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Unequal Aromatic Resonance Contributions Detected by Nuclear Overhauser Effect Difference Spectroscopy of Aromatic Methyl Ethers

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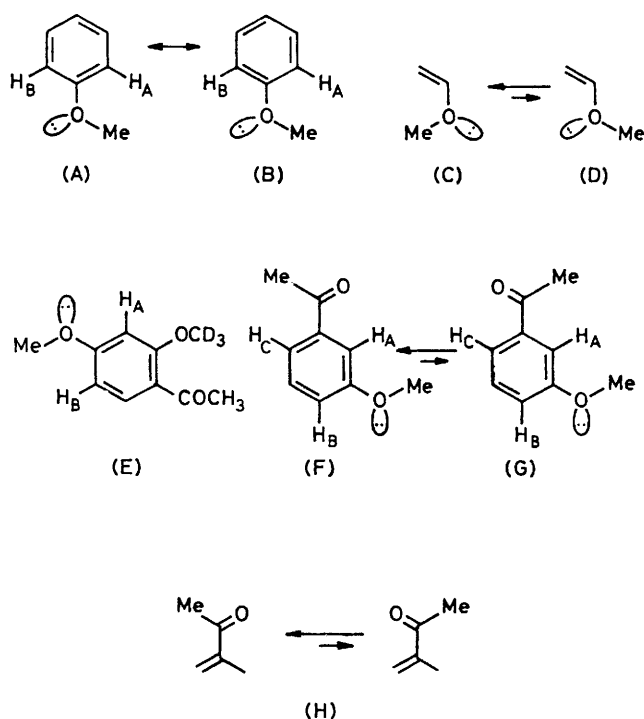
Nuclear Overhauser effect difference spectra of aryl methyl ethers reveal a striking conformational preference for the methoxy-group as *s-cis* to the *ortho*-position with the highest double bond character; this conformational preference correlates with the positional reactivity of the aromatic ring and is interpreted as arising from dissimilar resonance contributions.

The structure of methoxybenzene has been considered from a theoretical viewpoint,¹ and it has been demonstrated by i.r.,² microwave,³ and Raman spectroscopy⁴ to prefer a coplanar orientation of the methoxy-group with the aromatic ring so as to maximize interaction of the nonbonding oxygen p orbital with the aromatic π -electrons.

The low-energy conformer of methoxybenzene with the methoxy-group and aromatic ring coplanar will be a composite of the major resonance forms (A) and (B). However, the known,⁵ and now spectroscopically distinguishable,⁶ preference for the *s-cis*-orientation in methyl vinyl ether [(C) \rightleftharpoons (D)] suggests that the resonance form (A) should be weighted more heavily in the resonance composite for this conformer of methoxybenzene.† Conversely, the conformational equilibration of methoxy-aromatic compounds in solution suggests that the detection of a preferred methoxy-group conformation by nuclear Overhauser effect (n.O.e.) measurements should provide a sensitive probe of the relative contributions from the two major resonance forms and, therefore, indicate the relative energy levels of the two. Since the distances between the methoxy- and the *ortho*-protons are virtually identical in aromatic compounds, leading to comparable n.O.e. build-up rates, an unequal enhancement of the *ortho*-protons upon irradiation of the methoxy-group would be expected only for a preferred conformation of the methoxy-group.‡

† In this and subsequent discussions, resonance forms are discussed as canonical valence-bond isomers. A complementary molecular orbital description suggests that aromatic methyl ethers prefer a *s-cis*-orientation to the *ortho*-position of highest π -electron density.

‡ Although simple, and readily applied, it must be emphasized this treatment ignores the magnitude of competing relaxations, the effects of anisotropy of rotational diffusion, cross-correlation effects, and contributions of internal rotation to the effective correlation times of the internuclear vectors involved in relaxation.



Examination of a variety of methoxy-substituted aromatic and heteroaromatic systems by n.O.e. difference spectroscopy§ (Table 1) together with unequivocal assignment of the resonances for the *ortho*-protons, H_A and H_B, from careful study of

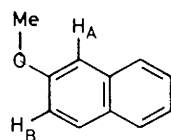
§ Nuclear Overhauser difference spectra were obtained using a saturation time of 10 s, with an R.F. power setting of 35L and a pulse width of 1.2, corresponding to a flip angle of ca. 20°.

Table 1. N.O.e. difference data for aromatic methyl ethers.^a

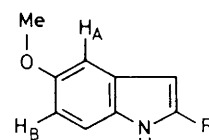
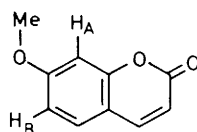
Compound	<i>ortho</i> -Protons (Chemical shift, ^b multiplicity, coupling constants ^c)	N.O.e.(%)	N.O.e.(H _A)	
			N.O.e.(H _A)	N.O.e.(H _B)
(1)	{ H _A (7.06, d, 2.4) H _B (7.12, dd, 2.4, 8.9)	9 2	4.5	
(2a)	{ H _A (7.11, d, 2.4) H _B (6.86, dd, 2.4, 8.8)	42 8	5.2	
(2b)	{ H _A (6.99, d, 2.5) H _B (6.76, dd, 2.5, 8.7)	17 4	4.2	
(3)	{ H _A (6.45, d, 2.4) H _B (6.51, dd, 2.4, 8.6)	19 10	1.9	
(4)	{ H _A (6.60, d, 2.6) H _B (6.66, dd, 2.6, 8.5)	6 6	1.0	
(5)	{ H _A (6.78, s ^d) H _B (6.68, d, 8.2)	8 8	1.0	
(6a)	{ H _A (7.34, d, 3.0) H _B (6.95, dd, 3.0, 8.9)	10 2	5.0	
(6b)	{ H _A (7.5, d, 3.1) H _B (7.11, dd, 3.1, 9.3)	11 3	3.7	
(6c)	{ H _A (7.57, d, 3.1) H _B (7.16, dd, 3.1, 9.2)	46 23	2.0	
(7a)	{ H _A (7.00, d, 3.1) H _B (7.15, dd, 3.1, 9.1)	41 12	3.4	
(7b)	{ H _A (7.33, d, 3.3) H _B (7.14, dd, 3.3, 9.1)	41 12	3.4	
(7c)	{ H _A (7.17, d, 3.0) H _B (7.11, dd, 3.0, 9.0)	10 6	1.7	
(7d)	{ H _A (7.29, d, 1.3) H _B (7.04, dd, 1.3, 8.9)	9 3	3.0	
(8a)	{ H _A (6.44, d, 2.3) H _B (6.55, dd, 2.3, 8.7)	32 13	2.5	
(8b)	{ H _A (6.44, d, 2.2) H _B (6.55, dd, 2.2, 8.7)	44 30	1.5	
(8c)	{ H _A (6.41, d, 2.6) H _B (6.28, dd, 2.6, 8.0)	42 10	4.2	
(8d)	{ H _A (6.45, d, 2.3) H _B (6.52, dd, 2.3, 8.7)	20 36	0.6	
(9a)	{ H _A (6.29, d, 2.7) H _B (6.22, dd, 2.7, 9.1)	20 19	1.0	
(9b)	{ H _A (7.72, t, 2.3) H _B (7.23, ddd, 0.9, 2.3, 9.2)	42 20	2.1	
(9c)	{ H _A (7.49, dd, 0.9, 1.6) H _B (7.11, ddd, 0.9, 2.7, 8.3)	21 12	1.8	

^a Measured at 360 MHz with a Bruker WM-360 spectrometer for degassed (argon) solutions in CDCl₃, C₆D₆, or CDCl₃-C₆D₆. ^b δ relative to internal Me₄Si. ^c J/Hz. ^d Broadened by very small coupling to H_B.

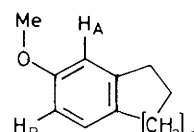
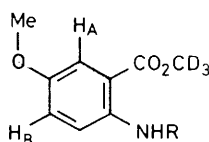
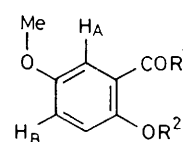
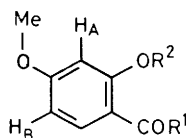
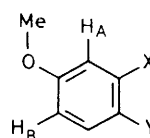
coupling constants, leads to several striking observations. Most importantly, the methoxy-groups in aromatic systems for which the contributions from the major resonance forms are unequal show a marked conformational preference. The maximum magnitude of the conformational preference observed [*ca.* 4–5:1 for compounds (1), (2a, b), and (6a); Table 1] is, as expected, less than for cyclic methyl vinyl ethers (*ca.* 8:1),⁶ since in aromatic systems the bonds to both *ortho*-



(1)

(2) a; R = H
b; R = Me

(3)

(4) n = 2
(5) n = 1(6) a; R = H
b; R = Ac
c; R = COCF₃(7) a; R¹ = R² = H
b; R¹ = H, R² = CD₃
c; R¹ = Me, R² = H
d; R¹ = Me, R² = CD₃(8) a; R¹ = R² = H
b; R¹ = H, R² = Me
c; R¹ = Me, R² = H
d; R¹ = Me, R² = CD₃(9) a; X = Me, Y = NO₂
b; X = NO₂, Y = H
c; X = Ac, Y = H

positions have a partial double bond character owing to aromatic resonance. While the absolute magnitudes of the enhancement [Table 1; n.O.e. (H_A) and n.O.e. (H_B)] show considerable variation from molecule to molecule, the relative ratios [n.O.e. (H_A)/n.O.e. (H_B)] establish a rank order which is a rough approximation of the relative energies of the individual resonance forms. Thus, the fused aromatic compounds (1) and (2a, b) and the highly polarized aromatic compounds (6a) and (8c) show the largest conformational preference, followed by systems with less polarization and/or intramolecular hydrogen bonding [compounds (6b, c), (7a–d), and (8a–c)], in turn followed by simple disubstituted, polarized systems [compounds (3), and (9b, c)]. Not surprisingly, compounds (4) and (5), ethers corresponding to the original 'Mills-Nixon' compounds,⁷ were found within the limits of detection to show equal populations of the methoxy-group conformers.[†]

[†] Critical reviews have attributed the somewhat inconsistent regiochemical outcome of reactions with phenols corresponding to compounds (4) and (5) (Table 1), the 'Mills-Nixon' compounds, to a variety of effects, including hyperconjugation and developing strain in the transition state. See G. Berthier and A. Pullman, *Bull. Chem. Soc. Fr.*, 1950, **17**, 88; G. M. Badger, *Quart. Rev.*, 1951, **5**, 147, and references cited therein. It seems likely the regioselectivity observed does not arise from energy differences for the two major resonance forms.

One compound, (**8d**), was observed to exist predominantly as the conformer (E), and therefore appears to be an exception to the trend established for the other compounds. The reasons for this 'anomalous' conformational preference are at present unclear and are being studied in detail, since the chemical reactivity of compound (**8d**) is well defined.**

Finally, results for acetophenone (**9c**) suggest that groups other than methoxy might also provide an insight into conformational preference and resonance character. Irradiation of the acetyl group of compound (**9c**) results in a *ca.* 2:1 enhancement ratio for the *ortho*-protons H_C and H_A [structures (F, G)], suggesting that (F) is the major conformer. This establishes that the preferred conformation of the acetyl group is *s-trans* with respect to the *ortho*-position of highest double bond character, and reinforces the results obtained in Table 1, since the related ketone (H) is known to prefer the *s-trans* conformation.⁸

In summary, study of aromatic methyl ethers *via* n.O.e. difference spectroscopy provides a powerful tool for exploring the relative stabilities of aromatic resonance forms, a result of practical importance since certain aromatic substitution reactions have been suggested to occur *via* an intermediate which

** Claisen rearrangement of the related compound 4-allyloxy-2-methoxy acetophenone provides the 5-allyl compound, in accordance with the observed 'anomalous' preferred orientation of the 4-methoxy-group as *s-cis* with respect to H_B (position 5) in structure (E).⁹

most closely resembles the resonance form of lowest energy.⁹ In addition, the preliminary n.O.e. result with compound (**9c**) suggests that further studies with other functional groups (*e.g.* aldehyde) of known conformational preference might also confirm the results for the methoxy-compounds.

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