

Origin of Apparent Stereoelectronic Effects in Structure and Reactivity of Benzoquinone Monooximes

Charles L. Perrin* and Richard E. Engler

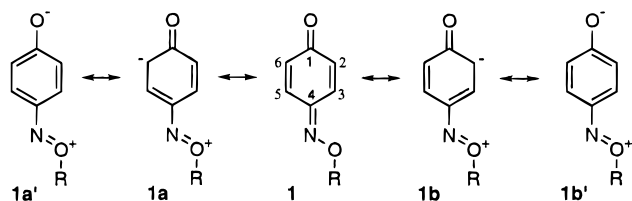
Department of Chemistry, University of California San Diego, La Jolla, California 92093-0358

Received July 22, 1996[®]

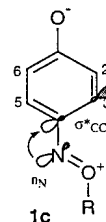
The origin of some unusual “sidedness” effects in 1,4-benzoquinone oximes is reinvestigated. It had been observed that (1) the NMR coupling constant J_{23} is larger than J_{56} , (2) substituents at the 2 position affect the position of the *E/Z* equilibrium, and (3) addition reactions show a syn stereoselectivity. It was proposed that the nitrogen lone pair is delocalized into the σ^* orbital of the antiperiplanar C3–C4 bond, thereby lengthening that bond and increasing the contribution of resonance forms with a C2–C3 double bond. Semiempirical MO calculations now show that the C3–C4 bond is not lengthened in benzoquinone oximes and analogous molecules. Protonated 1,4-benzoquinone 4-hydroxymethide is synthesized as a comparison lacking the nitrogen lone pair, and the H–H coupling constants are measured. Again J_{23} is larger than J_{56} . Therefore the difference in the coupling constants is not due to the nitrogen lone pair. The effect of 2-substituents on the *E/Z* equilibrium is attributed to electrostatic interactions. According to calculations, the hydroxyl oxygen is within van der Waals contact with H3. We therefore conclude that steric effects are primarily responsible for the observed sidedness, both in the stereoselectivity and the coupling constants in both quinone oximes and quinone methides.

Introduction

1,4-Benzoquinone monooximes (**1**) show a remarkable and novel “sidedness” in their structure and reactivity. Norris and Sternhell observed that the vicinal coupling constant J_{23} in **1** (R = H or anion) is 0.03 to 0.35 Hz greater than J_{56} .¹ Such differences are also seen in substituted derivatives, where the stereoisomer with the unsubstituted double bond syn to the OH has the larger coupling constant. They also observed that substituents at C2 of **1** (R = H or anion) affect the *E/Z* equilibrium, with electron withdrawal favoring the “anti” (*E*) form and electron donation favoring the “syn” (*Z*). For example, there is 28% *E* with a 2-CF₃ substituent but 86% *E* with 2-OCH₃. This same behavior of coupling constants and equilibrium constants is also seen in **1** (R = CH₃, COCH₃), with J_{23} as much as 0.6 Hz greater than J_{56} .² The substituent effects do not correlate with the steric bulk of the substituents, which are too far from the oxime OH to interact. Nor do they correlate with dipole moment. Norris and Sternhell therefore proposed that the canonical resonance form **1a** contributes more to the structure of **1** than does form **1b**. The inequalities of both negative charge and double-bond character would then account for the observations. However, the relative importance of the two resonance forms was an *ad hoc* assumption, and this seems questionable, in view of the greater charge separation in **1a**.



Baldwin and Norris found that the syn double bond (C2–C3) in **1** (R = CH₃) is more reactive toward addition of halogen and toward Diels–Alder addition of cyclopentadiene than is the anti bond (C5–C6).³ Yields of syn-substituted products (**2Z**) ranged from 72 to 98%. The halogenations are kinetically controlled, whereas the Diels–Alder products equilibrate under the reaction conditions and are under thermodynamic control. In neither case is there the polar effect proposed to account for the above equilibria of 2-substituted quinoneoximes. They therefore proposed a stereoelectronic effect to explain these observations and the previous ones. They hypothesized that the nitrogen lone pair donates electron density to the σ^* orbital of C3–C4, thereby lengthening that bond and reducing the contribution of resonance forms (**1b**, **1b'**) in which that bond is double. This corresponds to the delocalization that is often invoked to account for anomeric stabilization.⁴ Thus the C2–C3 bond would become a more isolated double bond, as exaggerated in **1c**. This hypothesis then justifies the

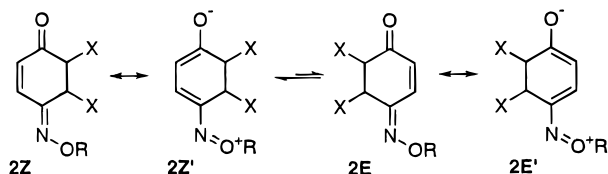


previous assumption that **1a** contributes more than **1b**. Also, lengthening of C3–C4 in **2E** destabilizes that isomer by destabilizing resonance form **2E'**, whereas **2Z'** contributes to and stabilizes **2Z**.

This hypothesis does not explain the stereospecificity of the halogenations, where the mechanism is uncertain. If C6 is the site of greatest electron density, as suggested by the substituent effects and by resonance form **1a**, then

[®] Abstract published in *Advance ACS Abstracts*, January 15, 1997.
 (1) Norris, R. K.; Sternhell, S. *Aust. J. Chem.* **1969**, *22*, 935.
 (2) Norris, R. K.; Sternhell, S. *Aust. J. Chem.* **1971**, *24*, 1449. Norris, R. K.; Sternhell, S. *Aust. J. Chem.* **1972**, *25*, 1907.

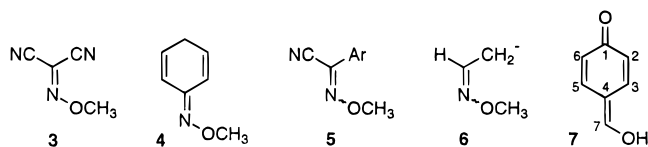
(3) Baldwin, J. E.; Norris, R. K. *J. Org. Chem.* **1981**, *46*, 697.
 (4) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: Berlin, 1983.



it should also be the site of attack by electrophilic halogen. Since halogen instead adds to the more isolated C2–C3 double bond, presumably the mechanism involves a halonium ion intermediate, as is consistent with the observed trans addition. Yet the oxime oxygen ought to stabilize the cation, as in halogenation of enols, and eliminate the necessity for the intermediacy of a halonium ion.

Other groups have noted similar stereochemical phenomena. Diels–Alder addition of cyclopentadiene to 3,6-cycloheptadiene-1,2,5-trione 5-(*O*-acetyloxime) shows 70% syn selectivity.⁵ A preference for electrophilic aromatic substitution syn-ortho to a methoxy or hydroxy group has been attributed to $n\text{-}\sigma^*$ donation of oxygen lone pairs.⁶ Variations in the infrared frequencies of some acylguanidines have been attributed to $n\text{-}\sigma^*$ donation.⁷

Two sets of MNDO calculations do not support $n\text{-}\sigma^*$ delocalization of lone pairs in oxime derivatives, leading to the lengthening of antiperiplanar bonds, as expressed by **1c**. In **3**, **4**, and **5** (Ar = Ph) the bonds anti to the nitrogen lone pair are 2–3 mÅ shorter than those syn.⁸ The C–C single bonds anti to the oxygen or nitrogen lone pair in several derivatives of oximes and enols are shorter and stronger than the syn bonds.⁹ The stereospecificity of addition reactions of **1** (R = CH₃) was then attributed to the shorter C–C bond, which provides better conjugation between the C–C and C–N double bonds. It is not clear why the better conjugation increases reactivity, rather than decrease it by reducing the double-bond character, as had been suggested previously.³



In contrast, 3-21+G *ab initio* calculations on the (*E*) and (*Z*) stereoisomers of acetaldehyde oxime and oximate (**6**) find that the bond antiperiplanar to the nitrogen lone pair is 1–2 mÅ longer than the syn.¹⁰ The greater stability of the stereoisomer of anion **6** with CH₂ cis to OH was attributed to electrostatics.

The origin of the sidedness of coupling constants, of the effect of 2-substituents, and of the addition stereoselectivity is still unknown. This is an intriguing puzzle. It cannot be accounted for by simple Hückel theory, since the two sides of the quinone oxime are equivalent in a topological or graph-theoretic sense. Besides, there is

(5) Saito, I.; Sakan, K.; Ito, S. *Chem. Lett.* **1977**, 253.

(6) Kruse, L. I.; Cha, J. K. *J. Chem. Soc., Chem. Commun.* **1982**, 1333.

(7) Greenhill, J. V.; Ismail, M. J.; Bedford, G. R.; Edwards, P. N.; Taylor, P. J. *J. Chem. Soc., Perkin Trans. 2* **1985**, 1265.

(8) Johnson, J. E.; Todd, S. L.; Ghafouripour, A.; Arfan, M.; Hamilton, W. S.; Exner, O. *J. Phys. Org. Chem.* **1990**, 3, 316.

(9) Elliott, R. J.; Richards, W. G. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1005.

(10) Glaser, R.; Streitwieser, A. *J. Am. Chem. Soc.* **1989**, 111, 7340.

(11) Bürgi, H. B.; Baldrige, K. K.; Hardcastle, K.; Frank, N. L.; Gantzel, P.; Stegel, J. S.; Ziller, J. *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 1454. Rouhi, A. M. *Chem., Eng. News* **1996** (April 1), p 27.

recent interest in the possibility of fixing benzene into a cyclohexatriene,¹¹ akin to the above proposal that resonance forms **1a** and **1a'** contribute more than **1b** and **1b'**. Accordingly we sought to reinvestigate these phenomena with additional calculations and experiments.

Previous results are inconclusive because they lack appropriate controls. To test whether the nitrogen lone pair is responsible for the observed sidedness phenomena, we carry out calculations not only on the quinone oximes (**1**, **8**, **9**, **12**) but also on their CH analogs (**7**, **10**, **11**, **13**) for comparison. These analogs are appropriate controls because the absence of the nitrogen lone pair precludes any stereoelectronic effect. We also examine other possible causes.

To confirm the computational results we would ideally compare the experimental behavior of **1** and **7**. The latter is a tautomer of *p*-hydroxybenzaldehyde and is very unstable. We attempted to synthesize the methyl ether of **7** from *p*-hydroxybenzaldehyde and trimethylxonium tetrafluoroborate. Although the 2,6-di-*tert*-butyl analog of this quinone methide is known,¹² the parent could not be isolated. Fortunately the conjugate acid (**14**), which is common to both the quinone methide and *p*-hydroxybenzaldehyde, is stable enough to measure the ¹H/¹H coupling constants J_{23} and J_{56} and is used as the model for a quinone methide to provide experimental evidence to corroborate the computational findings.

Experimental Section

Materials and Sample Preparation. Commercial *p*-hydroxybenzaldehyde, dimethyl sulfate, tetramethylsilane (Aldrich), acetone-*d*₆, chloroform-*d* (Cambridge Isotope Labs), and trifluoromethanesulfonic acid (3M) were used without further purification. *p*-Nitrosophenol (Aldrich) was taken up in acetone and filtered. The acetone was then evaporated.

1,4-Benzoquinone *O*-methyloxime (**1**, R = CH₃) was prepared from *p*-nitrosophenol and dimethyl sulfate in aqueous NaOH according to Veibel and Simeson:¹³ mp 80–82 °C, lit. mp 83 °C; NMR: see Table 6.

The conjugate acid of *p*-hydroxybenzaldehyde (protonated 1,4-benzoquinone hydroxymethide, **14**) was prepared by slowly dissolving ca. 0.4 g of *p*-hydroxybenzaldehyde in 1.0 mL of trifluoromethanesulfonic acid with occasional agitation. Acetone-*d*₆ was used as NMR lock signal and external reference (¹H δ 2.04, ¹³C δ 29.8) in the inner chamber of a Wilmad coaxial tube; NMR: see Table 7.

¹H and ¹³C NMR Spectroscopy. All NMR spectra were acquired on a Varian Unity 500 spectrometer operating at 499.84 MHz (¹H) or at 125.70 MHz (¹³C). Spectra of **1** (R = CH₃) were acquired at 25 °C. Cooling the sample to between –10 °C and 5 °C was required to slow the rotation around the C4–C7 double bond of **14**. Probe temperatures were measured with the instrument's thermocouple.

Proton NMR spectra were acquired with 32 scans. A sweep width of 4000 Hz and 121,088 data points were used, giving a digital resolution of 0.06 Hz/point. Pulse widths were 5.5 μs and acquisition times were ca. 15 s. Line broadening of 0.3 Hz was added but did not change observed coupling constants by more than the 0.06 Hz resolution, since the signals were already relatively broad. Significant second-order coupling was observed in the ¹H NMR spectrum of **1** (R = CH₃). Spectral simulations using the spectrometer software were necessary to extract chemical shifts and coupling constants.

Carbon NMR spectra were typically acquired with 1000 scans although peaks were clearly visible with as few as 50 or 100 scans. Sweep widths of 34995.6 Hz and 91008 points were

(12) Rieker, A.; Kessler, H. *Tetrahedron* **1968**, 24, 5133. Volod'kin, A. A.; Ershov, V. V.; Ostapets-Svesnikova, G. D. *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)* **1969**, 580.

(13) Veibel, S.; Simeson, M. *Chem. Ber.* **1930**, 63, 2476.

employed. Line broadening of 1.0 Hz was added. Spectra were acquired both with and without ^1H decoupling. $^1\text{H}/^{13}\text{C}$ coupling constants were read from the fully coupled spectra. Coupling constants smaller than 2 Hz are not reported. $^1\text{H}/^{13}\text{C}$ correlations were done by sequentially and selectively decoupling each of the ^1H signals and observing the disappearance of coupling in the ^{13}C spectra. Protons H2 and H6 could not be selectively decoupled.

Calculations. Molecular mechanics calculations were carried out with MMX (PCMODEL) on a Macintosh computer.¹⁴ All MO calculations were done on the Cray Y-MP supercomputer at the San Diego Supercomputer Center. Semiempirical calculations used MOPAC¹⁵ with both AM1¹⁶ and PM3¹⁷ parametrization. Since AM1 relative energies for the stereoisomeric **8**, **9**, and **12** do not agree with experimental results, only PM3 results are listed. When computations could be repeated with different starting geometries, bond lengths varied less than 10^{-5} Å, bond and dihedral angles varied less than 0.0001° , and heats of formation varied less than 10^{-5} kcal/mol. The conformation about the N–O bond was fixed as anti. All parameters were optimized except in the case of (*E*)-**12** and (*Z*)-**12**, where the global minima were nonplanar and ca. 2–3 kcal/mol lower in energy than the planar forms. Since we are modeling a Diels-Alder adduct, the structures of (*E*)-**12** and (*Z*)-**12** were forced to be planar. All other structures were within 0.2° of planar. Mulliken and natural population analysis (NPA)¹⁸ atomic charges were evaluated at PM3-optimized geometries but from RHF/STO-3G wave functions, calculated with Gaussian 94.¹⁹

Data Analysis. A stereoelectronic effect in an oxime, **1**, **8**, **9**, or **12**, should produce a longer C3–C4 bond (syn to the OH, anti to the nitrogen lone pair) relative to C4–C5 (or in **12Z** and **13Z** relative to **12E** and **13E**). (For consistency, this numbering scheme is used regardless of the position of substitution on the ring.) This bond-length difference is expressed by Δd (eq 1). A positive Δd indicates that the bond

$$\Delta d = d_{\text{C3-C4}} - d_{\text{C4-C5}} \quad (1)$$

anti to the lone pair is longer than the syn bond. However, since other effects besides the nitrogen lone pair may govern the bond lengths, one must compare the Δd 's of both the oxime and the model CH analog to attribute differences to the lone pair. If $\Delta\Delta d$ (eq 2) is positive, then the bond lengthening in the oxime could be due to a stereoelectronic effect (although other explanations of course would not be excluded).

$$\Delta\Delta d = \Delta d_{\text{N}} - \Delta d_{\text{CH}} \quad (2)$$

Stabilization of the *E* form over the *Z* form can be assessed with these computational methods. A positive ΔE , defined in eq 3, would indicate that the *E* form is more stable than the *Z*. Also, a positive $\Delta\Delta E$, defined in eq 4, would be expected if

$$\Delta E = \Delta H_f(\text{Z}) - \Delta H_f(\text{E}) \quad (3)$$

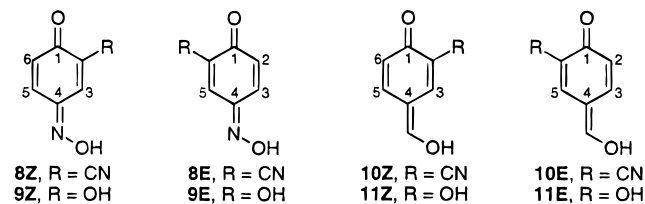
a stereoelectronic effect is operative, since the difference in stabilities would be larger in the oxime.

$$\Delta\Delta E = |\Delta E_{\text{N}}| - |\Delta E_{\text{CH}}| \quad (4)$$

Results

Computations. Table 1 shows the heats of formation for quinone oximes and quinone methides **1** and **7–13**

as calculated using PM3 parametrization. Table 2 compares the C–C single-bond lengths syn and anti to



the OH, as well as relevant through-space distances to the OH oxygen. Table 3 shows the calculated ΔE , $\Delta\Delta E$, Δd and $\Delta\Delta d$ values, obtained from the values in Tables 1 and 2. Table 4 compares the calculated lengths of the C2–C3 and C5–C6 double bonds in **1** (R = H, CH₃) and **7**. Table 4 also compares selected H–H distances and bond angles for **1** (R = CH₃) and **7**. As a measure of electronic asymmetry the net atomic charges calculated for the ring CH fragments of **1** (R = H) and **7** are listed in Table 5.

NMR Results. Tables 6 and 7 show the observed ^1H and ^{13}C chemical shifts, $^1\text{H}/^{13}\text{C}$ coupling constants, and $^1\text{H}/^{13}\text{C}$ signal correlations for **1** (R = CH₃) and **14**. The signal assignments are discussed below.

The observed $^1\text{H}/^1\text{H}$ coupling constants are reported in Table 8. For **14** the averages of 19 measurements on the same sample are reported. Precision is limited by the digital resolution rather than by the reproducibility of the measurements.

Signal Assignments. Since one measure of sidedness is the comparison of the ^1H – ^1H coupling constants J_{23} and J_{56} , it is essential to assign these protons. The ^1H NMR spectrum of **1** (R = CH₃) was reliably assigned by comparisons with the spectra of benzoquinone oxime, 3-methyl-1,4-benzoquinone-4-oxime (assumed to be *E*) and 2,6-dimethyl-1,4-benzoquinone 4-*O*-methyloxime, which lack some of the signals.^{2,20} The distinction between H2 and H6 is based on analysis of the ABMX spectrum, although this is not critical to the assignment of the coupling constants, which are measured from the H3 and H5 signals. The chemical shifts that we found are included in Table 6.

The ^{13}C assignment of **1** (R = CH₃), based on the ^1H assignments and $^1\text{H}/^{13}\text{C}$ correlation experiments, is given in Table 6. The assignments of C3 and C5 are clear from the large one-bond coupling constants to H3 and H5. The C2 and C6 signals cannot be unambiguously distinguished because H2 and H6 could not be selectively decoupled. We assume that C2 is further downfield than C6 by analogy to the ^1H spectrum. The only upfield signals correspond to OCH₃, and the most downfield signal can be assigned as C1, with C4 next. This

Table 1. PM3 Heats of Formation (kcal/mol)

compound	$\Delta H_f(\text{Z})$	$\Delta H_f(\text{E})$
1 (R = H)	6.2	
7	–33.3	
8	44.1	43.9
9	–37.6	–37.3
10	3.1	3.1
11	–76.2	–76.2
12	–16.4	–17.5
13	–54.2	–55.0

(14) Serena Software (1986 parameters), Box 3076, Bloomington, IN 47402.

(15) Stewart, J. J. P. *QCPE Bull.* **1985**, 5, 126, 133 [QCPE Program 455].

(16) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, 107, 3902.

(17) Stewart, J. J. P. *J. Comput. Chem.* **1989**, 10, 221.

(18) Foster, J. P.; Weinhold, F. *J. Am. Chem. Soc.* **1980**, 102, 7211. Reed, A. E.; Weinhold, F. *J. Chem. Phys.* **1983**, 78, 4066. Carpenter, J. E.; Weinhold, F. *J. Mol. Struct. (THEOCHEM)* **1988**, 169, 41.

(19) Frisch, M. J.; et al., Gaussian 94 (Revision A.1), Gaussian, Inc., Pittsburgh, PA, 1995.

(20) Norris, R. K.; Sternhell, S. *Aust. J. Chem.* **1966**, 19, 841.

Table 2. Calculated Bond Lengths and Through-Space Distances (Å)

compound	$d_{(C-C)Z^a}$	$d_{(C-C)E^b}$	$d_{(O-C)Z^c}$	$d_{(O-H)Z^d}$
1 (R = H)	1.466	1.470	2.834	2.545
1 (R = CH ₃)	1.467	1.470	2.838	2.546
7	1.455	1.457	2.839	2.522
(<i>Z</i>)- 8	1.464	1.468	2.830	2.542
(<i>E</i>)- 8	1.465	1.467	2.838	2.552
(<i>Z</i>)- 9	1.458	1.470	2.829	2.534
(<i>E</i>)- 9	1.467	1.462	2.828	2.533
(<i>Z</i>)- 10	1.450	1.456	2.830	2.514
(<i>E</i>)- 10	1.454	1.452	2.836	2.519
(<i>Z</i>)- 11	1.450	1.456	2.835	2.626
(<i>E</i>)- 11	1.454	1.453	2.834	2.513
(<i>Z</i>)- 12	1.462	1.502	2.804	2.487
(<i>E</i>)- 12	1.495	1.465	2.800	2.733
(<i>Z</i>)- 13	1.450	1.494	2.818	2.476
(<i>E</i>)- 13	1.489	1.451	2.800	2.715

^aC–C single bond *Z* (syn) to hydroxyl O. ^bC–C single bond *E* (anti) to hydroxyl O. ^cBetween hydroxyl O and syn C. ^dBetween hydroxyl O and H on syn C (or closest H if syn C is sp³).

Table 3. Summary of ΔE , $\Delta\Delta E$ (kcal/mol), Δd , and $\Delta\Delta d$ (mÅ)

compounds	$\Delta E(N)$	$\Delta E(C)$	$\Delta\Delta E$	$\Delta d(N)$	$\Delta d(C)$	$\Delta\Delta d$
1 (R = H)/ 7	–	–	–	–3	–2	–1
8/10	0.2	0.0	0.2	–1	–4	3
9/11	–0.3	0.0	0.3	–9	–4	–5
12/13	1.1	0.8	0.3	7 ^a	5 ^a	2

^aBetween C4 and the adjacent sp² carbon.

Table 4. Calculated Double-Bond Lengths (Å), Internuclear Distances (Å), and Bond Angles (deg) for **1** and **7**

compound	d_{C2-C3}	d_{C5-C6}	d_{H2-H3}	d_{H5-H6}	$\angle_{H3-C3-C2}$	$\angle_{H5-C5-C6}$
1 (R = H)	1.338	1.339	–	–	–	–
1 (R = CH ₃)	1.338	1.338	2.460	2.470	120.4	120.9
7	1.341	1.340	2.465	2.469	120.5	120.7

Table 5. Calculated Net Atomic Charges for CH Fragments in **1** (R = H) and **7**

	C2	C3	C5	C6
1 ^a	0.003	0.025	0.038	–0.005
1 ^b	–0.016	0.019	0.034	–0.028
7 ^a	–0.022	0.029	0.012	–0.024
7 ^b	–0.047	0.040	0.024	–0.049

^aRHF/STO-3G//PM3 Mulliken charges. ^bRHF/STO-3G//PM3 NPA charges.

Table 6. ¹H and ¹³C Chemical Shifts (δ in parentheses) and ¹H–¹³C Coupling Constants (Hz) for 1,4-Benzoquinone *O*-Methyloxime (**1**, R = CH₃) in Acetone-*d*₆

	H3 (7.68)	H5 (7.25)	H2/H6 (6.45/6.43)	OCH ₃ (4.15)
C1 (187.13)	9.3	9.3	–	–
C2 (132.93)	–	–	167.3/4.6	–
C3 (124.82)	168.5	5.1	–	–
C4 (149.52)	–	–	9.4/9.4	–
C5 (137.63)	5.7	166.7	–	–
C6 (130.64)	–	–	4.3/167.4	–
OCH ₃ (64.44)	–	–	–	146.2

distinction is consistent with the ³J_{CH}'s, which in aromatics are usually larger than ²J_{CH}.^{21a}

The assignments for the protonated quinone hydroxymethide **14** are listed in Table 7. The nonequivalence of the two sides at temperatures slightly below ambient is

(21) Levy, G. C.; Nelson, G. L. *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists*; Wiley-Interscience: New York, 1972. (a) pp 100–103. (b) pp 127–128.

Table 7. ¹H and ¹³C Chemical Shifts (δ in parentheses) and ¹H–¹³C Coupling Constants (Hz) for Protonated 1,4-Benzoquinone 4-Hydroxymethide (**14**) in Trifluoromethanesulfonic Acid

	H3 (7.40)	H5 (7.18)	H2/H6 (6.15/6.13)	H7 (8.12)
C1 (173.85)	9.1	9.1	–	–
C2 (119.25)	–	–	206.2/4	–
C3 (136.11)	169.1	6.2	–	≤ 2
C4 (120.38)	–	–	7.7/7.7	10.4
C5 (147.37)	5.8	166.9	–	≤ 2
C6 (117.61)	–	–	4/207.4	–
C7 (191.65)	2.5	2.5	–	184.6

Table 8. ¹H/¹H NMR Coupling Constants (Hz) for **1** (R = CH₃), **14**, and *p*-Hydroxybenzaldehyde

compound	$J_{2,3}$	$J_{5,6}$
1 (R = CH ₃)	10.5	10.1
14	8.98	8.63
<i>p</i> -hydroxybenzaldehyde	8.67	8.67

evidence for this structure. The new, downfield signal is clearly identifiable as H7. The crucial assignments are of H3 and H5 at δ 7.40 and 7.18, respectively, based on analogy to **1**. The ¹³C spectrum is then easy to assign. The C7 signal can be identified by its ¹J to H7 and this is confirmed by the ³J_s to H3 and H5. The C4 signal can be identified by the ²J to H7 and the ³J_s to the upfield H2 and H6 signals. This ²J is larger than the ³J_s because H7 is on an exocyclic fragment.^{21b} The remaining downfield singlet must be C1, which is appropriately coupled to both H3 and H5. The C2 and C6 signals can be identified by their ¹J_{CH}'s and the absence of further coupling. Finally, the crucial C3 and C5 signals at δ 136.11 and 147.37, respectively, can be identified by their ¹J_{CH}'s to H3 and H5 and confirmed by the ³J to H7. This is consistent with the expectation that C3 is upfield of C5 owing to a γ -effect,²² as was observed in **1** (R = CH₃). Although the ³J_{trans} between H7 and C3 should be larger than the ³J_{cis} between H7 and C5, no difference was detectable, so the distinction between C3 and C5 could not be further confirmed. Despite this lack of confirmation, the assignments are secure and do validate the assignments of H3 and H5.

Discussion

Reliability of Calculations. The first test of computational results is whether they match experimental observations. According to MMX calculations, (*E*)-**9** and (*Z*)-**9** are of identical stability. MMX could reproduce the greater stability of (*E*)-**8** over (*Z*)-**8**, but ascribes this to dipole–dipole interactions. Moreover, the C–C single bonds syn and anti to the nitrogen lone pair in **1** are of equal length. Of course, MMX is not well parametrized for anomeric effects of sp² nitrogen lone pairs, and these calculations are not sufficiently reliable, except as discussed below.

The PM3 values of ΔE in Table 3 are positive, negative, and positive for **8**, **9**, and **12**, in full agreement with the experimental observations.^{1,3} (The greater stability of **12E** corresponds to a greater proportion of *Z* product in the Diels–Alder reaction.) The ΔE 's are only slightly lower than the 0.6, –1.1, and 1.3 kcal/mol required to account for the equilibrium proportions observed for CF₃ and OCH₃ substitution and cyclopentadiene addition,

(22) Weigert, F. J.; Roberts, J. D. *J. Am. Chem. Soc.* **1967**, *89*, 2967.

respectively. Thus PM3 is adequate for investigating these phenomena.

To account for the position of the equilibria in **8** and **9**, the electron density at C6 was proposed^{2,3} to be greater than that at C2. Table 5 shows that the net atomic charge calculated for the C6H fragment in **1** (R = H) is indeed greater than for C2H. The difference is small, but the same asymmetry is seen for both Mulliken and NPA charges. Thus the equilibria will favor the forms with CN and CF₃ at C6 and with OCH₃ at C2. This asymmetry of electron densities at C2 and C6 is also seen in **7**, although much reduced. It would be of interest to test this calculation by determining the *E/Z* equilibrium in analogs of **10** and **11** with additional stabilizing substituents.

If the halogenations proceed via a halonium ion, reaction might preferentially occur at the more electron-rich C–C double bond. Table 5 shows that the sum of electron densities at C2 and C3 in **1** (R = H) is greater than at C5 and C6, and reaction does occur at C2–C3.³

The inequality of coupling constants in **1** (R = H, anion, CH₃, COCH₃) was attributed to a greater contribution from resonance forms **1a** and **1a'**.^{2,3} This would correspond to C2–C3 shorter than C5–C6. Yet according to the calculated double-bond lengths in Table 4, the C2–C3 bond is the same length as the C5–C6 bond in **1** (R = CH₃), and it is only 1 mÅ shorter in **1** (R = H), which is not significant. Therefore these calculations may not be as sensitive as the coupling constants to small distortions.

Assessment of Stereoelectronic Origin. The calculated C3–C4 and C4–C5 bond lengths in Table 2 do not provide any justification for a stereoelectronic origin for the observations. The Δd s (eq 1) in Table 3 show that the C3–C4 bond in **1** is shorter than C4–C5 by 3–4 mÅ. This is opposite to the hypothesis that the C3–C4 bond is lengthened owing to *n*- σ^* overlap.³ These results agree with both previous calculations,^{8,9} which gave syn bond lengths shorter than anti in **1** (R = CH₃), **5b**, **3**, and **4**.

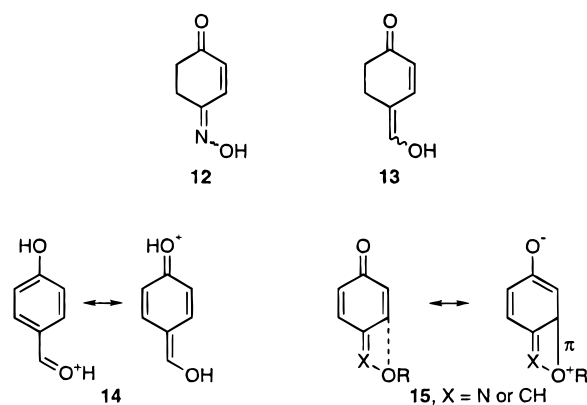
Even though the C–C bond antiperiplanar to the nitrogen lone pair is not lengthened, the lone pair may somehow be responsible for the structure and reactivity. Regardless of whether these are stereoelectronic phenomena, one cannot attribute them to the lone pair by studying only molecules that have such a lone pair. One must also make comparisons with a suitable control that lacks a lone pair. The quinone methides provide these controls.

If relative stabilities are due to stereoelectronic effects, the magnitude of ΔE (eq 3) should be greater for the quinone oximes than for the quinone methides, and $\Delta\Delta E$ (eq 4) should be positive. This is indeed seen for the data in Table 3. Yet the geometric changes do not parallel the energies. The specific role of a nitrogen in controlling bond-length differences Δd (eq 1) is measured by $\Delta\Delta d$ (eq 2). If *n*- σ^* donation lengthens the C3–C4 bond in the oxime, the $\Delta\Delta d$ s in Table 3 should be positive. They are positive for **8/10** and **12/13**, but negative for **1/7** and **9/11**. Thus *n*- σ^* donation is not confirmed as the origin of the energy differences, but this could be an artifact of an inadequacy of PM3 to calculate bond lengths.

Nevertheless, the bond-length differences do not reflect any lengthening of the bond anti to that lone pair. Therefore the origin of the sidedness is still unexplained. One source of confidence is that PM3 calculations can

reproduce the experimental observations, so that we may look to them for insight to propose alternative explanations.

Origin of Stereoselectivity in Additions. An alternative explanation is that through-space π overlap between the hydroxyl oxygen and the syn carbon is responsible for the differences observed. This would be expressed by resonance form **15** (X = N or CH), even though such 1,4 overlap was viewed as too small.¹⁰ If it can contribute, **15** has antiaromatic character due to the 4 π -electron OXCC system, so that this overlap would be a destabilizing interaction. In the dihydro compounds (**12** and **13**) such overlap is possible only in the *Z* configuration. Then the *E* form should be more stable, as confirmed by the positive ΔE s in Table 3 calculated for both **12** and **13**. Further evidence for such overlap comes from the through-space O–C distances for **8** listed in Table 2. Even though the *Z* form is less stable (for **8**), the shorter distance in the *Z* forms may be attributed to stabilization (or a reduction of the destabilization) of **15** by the syn cyano group. However, any contribution from **15** would increase the electron density at C2 relative to C6. This is contrary to the results in Table 5 and to the observed *E/Z* equilibria of 2-substituted quinone oximes. Therefore we seek an alternative explanation.



The possibility of O–C interaction suggests a simpler steric origin for the sidedness. Table 2 shows that the distance between the hydroxyl oxygen and H3 on the syn carbon in **1**, **7**, **8**, and **9** (except (*Z*)-**11**) is less than 2.6 Å, which is the sum of the van der Waals radii for O and H.²³ Even MMX calculations display this interaction for **1** and **7**. This is a steric repulsion that can be relieved by addition syn to the OH, which converts the syn carbon to sp³ and moves H3 out of the molecular plane. The results in Table 2 show that syn addition, to form a product modeled by **12E** or **13E**, increases the distance to the nearest hydrogen to >2.7 Å, whereas substitution anti decreases the distance (in **12Z** or **13Z**) to <2.5 Å. These differences are large and unequivocal, especially in comparison to the $\Delta\Delta d$ in Table 3. Thus a steric effect can account for the product mixtures from Diels–Alder reactions and halogenations. A quinone methide should show the same stereochemical behavior, even though it lacks the nitrogen lone pair. Unfortunately, this prediction could not be tested because **7** would not undergo addition reactions under the strongly acidic conditions used to protonate it, and its methyl ether was too unstable.

(23) *CRC Handbook of Chemistry and Physics*, 1st Student Edition; Weast, R. C., Ed., CRC Press, Inc.: Boca Raton, FL, 1988; p D-111.

Steric repulsion in such a context is not new. It was considered (and dismissed) to account for the low barrier to C–C rotation in (*Z*)-acetaldehyde oxime.¹⁰ The preference for electrophilic aromatic substitution syn-ortho to a methoxy group, which was attributed to *n*- σ^* donation, is reduced by steric hindrance.⁶ This differs from our proposal, whereby the steric repulsion is present in the reactant and relieved in the transition state, leading to acceleration.

Steric Origin of Inequality of Coupling Constants. The repulsion between the hydroxyl oxygen and H3 on the syn carbon may modify the H2–H3 coupling constant. Indeed, according to the calculations in Table 4, the through-space distance between H2 and H3 in **1** (R = CH₃) is 0.01 Å shorter than that between H5 and H6. Also the H3–C3–C2 bond angle is 0.5° smaller than the H5–C5–C6 bond angle. Even MMX calculations show this distortion, and it has also been seen, both experimentally and computationally, in comparing the CCN angles of the stereoisomers of **5**.⁸ Since ³*J*_{HH}'s are known to increase as the HCC bond angle decreases,²⁴ the difference in coupling constants could be due to these geometric differences, rather than a difference in the C–C double bonds.

If the difference in coupling constants arises from these steric interactions rather than from the nitrogen lone pair, then it should also occur in the CH analog. According to the results in Table 4, **7** is calculated to show the same geometric distortions as **1**. Table 8 shows that *J*_{2,3} in the protonated quinone hydroxymethide **14** is ca. 0.4 Hz greater than *J*_{5,6}, just as in **1** (R = CH₃). Therefore the difference in the coupling constants is not due to a stereoelectronic effect.

Origin of Substituent Effects on *E/Z* Equilibria. Steric repulsions do not account for the observed substituent effects on the *E/Z* equilibrium in **8** and **9** or for the differences in electron density calculated at C2 and C6 in **1**. The charges in Table 5 show that RHF/STO-3G//PM3 calculations can detect electronic differences that operate across space. We propose that these arise from electrostatic interactions with the oxime or hydroxymethylene functionality, rather than just the nitrogen lone pair of the oxime. Indeed, electrostatic interactions were proposed to account for the *E/Z* equilibrium in **6**.¹⁰ The dipole moment associated with the hydroxylic oxygen of **1** or **7** is positioned to stabilize positive charge at C2 and C3, relative to C5 and C6, while

the closer but weaker dipole moment of the nitrogen in **1** stabilizes negative charge at C3. These interactions can account, at least qualitatively, for the charges in Table 5, which govern the *E/Z* equilibria in **8** and **9**, without invoking delocalization of the nitrogen lone pair or lengthening of the antiperiplanar bond.

Conclusions

Stereoelectronic Origin. The calculated bond lengths in **1** are opposite to what is expected from *n*- σ^* delocalization of the nitrogen lone pair. Moreover, the general structural behavior of **7** is similar to that of **1**, showing that the lone pair is not responsible for the syn stereoselectivity in addition, the substituent effects on the *E/Z* equilibrium, or the NMR coupling constants.

Syn Stereoselectivity. PM3 calculations are quantitatively in reasonable agreement with the *E/Z* ratios observed in addition reactions to quinone oximes. The preference for syn addition is attributed to the relief of the steric strain associated with the short distance between the hydroxyl oxygen and H3 on the syn carbon. This steric interaction is independent of the nitrogen lone pair and is not a stereoelectronic effect.

Effect of 2-Substituents. RHF/STO-3G//PM3 calculations are also in agreement with the *E/Z* ratios observed for 2-substituted quinone oximes. Calculated electron densities in **1** are consistent with the substituent effects. These are attributed to electrostatic interactions, rather than to the nitrogen lone pair.

Coupling Constants. The PM3 calculations could not detect a shortening of C2–C3 in **1** relative to C5–C6. The inequality of coupling constants was traced to steric repulsion with the hydroxyl oxygen, which decreases the H3–C3–C2 angle.

If this inequality arises from steric interactions rather than from the nitrogen lone pair, then it should also occur in the CH analog. The key experimental result is that *J*_{2,3} in the protonated quinone hydroxymethide **14** is greater than *J*_{5,6}, just as in **1**. Therefore the difference in coupling constants cannot be a stereoelectronic effect.

Acknowledgment. This research was supported by National Science Foundation Grants CHE90-25113 and CHE94-20739. Purchase of the 500-MHz NMR spectrometer was made possible by NIH Grant No. RR04733 and NSF Grant No. CHE88-14866. We are grateful to Dr. Kim Baldrige (San Diego Supercomputer Center) for the RHF/STO-3G//PM3 calculations.

(24) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870.