is again believed to have the (*Z*)-endo configuration, **30**. The

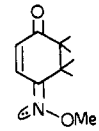


30

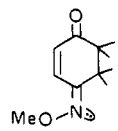
chemical shifts for H4 and H5 and the coupling constants for **30** (see Table III, entry 9) are very similar to those found in **23** (entry 3). The significant differences in chemical shifts between protons in **30** relative to their counterparts in **23** (other than a general downfield shift of 0.06–0.11 ppm) are found for H2 (0.17 ppm downfield), H7 (0.12 *upfield*), and H8 (0.33 downfield), and this is consistent with their proximity to the anisotropic benzene ring in the *E* isomer.

Discussion and Conclusions

The most remarkable result of the above addition reactions is the overwhelming predominance of products which have the configuration **31**, where the oxime group is anti to the remaining double bond, rather than the alternative arrangement **32**.



31



32

The kinetically controlled addition of either bromine or chlorine results in over 70% production of compounds with the configuration **31**, and even in the (*Z*)-2-methyl derivative (**3a**) substantial production of **8** (having arrangement **31**) takes place, despite the well-established mode of behavior of quinones to add halogens to the unsubstituted double bond (e.g., *p*-toluquinone).[7] The ratio of **6** to **7** (Table II, entry 3) of 1:10 contrasts strikingly with the ratio of **8** to **9** (entry 5) of 1:1.5. The Diels–Alder reactions likewise produce in excess of 93% of products having the arrangement **31** under conditions where equilibration about the C=N bond takes place. In similar fashion, isomerization of the adduct **9** gives predominantly **10**, which has the array **31**. It is somewhat gratifying that these results confirm the intrinsic higher stability of species having the array **31**, which is inherent in the original proposal[2-5] of a greater contribution of form **1a** to **1** than that from **1b**.

We believe that a simple but compelling argument can be constructed which explains the above stability difference. This explanation invokes a stereoelectronic effect involving the nonbonding electrons on the oxime nitrogen.

It has become increasingly obvious that the interaction of nonbonded electrons with adjacent bonds can affect conformational equilibria and bond reactivities. The phenomenon of n → σ* interactions of lone pairs on heteroatoms which are antiperiplanar (app) to an adjacent σ bond was first proposed as a possible explanation of the anomeric effect.[20] Since this proposal and early calculations on the importance of this interaction,[21,22] the n → σ* effect has been invoked to explain such diverse phenomena as cleavage of tetrahedral intermediates,[23] geo-

(18) Typical ranges are[19a] $J_{exo,exo}$ = 9–10 Hz, $J_{bridgehead,exo}$ = 3–4 Hz, $J_{endo,endo}$ = 6–7 Hz, and $J_{bridgehead,endo}$ = 0–2 Hz.
(19) (a) Jackman, L. M.; Sternhell, S. "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry"; Pergamon: Oxford, 1969; p 289. (b) *Ibid.*, p 230.

(20) Altona, C. Thesis, Leiden, 1964. This was referred to by: Romers, C.; Altona, C.; Buys, H. R.; Havinga, E. *Top. Stereochem.* **1969**, *4*, 76–77.
(21) Radom, L.; Hehre, W. J.; Pople, J. A. *J. Am. Chem. Soc.* **1972**, *94*, 2371.
(22) David, S.; Eisenstein, O.; Hehre, W. J.; Salen, L.; Hoffmann, R. *J. Am. Chem. Soc.* **1973**, *95*, 3806.
(23) Lehn, J.-M.; Wipff, G. *J. Am. Chem. Soc.* **1980**, *102*, 1347 and references therein.

Table III. ^{1}H NMR Data for Cyclopentadiene Adducts with Oxime Derivatives

entry	compd	chemical shifts, ppm											coupling constants, Hz
		H1	H2	H4	H5	H7	H8	H9	H10	H11a	H11b	OMe	
1	21	3.43 m	2.99 dd	5.92 q	2.00 d[a]	3.57 dd	3.64 m	6.00 dd	5.97 dd	1.43 dt	1.39 dt	4.00 s	$J_{1,2} = 4.1, J_{2,7} = 8.9, J_{4,5} = 1.3, J_{7,8} = 3.7, J_{8,9} \approx J_{1,10} \approx 2.9, J_{9,10} = 5.7, J_{1,11a} \approx J_{8,11a} \approx 1.7, J_{1,11b} \approx J_{8,11b} \approx 1.5, J_{11a,11b} = 8.7$
2	22	3.14 m	2.30 br d	6.14 q	2.12 d[a]	2.94 br d	3.17 m	6.33 dd	6.26 dd	1.30 br d	1.23 br d	4.06 s	$J_{1,2}$ and $J_{7,8} < 1.5, J_{2,7} = 8.0, J_{4,5} \approx 1, J_{8,9} \approx J_{1,10} \approx 3, J_{9,10} \approx 6, J_{11a,11b} \approx 9$
3	23	3.47 m	3.01 dd	6.00 d	6.82 d	3.53 dd	3.69 m	6.00 m	6.00 m	1.45 dt	1.39 dt	4.05 s	$J_{1,2} = 4.4, J_{2,7} = 8.8, J_{4,5} = 10.2, J_{7,8} = 3.5, J_{1,11a} \approx J_{8,11a} \approx 1.7, J_{1,11b} \approx J_{8,11b} \approx 1.4, J_{11a,11b} \approx 9$
4	24	3.22 m	2.34 br d	6.22 d	7.02 d	2.90 br d	3.22 m	6.34 dd	6.29 dd	1.31 br d	1.27 br d	4.06 s	$J_{1,2}$ and $J_{7,8} < 1.5, J_{2,7} = 8.0, J_{4,5} = 10.1, J_{8,9} \approx J_{1,10} \approx 3, J_{9,10} \approx 6, J_{11a,11b} \approx 9$
5	25	*c*	3.08 dd	6.48 d	7.49 d	3.34 dd	*c*	6.10 dd	6.0 m[b]	~1.3 m[b]	~1.3 m[b]	3.93 s	$J_{1,2} = 4.1, J_{2,7} = 8.9, J_{4,5} = 10.1, J_{7,8} = 3.7, J_{8,9} \approx 3, J_{9,10} \approx 6$
6	26	3.45 m	3.03 dd	1.81 d[a]	6.68 q	3.52 dd	3.67 m	5.98 dd	5.94 dd	1.43 dt	1.39 dt	4.00 s	$J_{1,2} = 4.0, J_{2,7} = 8.6, J_{4,5} = 1.3, J_{7,8} = 3.7, J_{8,9} = 2.8, J_{1,10} = 2.9, J_{9,10} = 5.7, J_{1,11a} \approx J_{8,11a} \approx 1.7, J_{1,11b} \approx J_{8,11b} \approx 1.4, J_{11a,11b} = 8.8$
7	27	3.17 m	2.35 br d	1.93 d[a]	6.88 q	2.89 br d	3.21 m	6.32 dd	6.30 dd	~1.3 m[b]	~1.3 m[b]	4.03 s	$J_{1,2}$ and $J_{7,8} < 1.5, J_{2,7} = 7.9, J_{4,5} = 1.2, J_{8,9} \approx J_{1,10} \approx 3, J_{9,10} \approx 5.5$
8	28	*c*	3.09 dd	1.82 d[a]	7.34 q	3.33 dd	*c*	6.08 dd	6.0 m[b]	~1.3 m[b]	~1.3 m[b]	3.93 s	$J_{1,2} = 4.3, J_{2,7} = 9.0, J_{4,5} \approx 1.4, J_{7,8} = 3.9, J_{8,9} \approx 3, J_{9,10} \approx 6$
9	30[d]	3.56 m	3.18 dd	6.06 d	6.88 d	3.45 dd	4.02 m	6.06 dd	5.97 dd	1.56 dt	1.45 dt		$J_{1,2} = 4.0, J_{2,7} = 8.6, J_{4,5} = 10.3, J_{7,8} = 3.7, J_{8,9} = 2.8, J_{1,10} = 2.9, J_{9,10} = 5.7, J_{1,11a} \approx J_{8,11a} \approx 1.8, J_{1,11b} \approx J_{8,11b} \approx 1.4, J_{11a,11b} = 8.8$

[a] Methyl groups. [b] Overlapped by other resonances. [c] The resonances for these peaks (very broad, low-intensity multiplets) are partly obscured by other peaks and/or could not be unambiguously assigned. [d] Aromatic protons (AA'XX' system): δ 7.38 (m, 2 H, ortho to S), 7.52 (m, 2 H, ortho to Cl); $J_{AX} + J_{AX'} = 8.7$ Hz.

metrical isomerism in nitrogen fluoride (N_2F_2) and related species,[24] the mode of cleavage of cyclic dioxenium salts,[25] and the stability of the α anions from imines.[26] We propose that the nonbonding electrons on the nitrogen atom in the oxime group exert a subtle but significant effect by interacting with the app C–C bond in the six-membered ring. This n → σ^* interaction will produce some antibonding character in the app bond with concomitant lengthening of the bond. It is apparent, on consideration of structures **31** and **32**, that the bonds being lengthened are those syn to the oxime substituent. Lengthening of this syn bond in **32** will reduce the effective p–p orbital overlap between carbon atoms 3 and 4, reducing in turn the delocalization of the lone pair on the oxime oxygen atom, through the conjugated system, onto the carbonyl oxygen. No such bond lengthening and resultant reduction in delocalization occurs in **31**, leading to a greater inherent stability of this configuration over **32**. It is also a logical consequence of this proposal that in quinonoid derivatives, e.g., **1**, the contributor **1a** should be more important than **1b**, which is in accord with the hypothesis suggested to explain the ^{1}H NMR coupling constants and the position of syn–anti equilibrium in these derivatives.

Experimental Section

Melting points were obtained with a Büchi 510 melting point apparatus. Mass spectra were obtained on a Vacuum Generators MM 16F spectrometer, NMR spectra were taken on a Hitachi Perkin-Elmer R-24B (60 MHz) or Bruker WH-300 spectrometer with Me_4Si as internal standard, IR spectra were obtained on a Perkin-Elmer 257 spectrophotometer, and UV–visible spectra were taken on a Perkin-Elmer 555 spectrophotometer. Bromine (bp 58–60 °C) and cyclopentadiene (bp 38–40 °C) were freshly distilled. Chloroform, carbon tetrachloride, and dichloromethane were filtered through alumina prior to use in addition reactions. 1,4-Benzoquinone 4-(*O*-methyloxime) (mp 83 °C) was prepared from 1,4-benzoquinone.[5]

2- and 3-Methyl-1,4-benzoquinone 4-(*O*-Methyloximes). Toluquinone (4.88 g, 40 mmol) was finely powdered, stirred with a solution of methoxyammonium chloride (3.34 g, 40 mmol) in water (10 mL) for 1 h, warmed to 70–80 °C for 5 min, chilled, and extracted with ether (2 × 50 mL). The ether extracts were washed successively with an equal volume of 5% sodium sulfite, saturated sodium carbonate, water, and brine. The extract was then dried over magnesium sulfate, and the solvent was removed under reduced pressure. The crude extract was filtered through alumina (25 g) in 50% ether–petroleum ether to give a deep yellow crystalline mixture (3.9 g, 63%) which consisted (^{1}H NMR) of **2** and **3** in a 1:2 ratio. Chromatography[27] of the mixture (3.7 g) on Merck silica gel 9385 (650 g) in 25% dichloromethane–petroleum ether followed by 75% dichloromethane–petroleum ether gave a mixture of the *Z* and *E* isomers, **3a** and **3b**, respectively, of 2-methyl-1,4-benzoquinone 4-(*O*-methyloxime) (**3**, 2.3 g), whose ^{1}H NMR spectrum was in accord with that in the literature.[5] Recrystallization from cyclohexane gave the pure *Z* isomer **3a**, mp 74 °C (lit.[5] mp 74 °C). Further elution gave 3-methyl-1,4-benzoquinone 4-(*O*-methyloxime) (**2**): 1.1 g; mp 69–70 °C (from ethanol or cyclohexane) (lit.[8,28] mp 69–73 °C); ^{1}H NMR ($CDCl_3$) δ 2.20 (d, 3 H, Me, J = 1.20 Hz), 6.31 (dq, 1 H, H-2, J = 1.2, 2.0 Hz), 7.37 (dd, 1 H, H-6, J = 10.2, 2.0 Hz), 7.61 (d, 1 H, H-5, J = 10.2 Hz).

***N*-[(*p*-Chlorophenyl)thio]-1,4-benzoquinone 4-Imine (29).** Bis(*p*-chlorophenyl) disulfide (13.0 g, 45 mmol) was dissolved in dry carbon tetrachloride (50 mL) and treated with chlorine gas at 0 °C until formation of the sulfenyl chloride was complete. The excess chlorine and solvent were removed under reduced pressure, and the resulting *p*-chlorobenzenesulfenyl chloride was dissolved in dry benzene (25 mL). A suspension of *p*-aminophenol (3.3 g, 30 mmol) in pyridine (10 mL) was added, and the mixture was stirred at room temperature for 40 min. The dark reaction mixture was diluted with chloroform (300 mL) and washed successively with equal volumes of water, 2 M hydrochloric acid, water, and brine. The extract was dried over magnesium sulfate, and the solvent was removed under reduced pressure. Medium-pressure chromatography[27] with 20% ethyl acetate–chloroform as eluent gave deep red fractions which on evaporation followed by recrystallization from benzene gave red crystals of *N*-[(*p*-chlorophenyl)thio]-1,4-benzoquinone 4-imine (**29**): 2.4 g (32%); mp 153 °C; ^{1}H NMR ($CDCl_3$) δ 6.49 (dd, 1 H, H-6, J = 10.0, 2.8 Hz), 6.57 (dd, 1 H, H-2, J = 10.1, 2.8 Hz), 7.12 (dd, 1 H, H5, J = 10.0, 2.15 Hz), 7.41 (dd, 1 H, H-3, J = 10.1, 2.15 Hz), AA′XX′ pattern 7.41 (m, 2 H, aromatic protons ortho to S), 7.53 (m, 2 H, aromatic protons ortho to Cl), $J_{AX} + J_{AX'}$ = 8.8 Hz; IR ($CHCl_3$) 1635, 1605, 1475, 1155, 1090, 865, 820 cm^{-1}; UV (CH_2Cl_2) 283 nm (ϵ 1.5 × 10^4), 441 (2.0 × 10^4); mass spectrum, *m/e* (relative intensity) 251 (38, M^+), 249 (100, M^+), 214 (16, M – Cl), 145 (32, *p*-$ClC_6H_4S^+$), 143 (90, *p*-$ClC_6H_4S^+$), 108 (62), 99 (14), 80 (19).

Anal. Calcd for $C_{12}H_8ClNOS$: C, 57.72; H, 3.23; Cl, 14.20; N, 5.61; S, 12.84. Found: C, 57.83; H, 2.98; Cl, 14.38; N, 5.70; S, 12.44.

The thioxime was converted to the *S*-oxide with *m*-chloroperbenzoic acid in dichloromethane in the usual fashion[29] in 65% yield: mp 115–116 °C (ethanol); ^{1}H NMR ($CDCl_3$) 6.59 (br d, 2 H, H2 and H6, $J \simeq$ 10 Hz), 7.02 (m, 1 H, H5), 8.47 (m, 1 H, H3), AA′XX′ pattern 7.52 (m, 2 H, aromatic protons ortho to Cl), 7.74 (m, 2 H, aromatic protons ortho to S→O), $J_{AX} + J_{AX'}$ = 8.8 Hz; IR 1655, 1620, 1470, 1085, 1010, 870 cm^{-1}; UV (ethanol) 213 nm (ϵ 1.31 × 10^4), 257 (2.02 × 10^4), 297 (1.17 × 10^4), 392 (3.7 × 10^3).

Anal. Calcd for $C_{12}H_8ClNO_2S$: C, 54.24; H, 3.03; Cl, 13.34; N, 5.27. Found: C, 54.39; H, 3.22; Cl, 13.19; N, 5.14.

Addition of Bromine and Chlorine to Methyloximes 1–3. A solution of the appropriate methyloxime (10–15 mmol) in the solvent (10–20 mL) specified in Table II was stirred at 20 °C, bromine (5% excess) was added by syringe (or dry chlorine was passed through the solution), and the reaction was allowed to stand until complete (10–90 min). The solvent was removed under reduced pressure, and the products were identified (see Table I) and their proportions estimated (see Table II) by ^{1}H NMR. In all cases yields in excess of 95% were obtained. The individual reaction mixtures were partly separated into components as follows.

Bromine and 1. Three recrystallizations of the reaction mixture from cyclohexane gave (*Z*)-*trans*-5,6-dibromo-2-cyclohexene-1,4-dione 4-(*O*-methyloxime) (**4**): mp 117–118 °C (lit.[7] mp 123 °C); ^{1}H NMR data, see Table I, entry 1; IR ($CHCl_3$) 1690, 1600, 1055, 1030 cm^{-1}; UV (cyclohexane) 285 nm (ϵ 7.2 × 10^3).

Bromine and 2. Recrystallization of the reaction mixture from cyclohexane gave (*Z*)-*trans*-5,6-dibromo-3-methyl-2-cyclohexane-1,4-dione 4-(*O*-methyloxime) (**7**): 70–80% yield; mp 109.5–110 °C (lit.[8] mp 112 °C); ^{1}H NMR, see Table I, entry 4; IR ($CHCl_3$) 1680, 1050 cm^{-1}; UV (cyclohexane) 284 nm (ϵ 6.9 × 10^3).

Bromine and 3a and 3b. Recrystallization of the reaction mixture from cyclohexane gave initially the isomer **9**. Later fractions consisting of **9** and **10** and even those containing high proportions of **10** could not be purified (by preparative LC or recrystallization) to yield pure **10**. Further recrystallization of the early crystalline fractions from cyclohexane gave (*E*)-*trans*-5,6-dibromo-2-methyl-2-cyclohexene-1,4-dione 4-(*O*-methyloxime) (**9**): 30–40% yield; mp 110–111 °C; ^{1}H NMR data, see Table I, entry 6; IR ($CHCl_3$) 1685, 1055, 1035, 1000, 920 cm^{-1}; UV (cyclohexane) 247 nm (ϵ 6.12 × 10^3), 304 (7.75 × 10^3).

Anal. Calcd for $C_8H_9Br_2NO_2$: C, 30.90; H, 2.92; Br, 51.39; N, 4.51. Found: C, 31.08; H, 3.01; Br, 51.39; N, 4.64.

The reaction mixture containing **8–10** from treatment of **3** (**3a**/**3b** ratio of 9:1) with bromine in dichloromethane was treated with an excess of triethylamine (see the general procedure below). The isomers **9** and **10** (nearly identical with isomer **8** on TLC)

(24) Epiotis, N.; Yates, R. L.; Larson, J. R.; Kirmaier, C. R.; Bernardi, F. *J. Am. Chem. Soc.* **1977**, *99*, 8379.
(25) Beaulieu, N.; Deslongchamps, P. *Can. J. Chem.* **1980**, *58*, 164.
(26) Houk, K. N.; Strozier, R. W.; Rondan, N. G.; Fraser, R. R.; Chuaqui-Offermanns, N. *J. Am. Chem. Soc.* **1980**, *102*, 1426 and references therein.
(27) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
(28) Veibel, S.; Simesen, M. H. *Chem. Ber.* **1930**, *63*, 2476.
(29) Almog, J.; Barton, D. H. R.; Magnus, P. D.; Norris, R. K. *J. Chem. Soc., Perkin Trans. 1* **1974**, 853.

were converted to the more polar compounds **17** and **18** (see below), allowing isolation of **8** by preparative LC in 15–20% yield. (*Z*)-*trans*-5,6-Dibromo-6-methyl-2-cyclohexene-1,4-dione 4-(*O*-methyloxime) (**8**) was an oil, which decomposed at room temperature after several weeks to mixtures of **8–10** (the latter predominating). The ether **8** had the following spectroscopic data: ^{1}H NMR, see Table I, entry 5; IR ($CHCl_3$) 1690, 1605, 1050 cm^{-1}; UV (cyclohexane) 290 nm (ϵ 2.99 × 10^4).

Anal. Calcd for $C_8H_9Br_2NO_2$: C, 30.90; H, 2.92; Br, 51.39; N, 4.51. Found C, 31.10; H, 2.96; Br, 51.59; N, 4.43.

Chlorine and 1. Recrystallization of the reaction mixture from cyclohexane several times gave (*Z*)-*trans*-5,6-dichloro-2-cyclohexene-1,4-dione 4-(*O*-methyloxime) (**11**): 40–50% yield; mp 92–93 °C (lit.[6] mp 93 °C); for ^{1}H NMR data, see Table I, entry 8; IR ($CHCl_3$) 1695, 1605, 1055, 1035 cm^{-1}; UV (cyclohexane) 278 nm (ϵ 1.71 × 10^4).

Elimination of Hydrogen Halide from 4, 5, 7, and 9–12. The purified dihalide (see above) or mixture of dihalides (ca. 200 mg) was dissolved in dichloromethane (10 mL), and excess triethylamine (ca. 0.5 mL) was added. The elimination reactions were complete in less than 5 min. The workup consisted of dilution with dichloromethane (20 mL) and consecutive washing with 2 M hydrochloric acid (50 mL), water (100 mL), and brine (50 mL). The organic phase was dried over potassium carbonate and the solvent removed under reduced pressure to give high recoveries (over 90%) of the dehydrohalogenated compounds. Similar experiments were monitored in $CDCl_3$ by ^{1}H NMR by addition of triethylamine to solutions of the appropriate dihalides. In no cases were 3- and 5-halogenated products formed.

Conversion of 4 (and 5) into 13 and 14. Treatment of **4** in $CDCl_3$ with triethylamine was shown by ^{1}H NMR to give the *Z* isomer **13** which slowly equilibrated with the *E* isomer **14**. Reactions on a preparative scale with **4** alone or mixtures of **4** and **5** (see above) gave nearly quantitative yields of mixtures of (*Z*)-2-bromo-1,4-benzoquinone 4-(*O*-methyloxime): ^{1}H NMR δ 4.22 (s, 3 H, OMe), 6.62 (d, 1 H, H6, J = 9.9 Hz), 7.22 (dd, 1 H, H5, J = 9.9, 2.4 Hz), 8.13 (d, 1 H, H3, J = 2.4 Hz). Also obtained was (*E*)-2-bromo-1,4-benzoquinone 4-(*O*-methyloxime): ^{1}H NMR δ 4.21 (s, 3 H, OMe), ABX system 6.60 (H6), 7.65 (H5), 7.66 (H3), $J_{3,5}$ = 2.4 Hz and $J_{5,6}$ = 10.2 Hz. Recrystallization of the mixture of isomers from benzene–petroleum ether gave the pure *Z* isomer **13**: mp 124.5–125 °C (lit.[30,31] mp 105–106 °C); IR ($CHCl_3$) 1640, 1560, 1510, 1310, 1055, 985, 870 cm^{-1}; UV (ethanol) 234 nm (ϵ 3.33 × 10^3), 325 (2.13 × 10^4).

Anal. Calcd for $C_7H_6BrNO_2$: C, 38.92; H, 2.80; Br, 37.00; N, 6.48. Found: C, 38.72; H, 2.73; Br, 37.35; N, 6.65.

Conversion of 11 (and 12) into 15 (and 16). The above conversions took place readily without significant *E*/*Z* isomerization. No trace of the 3-chloro isomer could be detected (<1% by ^{1}H NMR) and the *Z* and *E* isomers **15** and **16** had identical ^{1}H NMR parameters with those reported in the literature.[5] Recrystallization from dichloromethane–cyclohexane gave (*Z*)-2-chloro-1,4-benzoquinone 4-(*O*-methyloxime) (**15**), mp 120–121 °C (lit.[5] mp 121–122 °C).

Conversion of 9 (and 10) into 18 (and 19). Pure samples of **9** or mixtures with **10** were converted in the usual fashion to **18** which equilibrated under the reaction conditions with isomer **19** (**18**/**19** ratio of ~1:1). Recrystallization from ethanol gave yellow needles (mp 110–111 °C) of (*E*)-2-bromo-6-methyl-1,4-benzoquinone 4-(*O*-methyloxime) (**19**): ^{1}H NMR ($CDCl_3$) δ 2.10 (d, 3 H, Me, J = 1.5 Hz), 4.18 (s, 3 H, OMe), 7.47 (dq, 1 H, H5, J = 2.4, 1.5 Hz), 7.57 (d, 1 H, H3, J = 2.4 Hz); IR ($CHCl_3$) 1645, 1515, 1285, 1055, 1010, 925, 910 cm^{-1}; UV (ethanol) 323 nm (ϵ 1.87 × 10^4).

Anal. Calcd for $C_8H_8BrNO_2$: C, 41.77; H, 3.50; Br, 34.73; N, 6.09. Found: C, 41.82; H, 3.62; Br, 35.04; N, 6.31.

The *E* isomer **18** had the following ^{1}H NMR ($CDCl_3$): δ 2.09 (d, 3 H, Me, J = 1.45 Hz), 4.16 (s, 3 H, OMe), 7.01 (dq, 1 H, H5, J = 2.60, 1.45 Hz), 8.07 (d, 1 H, H3, J = 2.60 Hz).

Conversion of 7 into 20. Treatment of **7** in the usual way gave a nearly quantitative yield of **20**, which on recrystallization from ethanol gave bright yellow needles of (*E*)-2-bromo-5-methyl-1,4-benzoquinone 4-(*O*-methyloxime) (**20**): mp 115 °C; ^{1}H NMR δ 2.20 (d, 3 H, Me, J = 1.3 Hz), 4.18 (s, 3 H, OMe), 6.43 (q, 1 H, H6, J = 1.3 Hz), 8.08 (s, 1 H, H3); IR ($CHCl_3$) 1645, 1510, 1330, 1060, 930, 855 cm^{-1}; UV (ethanol) 233 nm (ϵ 1.74 × 10^3), 326 (1.72 × 10^4).

Anal. Calcd for $C_8H_8BrNO_2$: C, 41.77; H, 3.50; Br, 34.73; N, 6.09. Found: C, 41.66; H, 3.69; Br, 34.63; N, 6.30.

Isomerization of 9 with Hydrogen Bromide. Hydrogen bromide was bubbled through a 10% solution of **9** (or mixtures of **8–10**) in dry chloroform at room temperature. A white precipitate formed, which on being shaken with an equal volume of water redissolved. Evaporation of the dried chloroform layer gave mixtures in which the proportion of **9** (and **8** if originally present) had decreased and has been replaced by **10**. A repeat of this procedure (readily accomplished in an NMR tube with $CDCl_3$ as solvent and with D_2O washes) gave a mixture of **9** and **10** (with traces of **8** and **3**) in the approximate ratio of **9**/**10** of 1:3.

Diels–Alder Reactions of Cyclopentadiene with Methyloximes 1–3. The appropriate methyloxime (10–15 mmol) was heated under reflux with freshly distilled cyclopentadiene (4–7 mL) in a flask immersed in an oil bath at 50–60 °C for the times specified below. Reflux ceased after 4.5–5 h, and reactions performed for longer than 5 h were supplemented by addition of a further aliquot (4–7 mL) of freshly distilled cyclopentadiene. The crude product was chromatographed on a silica column under medium pressure.[27] The neat reaction mixture was applied to the column, which was then eluted with cyclohexane to remove all cyclopentadiene-derived hydrocarbons. The column was then eluted with acetone to remove all the Diels–Alder adducts. A nearly quantitative yield of 1:1 adducts was obtained in all cases. ^{1}H NMR spectroscopy in $CDCl_3$ was performed to estimate product ratios, and the major products were isolated by recrystallization. Similar product distributions were obtained (but the products were contaminated with hydrocarbon impurities) when the cyclopentadiene dimer was removed at 50–60 °C (0.01 mm).

The ^{1}H NMR data for the products from these reactions are collected in Table III.

The following compounds were isolated.

(*Z*)-*endo*-Tricyclo[6.2.1.0^{2,7}]undeca-4,9-diene-3,6-dione 6-(*O*-methyloxime) (23) was obtained in 60% yield from **1** after 4 h: mp 95–96 °C (several recrystallizations from petroleum ether); IR ($CHCl_3$) 1655, 1605, 1570, 1070, 1040, 930, 900, 850, 830 cm^{-1}; UV (cyclohexane) 226 nm (ϵ 3.6 × 10^3), 281 (6.8× 10^3); mass spectrum, *m*/*e* 203 (M$^+$).

Anal. Calcd for $C_{12}H_{13}NO_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.76; H, 6.42; N, 7.15.

(*E*)-*endo*-4-Methyltricyclo[6.2.1.0^{2,7}]undeca-4,9-diene-3,6-dione 6-(*O*-methyloxime) (26) was obtained from **3** in 20–30% yield after 8–17 h: mp 71–72 °C (after four recrystallizations at 0 °C from petroleum ether (bp 30–40 °C)); IR ($CHCl_3$) 1655, 1570, 1065, 1045, 900 cm^{-1}; UV (cyclohexane) 287 nm (ϵ 1.38 × 10^4), 230 (7.4 × 10^3).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 71.93; H, 6.94; N, 6.50.

(*E*)-*endo*-5-Methyltricyclo[6.2.1.0^{2,7}]undeca-4,9-diene-3,6-dione 6-(*O*-methyloxime) (21) was obtained in 70% yield from **2** after 5 h: mp 65–66 °C (after two recrystallizations from petroleum ether (bp 30–40 °C)); IR ($CHCl_3$) 1650, 1610, 1060, 1045 cm^{-1}; UV (cyclohexane) 280 nm (ϵ 1.11 × 10^4).

Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.86; H, 6.96; N, 6.45. Found: C, 72.06; H, 6.97; N, 6.57.

(*Z*)-*endo*-6-[[(*p*-Chlorophenyl)thio]imino]tricyclo-[6.2.1.0^{2,7}]undeca-4,9-dien-3-one (30) was obtained in 75% yield from **29** in 1.5 h: mp 103 °C (from cyclohexane); IR ($CHCl_3$) 1655, 1595, 1475, 1270, 1090, 1015, 820 cm^{-1}; UV (cyclohexane) 269 nm (ϵ 1.06 × 10^4), 361 (1.7 × 10^4).

Anal. Calcd for $C_{17}H_{14}ClNOS$: C, 64.66; H, 4.47; N, 4.44; Cl, 11.23; S, 10.15. Found: C, 64.77; H, 4.50; N, 4.55; Cl, 10.99; S, 9.89.

Acknowledgment. We are grateful to the Royal Society for financial assistance (to R.K.N.).

(30) Hodgson, H. H.; Donaldson, D. E. *J. Chem. Soc.* **1940**, 810.
(31) Ramart-Lucas, P.; Martynoff, M.; Grumez, M.; Chauvin, M. *Bull. Soc. Chim. Fr.* **1949**, 901.

Registry No. **1**, 15312-05-7; **2**, 18424-78-7; **3a**, 37405-19-9; **3b**, 37405-33-7; **4**, 75626-24-3; **5**, 75684-21-8; **6**, 75626-25-4; **7**, 75626-26-5; **8**, 75626-27-6; **9**, 75626-28-7; **10**, 75684-22-9; **11**, 75626-29-8; **12**,

75684-23-0; **13**, 75626-30-1; **14**, 75626-31-2; **15**, 17302-56-6; **16**, 17302-57-7; **18**, 75626-32-3; **19**, 75626-33-4; **20**, 75626-34-5; **21**, 75626-35-6; **22**, 75684-24-1; **23**, 75626-37-7; **24**, 75684-25-2; **25**, 75684-26-3; **26**, 75626-37-8; **27**, 75684-27-4; **28**, 75684-28-5; **29**, 75142-03-9; **29** *S*-oxide derivative, 75626-38-9; **30**, 75626-39-0; toluquinone, 553-97-9; bis(*p*-chlorophenyl) disulfide, 1142-19-4; *p*-chlorobenzenesulfenyl chloride, 933-01-7; *p*-aminophenol, 123-30-8; cyclopentadiene, 542-92-7.

Computer-Assisted Structural Interpretation of Carbon-13 Spectral Data[1]

Neil A. B. Gray, Christopher W. Crandell, James G. Nourse, Dennis H. Smith,*
Mary L. Dageforde, and Carl Djerassi*

Department of Chemistry, Stanford University, Stanford, California 94305

Received July 8, 1980

Computer programs for interpretation and prediction of ^{13}C resonance spectra are described. These programs utilize a data base containing representations of the substructural environments of resonating nucleii together with their chemical shifts. These representations capture both molecular constitution and configuration, permitting for the first time in a computer program a comprehensive treatment of configurational stereochemical influences on ^{13}C chemical shifts. Substructural features of an unknown structure are derived directly and automatically by ^{13}C interpretive procedures. These features, together with additional structural information, are used to construct structural candidates for the unknown. ^{13}C predictive procedures permit rank ordering of the candidates on the basis of agreement between predicted and observed ^{13}C spectra. Applications of these programs to organic structure determination are illustrated through analyses of the structures of some diterpenes.

Early in the decade it was suggested that ^{13}C spectroscopy was likely to prove the most important physical method of analysis in the 1970's.[2] ^{13}C resonance data are indeed now routinely reported in papers on structure elucidation of natural products. Generally, however, the interpretation of a ^{13}C spectrum is limited to deriving the number of CH_3's, CH_2's, and CH's from the multiplicities in the SFORD (single-frequency off-resonance decoupled) spectrum and determining the number of sp^2 carbon atoms from the gross chemical shifts. This is in spite of the fact that the chemical shift for a carbon nucleus is a sensitive probe of its stereochemical environment; observed shift values should reveal much about the bonding of individual atoms in an unknown structure. There is an obvious potential for automated systems that can help analyze ^{13}C data in order to derive more of the implicit structural information. Such automated systems would aid both manual and computer-assisted explorations of structural possibilities for an unknown.

Programs for computer-assisted structure determination[3-7] can make use of spectral data such as ^{13}C resonances in two distinct ways. The first is in *interpretation* of data to obtain substructural information. These programs typically work by finding all ways of assembling or generating candidate structures for an unknown from substructural fragments (which may overlap in the case of GENOA[4]) whose presence has been inferred by interpretation of IR, proton resonance, and chemical data. Programs that could infer substructural fragments from ^{13}C data would constitute a valuable adjunct to these standard sources of structural information. The second use is in *prediction* of spectra to evaluate the merit of each candidate. Once the structure-generating programs have created a set of candidate structures compatible with all given substructural constraints and, where appropriate, incorporating configurational stereochemistry,[1] the structural candidates can be ranked by determining some measure of how well each serves to rationalize observed spectral data. This approach has been applied previously in the context of mass spectral data.[8,9] ^{13}C spectral data can be used in similar fashion given suitable spectrum prediction and comparison functions.

In this paper we describe computer programs for inferring substructural information from ^{13}C data and for ^{13}C spectrum prediction together with ranking of candidate structures. The system that we have devised for these primary tasks has also proven of value in secondary applications such as aiding in the assignment of observed ^{13}C resonances to the respective atoms of a known structure.

In contrast to the very extensive work on computer systems for processing mass spectral data,[10] only a limited amount has been published on computerized analysis of ^{13}C data. Pattern-recognition methods, for classifying ^{13}C spectra according to the presence or absence of specific

(1) Part 34 of the series "Applications of Artificial Intelligence for Chemical Inference". For part 33 see J. G. Nourse, D. H. Smith, R. E. Carhart, and C. Djerassi, *J. Am. Chem. Soc.*, **102**, 6289 (1980).
(2) C. Djerassi, "^{13}C NMR Spectroscopy", E. Breitmaier and W. Voelter, Eds., Verlag Chemie, Weinheim/Bergstr., Germany, 1974, preface.
(3) R. E. Carhart, D. H. Smith, H. Brown, and C. Djerassi, *J. Am. Chem. Soc.*, **97**, 5755 (1975).
(4) R. E. Carhart, D. H. Smith, N. A. B. Gray, J. G. Nourse, and C. Djerassi, *J. Org. Chem.*, in press.
(5) M. E. Munk, C. S. Sodano, R. L. McLean, and T. H. Haskell, *J. Am. Chem. Soc.*, **89**, 4158 (1967).
(6) S. Sasaki, Y. Kudo, S. Ochiai, and H. Abe, *Mikrochim. Acta*, 726 (1971).
(7) L. A. Gribov and M. E. Elyashberg, *CRC Crit. Rev. Anal. Chem.*, 8, 110 (1979).
(8) N. A. B. Gray, R. E. Carhart, A. Lavanchy, D. H. Smith, T. Varkony, B. G. Buchanan, W. C. White, and L. Creary, *Anal. Chem.*, **52**, 1095 (1980).
(9) A. Lavanchy, T. Varkony, D. H. Smith, N. A. B. Gray, W. C. White, R. E. Carhart, B. G. Buchanan, and C. Djerassi, *Org. Mass Spectrom.*, **15**, 355 (1980).
(10) G. M. Pesyna and F. W. McLafferty in "Determination of Organic Structures by Physical Methods", Vol. 6, F. C. Nachod, J. J. Zuckermann, and E. W. Randall, Eds., Academic Press, New York, 1976, p 91.

0022-3263/81/1946-0703$01.00/0