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PREFERRED CONFORMATIONS OF ENOL ETHERS IN SOLUTION: DETECTION OF AN EQUILIBRIUM BY KINETIC NUCLEAR OVERHAUSER EFFECTS

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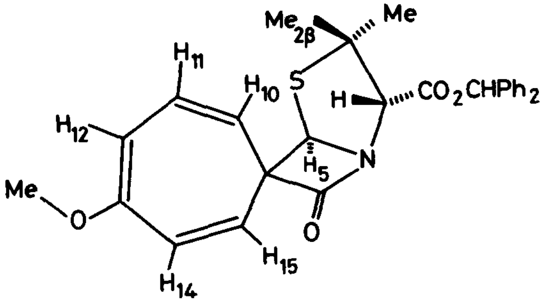
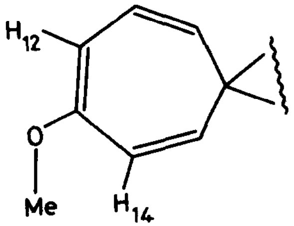
SUMMARY. n.O.e. difference spectra reveal that the preferred solution conformation of methyl enol ethers has the methyl group <u>*syn*</u>*-periplanar to the double bond; n.O.e kinetics in a methoxy-heptatriene demonstrate the presence of both possible periplanar conformations, the energy difference being* <u>*ca*</u> *1 kcal/mole.*

The reaction of anisole with a carbenoid derived from 6-amino penicillanic acid yields the methoxy heptatriene product 1.[1] The structure and stereochemistry of this compound were determined by us[1] using n.O.e difference spectroscopy;[2] during the course of that study we noticed that the methoxyl group appeared to be overwhelmingly in conformation (a) rather than (b). We show here that in solution this is a general property of enol ethers and that in certain cases it is possible to estimate an equilibrium constant for competing conformations.



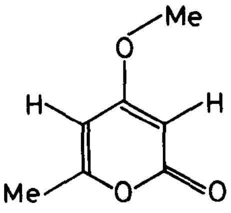
1(a)



1(b)

Saturation of the methoxyl group of 1 for 10 seconds leads in undegassed $CDCl_3$ solution to a 19% enhancement for H_{12} but only 1.7% enhancement for H_{14}. This effect is reciprocal: irradiation of H_{12} enhances the methoxyl but no effect is detected when H_{14} is irradiated. Given that the H_{11}-H_{12} and H_{14}-H_{15} distances are very similar, the conclusion is that the methoxyl group must on average be closer to H_{12}.

The generality of this conformational preference in solution was demonstrated in a variety of molecules exemplified by 2 - 4. In the vinylogous ester 2 only the conformer drawn was detected by n.O.e difference spectroscopy,[4,6] but this is not too surprising as esters are known to prefer the cis conformation. More remarkably in 3, H_4 receives n.O.e's from and gives n.O.e's to the 5-methoxyl exclusively; H_4 is a proton flanked by two "equidistant" methoxy groups but it is relaxed by just one of them. The n.O.e results and near equality of T_1 for H_2 and H_4 confirm that both methoxyl groups spend effectively all their time in the conformation shown. Similarly in 4 only the conformation drawn can be detected.



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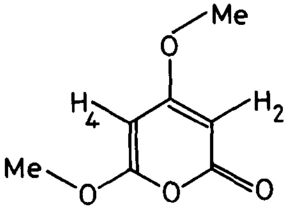

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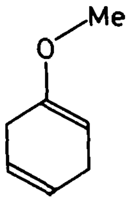

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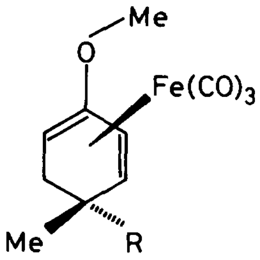
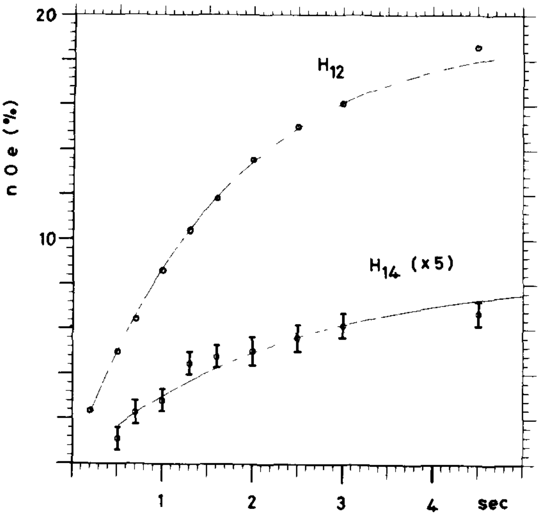


5

It is clear that in general the alkyl substituent lines up cis periplanar to the region of highest bond order. A stringent test of this generalisation was given by the iron tricarbonyl complex 5 whose synthetic utility lies in the fact that bond order is highest in the centre of the conjugated system.[7] As predicted, n.O.e's show that the methoxyl protons are now cis to the formal single bond. X-ray analysis of 5 shows that this unusual but now predictable orientation is maintained in the solid state.[7]

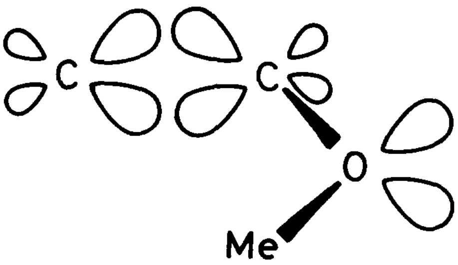
In 1 we were able to demonstrate that the n.O.e's to H_{12} and H_{14} arise from two different conformers by measuring their kinetics: the effective rate constant for the build up of n.O.e's is proportional to the inverse sixth power of the distance between irradiated and observed nuclei. The figure shows the time development of the n.O.e on methyl irradiation. Solid lines are the best fit single exponentials corresponding to rate constants of 0.59 (± 0.03) sec^{-1} for H_{12} and 0.43 (± 0.04) sec^{-1} for H_{14}. Thus the distance ratio ($Me - H_{14}/Me-H_{12}$) is $1.05[= (0.59/0.43)^{1/6}]$. We would expect precisely this sort of result for conformations 1(a) and 1(b) as a result of bond alternation in the carbon skeleton.[8] We would therefore also expect that for equal populations of (a) and (b), H_{12} would experience an n.O.e 1.37 times (= 0.59/0.43) larger than H_{14}. From this reasoning we conclude that the observed n.O.e ratio of 11 reflects a population distribution of 1a:1b of ca 8:1.[9]

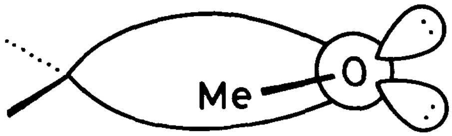
Fig 1: Evolution of n.O.e's in 1. Results for H_{14} are plotted x 5 vertically for clarity.



The conformational preferences we have demonstrated for enol ethers in solution have been previously documented in both gaseous and solid states,[4-8,10] and are strikingly similar to those observed in crystalline enamines.[11] They also demand a convincing theoretical explanation. Numerous possibilities related to the anomeric effect (well summarised in ref. 6) have been invoked including σ-hyperconjugative effects.[6] Similar hyperconjugative effects have also been invoked by Baldwin[12] and Norris to explain regio-selectivity in the reactions of benzoquinone-methyloximes.

There remains however another intriguing possibility : to return to the Pauling "bent bond"[13] illustrated below. In this model favourable bonding interactions between double bond and lone pairs are maximised by precisely that anti-periplanar geometry which is generally observed. Eschenmoser has used the bent bond concept to explain successfully both the observed geometry of enamines[11] and the stereochemistry of S_n2' reactions.[14]





In addition to posing this particular theoretical problem, the results presented here illustrate the potential of n.O.e difference spectroscopy in elucidating unprecedented details of conformational preferences and equilibria in solution.

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9. This is actually a slight overestimate: as the H_{11}-H_{12} distance is presumably bigger than that for H_{14}-H_{15} a methoxyl group equidistant from H_{12} and H_{14} would enhance the former to a greater extent.
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