Tetrahedron Letters,Vol.29,No.4,pp 471-474,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

THE EFFECT OF PARA-SUBSTITUENTS ON THE CONFORMATIONAL BEHAVIOUR OF 2-ARYLOXYTETRAHYDROPYRANS

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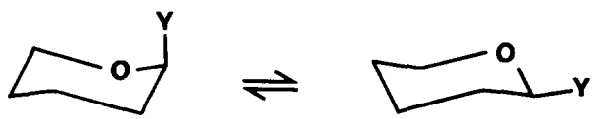
Summary. In chloroform solution, the chair ⇌ chair equilibrium for 2-aryloxytetrahydropyrans is sensitive to para-substituents on the aromatic ring. However, this effect is no longer evident when the solvent is cyclohexane. The results are discussed in terms of the perturbation and suppression of n-σ^* interactions.

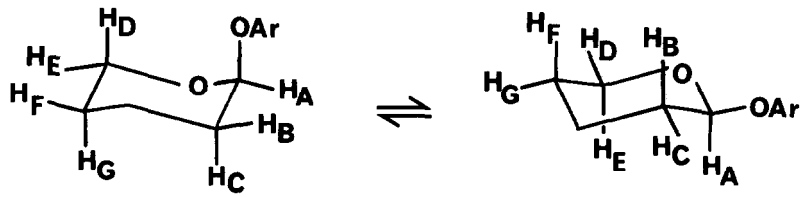
The unexpected axial preference of a polar substituent Y located alpha to the ring oxygen atom of a tetrahydropyran ring is a classic manifestation of the anomeric effect, the origins of which have been much discussed.[1] The solvent sensitivity[2] of equilibria of type (1a) ⇌ (1e) points to a role played by dipole effects but there is also broad acceptance of the importance of stabilising orbital:orbital interactions involving a heteroatom lone pair orbital, n, and a neighbouring σ^* orbital.[3] The endo anomeric effect[4] involves a lone pair orbital of the ring oxygen atom as donor and the anti-bonding orbital of the C-Y linkage as acceptor. The overlap is maximised when n and the bond are antiperiplanar and, consequently, is important only when Y is axial. On the other hand, the exo anomeric effect, where Y is donor and the ring C-O bond is acceptor, can arise in appropriate rotamers when Y is either axial or equatorial. There is, however, reason to believe that the exo anomeric effect is more important when Y is equatorial.[5] The position of the equilibrium (1a) ⇌ (1e) is thus governed largely by the relative strengths of the endo and exo anomeric effects. This, in turn, depends upon the acceptor power of the C-Y bond and the electron donating ability of Y, as has been discussed by Booth and co-workers[1] with regard to the series (1), Y = Cl, OMe, and NHMe.



(1a) (1e)

The present paper is concerned with aryloxy substituents. The introduction of para substituents onto the aromatic ring offers the

possibility of varying the donor and acceptor strength of the ArO group, without significantly changing the magnitude of 1,3-diaxial steric interactions. Evidence that <u>para</u> electron withdrawing and electron donor groups do indeed influence the extent of n-σ^* overlap is available from x-ray data which show significant fluctuations in C-O bond lengths in model compounds.[6] These are most apparent when the ArO group is axial. Interestingly, however, Pericas et al concluded from a study of the conformational equilibria for 2,3-diaryloxy-1,4-dioxanes that the presence of <u>para</u> electron donor or withdrawing groups is irrelevant to the manifestation of the anomeric effect.[7] We show here that the chair ⇌ chair equilibrium for 2-aryloxytetrahydropyrans, (2a) ⇌ (2e), in $CDCl_3$ <u>is</u> sensitive to <u>para</u> substituents but not in a fully systematic way: the results also suggest that n-σ^* interactions are suppressed in cyclohexane-d_6.



(2a) (2e)

Table 1. ^{1}H-Nmr data and percentage population, n, of conformer (2a) for a series of 2-aryloxytetrahydropyrans at 20° C.[a]

2-ArO	$CDCl_3$				Cyclohexane-d_6			
	J_S Hz	n %	J_{DG} Hz	n %	J_S Hz	n %	J_{EF} Hz	n %
<u>p</u>-NO_2.C_6H_4	6.0	78	10.2	78	5.6	84	3.1	87
<u>p</u>-CN.C_6H_4	6.0	78	10.3	79		b		
<u>p</u>-Cl.C_6H_4	6.4	70	9.6	72	5.6	84	3.0	88
C_6H_5	6.6	67	9.4	70	5.7	83	3.0	88
<u>p</u>-Me.C_6H_4	6.6	67	9.5	71	5.6	84	3.0	88
<u>p</u>-MeO.C_6H_4	6.5	68	9.5	71	5.7	83	3.1	87

[a] J values were obtained by first order analysis of 400 MHz spectra (Bruker WH 400 or a Jeol GX 400 spectrometer) run with digital resolution better than 0.09 Hz/pt. [b] Insufficiently soluble.

The conformational equilibria were investigated using ^{1}H-nmr spectrometry. <u>Vicinal</u> <u>trans</u> coupling constants involving the proton at C2, H_A, and the two protons at C6, H_D and H_E, provide useful conformational probes. In practice, there is overlap of the two central lines of the signal for H_A because of the similar magnitudes of J_{AB} and J_{AC}. However, the separation J_S of the outer lines is the sum of these couplings and varies with the percentage population, n, of (2a) according to the equation

$$J_S = n.J_{S(2a)} + (100-n).J_{S(2e)}$$

where $J_{S(2a)}$ and $J_{S(2e)}$ are the separation of the outer lines of H_A in the two chair conformers.

The vicinal trans coupling constant, J_{DG}, can be measured reliably from the eight line signal for H_D observed in the spectra of the compounds in $CDCl_3$ solution. Spectra obtained of cyclohexane-d_6 solutions show only six lines for H_D because J_{DG} is now similar in magnitude to ^2J (ca 11 Hz) and this precludes accurate evaluation. Fortunately, values for the other trans coupling, J_{EF}, can be measured for the compounds in cyclohexane-d_6 (though not in $CDCl_3$). J_{DG} and J_{EF} are dependent upon n thus

$$J_{DG} = n.J_{aa} + (100-n).J_{ee}$$

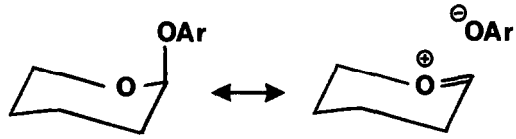
$$J_{EF} = (100-n).J_{a'a'} + n.J_{e'e'}$$

where J_{aa}, J_{ee}, $J_{e'e'}$ and $J_{a'a'}$ are the limiting values.

Table 1 lists data obtained for J_S, J_{DG} and J_{EF}. Also tabulated are values for n calculated using $J_{S(2a)}$ = 4.7 Hz and $J_{S(2e)}$ = 10.5 Hz after Pierson and Runquist[7] and J_{aa} = 12.6 Hz, J_{ee} = 1.9 Hz, $J_{a'a'}$ = 12.0 Hz and $J_{e'e'}$ = 1.8 Hz from ref. 1. Values for n obtained by the two methods of calculation are in reasonable accord: more importantly they reveal the same trends. We note the following points.

i Each derivative shows a reduced preference for the axial ArO conformer in the more polar solvent $CDCl_3$. This is a trend exhibited by other OR substituents[2] on a tetrahydropyran ring and may, in part, be a consequence of dipolar interactions within the molecule.

ii In $CDCl_3$ solution the more electron withdrawing para substituents, NO_2 and CN, increase the population of (2a). Assuming $\Delta S°$ is constant within the series, the trend is consistent with an enhancement of the endo anomeric interaction in (2a) brought about by the electron withdrawing groups. In valence bond terms this can be pictured as an increased contribution of B to the resonance A ↔ B.

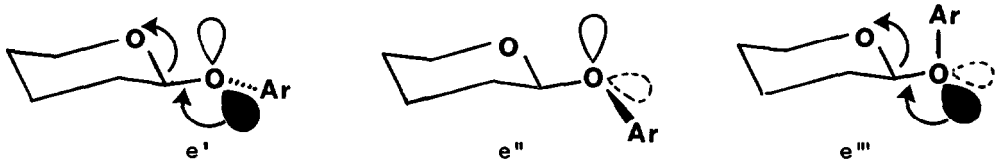


A B

At the same time, the exo anomeric effect in (2e) becomes weaker because of the poorer donor capability of the ArO oxygen atom.

The electron donating substituents OMe and Me do not, however, reduce the axial preference any further than that in the parent unsubstituted compound. This implies that any further weakening of the endo anomeric effect in (2a) is compensated by an unexpected weakening of the exo anomeric effect in (2e). One possible explanation is that, within the series, there is a change in the populations of rotamers e', e" and e"'. Earlier we demonstrated an enhanced population of the anti arrangement of Ar and OR groups in an Ar-C-C-O- fragment as electron donor groups are introduced onto the aromatic

ring.[8] A similar phenomenon in an Ar-O-C-O fragment would favour e", in which rotamer the exo anomeric effect cannot participate.



e' e" e'''

iii The equilibrium (2a) ⇌ (2e) is essentially insensitive to para substituents in cyclohexane-d_6. The contrast with the results obtained for $CDCl_3$ solution suggests that the anomeric interaction represented above by the resonance A ⟷ B becomes suppressed in non-polar solvents, a conclusion in accord with that reached recently by Fuchs' group from their study of some 1,4-dioxane derivatives.[9]

Finally we return to the results for 2,3-diaryloxy-1,4-dioxanes reported by Pericas et al.[7] We suggest that the apparent insensitivity of the conformational equilibrium to para substituents, even in polar solvents, may arise because the equilibria in question are very highly biased in favour of the diaxial isomer. Consequently, small perturbations in $\Delta G°$ within the series cause changes in population too small to be detected by the methods employed.

References and Notes

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(Received in France 25 November 1987)