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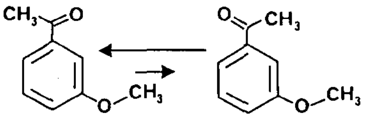
CONFORMATIONAL PREFERENCE OF AROMATIC KETONES AND ALDEHYDES DETERMINED BY NUCLEAR OVERHAUSER EFFECT DIFFERENCE SPECTROSCOPY INDICATES AROMATIC π-ELECTRON DENSITY

Lawrence I. Kruse*
Department of Medicinal Chemistry, Smith Kline & French Laboratories,
1500 Spring Garden Street, Philadelphia, Pennsylvania 19101, U.S.A.
Jin K. Cha
Department of Chemistry, Harvard University,
12 Oxford Street, Cambridge, Massachusetts 02138, U.S.A.

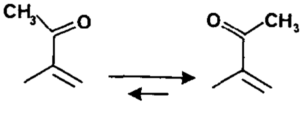
Summary: NOE difference spectra of aromatic aldehydes and ketones demonstrate the carbonyl group favors an *s-trans* orientation to the *ortho* position of highest double bond character.

During the study of aromatic methyl ethers by NOE difference spectroscopy it was noted the acetyl group in 3-methoxyacetophenone, (1), existed (∿2:1) in the conformation with the carbonyl group *s-trans* to C-6, the *ortho* position of highest double bond character.[1] This observation prompted the present study of aromatic carbonyls which implies generality to the use of functional groups as indicators of aromatic π-density and, therefore, chemical reactivity.[2]

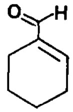
NOE difference spectra[3] of representative aromatic and heteroaromatic carbonyl compounds of well defined bond order establish a consistent conformational preference (Table 1). In each case, irradiation of the aldehyde methine or ketone methyl group results in



(1)

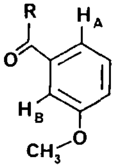
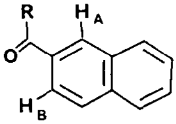
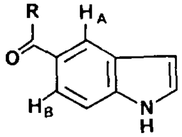


(2)



(3)

Table 1. NOE difference data for aromatic aldehydes and ketones.[a]

Entry	Structure	% NOE H_A / % NOE H_B [b]	T_1 H_B / T_1 H_A [d]
(4a) R=CH_3-		1.8	0.99
(4b) R=H-		1.8[c]	e
(5a) R=CH_3-		2.1	1.34
(5b) R=H-		3.4	1.14
(6a) R=CH_3-		2.0	0.79
(6b) R=H-		2.4	0.87

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[a] Determined at 360 MHz with a Bruker WM-360 spectrometer as solutions in $CDCl_3$ or C_6D_6

[b] Unambiguous assignments for H_A and H_B were based on coupling constants.

[c] Approximate. H_A peaks are partially occluded by other aromatic signals.

[d] Determined by a 180°-τ-90° pulse sequence.

[e] Insufficient chemical shift differences preclude measurement.

unequal ortho proton enhancements to indicate unequal populations of carbonyl conformers. The ratios NOE_{H_A}/NOE_{H_B} (Table 1) demonstrate the preferred carbonyl conformation is s-trans to the ortho position of highest double bond character,[4] a result which correlates well with related α,β-unsaturated aliphatic carbonyls, since (2) prefers the s-trans conformation[5] and irradiation of the aldehyde methine of cyclohexenecarboxaldehyde, (3), leads to exclusive enhancement (21%) of the vinyl proton.

Is the ratio NOE_{H_A}/NOE_{H_B} an adequate estimate of the relative conformer populations, or does the host of factors already noted,[1] competing relaxations, cross correlation effects, and anisotropy of rotational diffusion combine to make this ratio misleading? T_1 measurements illustrate the impact of competing relaxations upon the apparent conformational equilibria as determined by the direct ratio NOE_{H_A}/NOE_{H_B}. The ratio $T_1\ H_B/T_1\ H_A$ represents the error arising from different relaxation times for H_A and H_B. For the compounds in Table 1 this error varies from negligible (4a) to ca. 35% (5a). The combination of NOEs and relaxation times is best illustrated by considering indole (6b) which we have studied as part of a more rigorous and extensive investigation.[6] In (6b) the relaxation times of H_A (6.5 sec) and H_B (5.65 sec) taken in combination with the observed NOEs yields values for the contribution of the aldehyde proton to the relaxation of H_A (8.6 sec) and H_B (17.7 sec). The observed conformational preference (2.4) can be corrected to 2.06 to account for the effects of competing relaxations. Furthermore, study of carbon relaxation times of (6b) indicates that proton relaxation times are not greatly affected by anisotropy of rotational diffusion. For these compounds, one may conclude a more rigorous approach yields conformational equilibria in good agreement with the ratio of observed NOEs.

In summary, the use of NOE to determine the conformational preference of functional groups provides a general and powerful tool for refinement of molecular geometry; knowledge of functional group conformational preference aids prediction of positional reactivity of aromatic systems.[2]

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References and Notes

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