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STEREOCHEMICAL INVESTIGATIONS—XII

CONFORMATIONS OF 2-SUBSTITUTED 1,4-OXATHIANS

N. S. ZEFIROV, V. S. BLAGOVESHCHENSKY, I. V. KAZIMIRCHIK and N. S. SUROVA
Department of Chemistry, Moscow State University, Moscow, USSR

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Abstract—In 2-substituted 1,4-oxathians, the portion of axial form is sharply diminished as compared with analogously substituted tetrahydropyrans and 1,4-dioxans. This phenomenon is discussed in terms of "anomeric" and "hockey-sticks" effects.

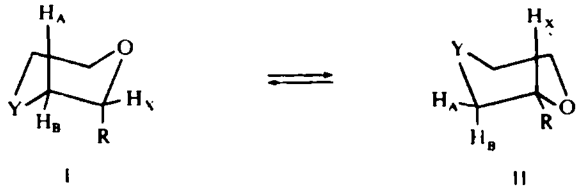
THE stability of the axial position of tetrahydropyran derivatives containing electronegative 2-substituents, provides one of the conformational distinctions of tetrahydropyran from cyclohexane. This phenomenon, which received the name "anomeric effect"[1] has been investigated in detail for carbohydrates,[2] substituted dihydropyrans[3] and related condensed systems,[4] tetrahydropyrans[3, 5–8] 1,3-dioxans,[5] 1,4-dioxans[9] and some sulfur-containing heterocyclics.[10, 11] This effect is observed for a large number of substituents such as —OAlk,[3, 5, 6, 8] —OAr,[3, 6] —OSir$_3$,[3] —OAc,[3, 8] halogens,[8, 12] —OOR,[13] —SR,[3, 5] —N$_3$[13] and —N=C=O.[13] Usually the "anomeric effect" is discussed in terms of the dipole-dipole and "rabbit-ears" interactions.[5, 7, 8, 14]

Earlier, a distinct anomeric effect was found for polychlorinated oxathians.[15] However, a preliminary study of the conformation equilibrium of 2-methoxyoxathian (III)[10, 16] showed a sharp distinction from those observed for 2-methoxytetrahydropyran and 2-methoxy-1,4-dioxan. The present paper is concerned with a detailed investigation of the conformation equilibrium of 2-substituted 1,4-oxathians by means of the PMR method.

RESULTS

Assuming the chair conformation for oxathian,[17] the conformational equilibrium of its 2-substituted derivatives may be represented by the following scheme: In this case, the position of conformational equilibrium can be estimated using the values (J_{AX} + J_{BX}) from equation:

$$|J_{AX} + J_{BX}| = N\cdot\sum J_{I} + (1 - N)\cdot\sum J_{II} = N(J_{ae} + J_{ee}) + (1 - N)(J_{aa} + J_{ae})$$



I II

Series: A (y = CH$_2$), B (y = O), C (y = S)

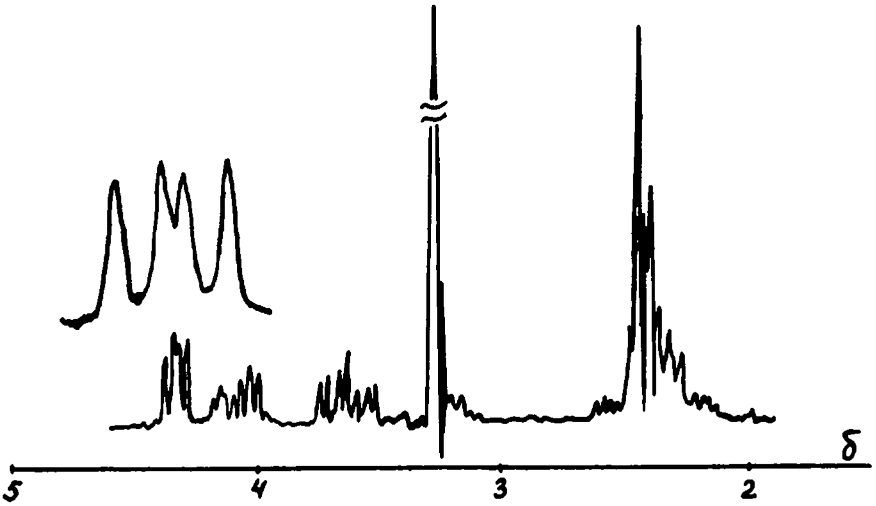


FIG 1. PMR spectrum of 2-methoxy-1,4-oxathian (III) (100 mHz).

At the present time, this semi-quantitative estimation of conformational equilibrium has received wide application. Since for a majority of compounds investigated the C_2 proton signal represented the X part of the ABX system, the value $|J_{AX} + J_{BX}|$ could be obtained directly from the spectrum. Fig 1 shows a typical spectrum of 2-methoxyoxathian (III) and signal C_2 proton is quadruplet (δ 4·2 ppm). For XII and XIII, the proton signals at C_2 appear as doublet of quadruplets (δ 5·5– – 5·7 ppm) as a result of splitting by phosphorus (Fig 2). It was mentioned earlier[4, 9, 18] that the ethoxy CH_2 protons in ethoxy derivatives of di- and tetrahydropyrans and 1,4-dioxans are anisochronous due to diastereotopy.[19] An analogous phenomenon was observed in the PMR spectra of IV and V. It is most interesting that diastereotopic Me groups in XII also produce anisochronous signals, since in the PMR spectrum of this compound they appear as two doublets with δ 3·8 ppm, J = 15·8 Hz, anisochronicity of Me groups being I Hz (Fig 2).

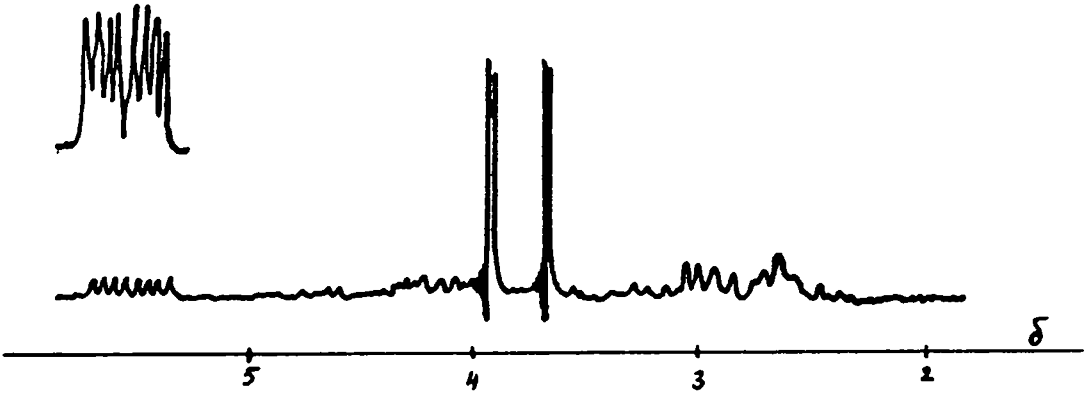


FIG 2. PMR spectrum of compound XII (60 mHz)

The greatest difficulty in estimating the conformational equilibrium using the above equation concerns the indefinite values J_{aa}, J_{ae} and J_{ee}. For oxathian itself $J_{aa} + J_{ee}$ = 14·7 Hz and J_{ae} = 2·65 Hz.[20] Thus, accounting for an increase in "R" for oxathian with respect to cyclohexane,[20] and a sequential increase in J_{aa}, it can be assumed that $J_{ee} = J_{ae}$ and hence J_{aa} = 12·05 Hz. But analysis of the data in the literature on the PMR spectra of substituted oxathians allows the choice of the following "optimal set" of the standard coupling constants: J_{aa} = II Hz, $J_{ae} = J_{ee}$ = 2·5 Hz. Table 1 lists the data on the position of the conformational equilibrium calculated with this set of standard constants. Maximal and minimal contents of axial form I (series C) could also be estimated using the "maximal" (J_{aa} = 12.5 Hz. J_{ae} = 3·5 Hz, J_{ee} = 3·0 Hz) and "minimal" (J_{aa} = 9·5 Hz, J_{ae} = 2·5 Hz, J_{ee} = 1·5 Hz) sets of constants. Fig 3 shows the dependence of the calculated content of axial conformation upon the value $|J_{AX} + J_{BX}|$ based on the use of the various sets of standard constants. For comparison, the data in the literature on conformational equilibrium for the analogously substituted tetrahydropyrans (series A) and 1,4-dioxans (series B) are also presented in Table 1.

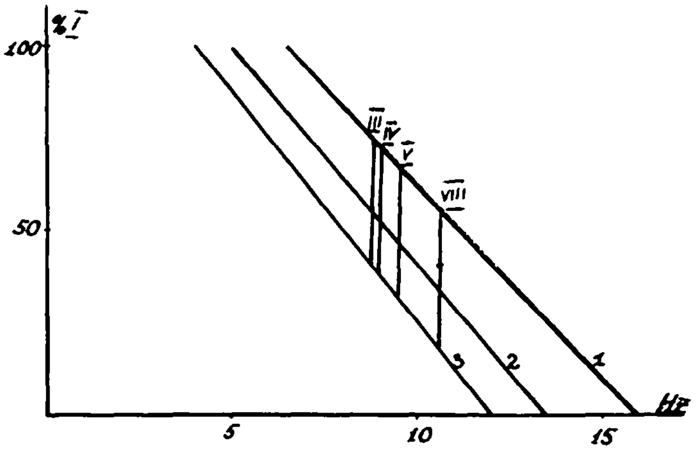


FIG 3. Position of conformational equilibrium vs. the value $|J_{AX} + J_{BX}|$ with the following sets of standard constants:

1. J_{aa} = 12·5 Hz, J_{ae} = 3·5 Hz, J_{ee} = 3·0 Hz.
2. J_{aa} = II Hz, $J_{ae} = J_{ee}$ = 2·5 Hz.
3. J_{aa} = 9·5 Hz, J_{ae} = 2·5 Hz. J_{ee} = 1·5 Hz.

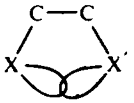
DISCUSSION

It can be seen from the data in Table 1 that a position of conformational equilibrium undergoes a slight change with solvent polarity (in going from CCL_4 to MeCN), the direction of this change being uncertain. For tetrahydropyran derivatives, a regular increase in the equatorial form IIA content is observed with an increasing solvent polarity.[5–7] On the other hand, for the 1·4-dioxan derivatives the portion of axial conformation decreases somewhat in passing to a non-polar solvent.[9] Such peculiarities are probably associated with specific solvation of the heteroatom Y in series B and C.

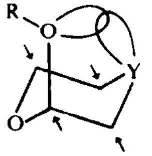
Earlier, 2-alkylthiotetrahydropyrans[3,5] and 2-alkoxytetrahydrothiopyrans[11] have been found to show weaker dipole repulsion in the O—C—S fragment than that found in O—C—O. This behaviour is valid again for 2-substituted oxathians. For all alkylthiosubstituted derivatives, VII–XI, the content of equatorial conformation IIC is larger than that in alkoxy derivatives III–V. It is quite logical that a higher quantity of axial form for XII and XIII could be a result of a larger substituent electronegativity.[3,6]

However, the following fact is evident: in going from series A to B, the content of axial form I changes little, unlike its sharp change in passing to 1,4-oxathians. For all derivatives of 1,4-oxathians (series C) the proportion of axial form I is relatively small and the "anomeric" effect is insignificant. This phenomenon is rather difficult to explain by the dipole-dipole repulsion between substituent and heteroatom Y, since this should be most pronounced for series B.

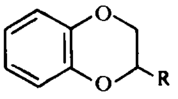
In our opinion, this abnormality can be generally interpreted in terms of the "hockey-sticks" effect.[21] In the case of the R—X—C—C—X'—R' fragment with the staggered or gauche conformation about the C—C bond (scheme XIV), an overlap of the X and X' atomic orbitals might be essential in influencing the position of conformational equilibrium and determining the fragment geometry. Due to such overlap, bonding and antibonding orbitals occupied by four electrons are produced which results in an instability of the conformation.



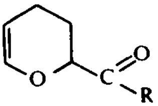
XIV



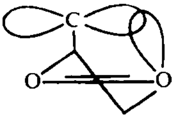
XV a: y = S
b: y = O



XVI a: R = COOMe
b: R = COCl
c: R = CN



XVII a: R = H
b: R = OMe



XVIII

It is probable that the energy of such destabilization would be proportional to the square of the overlap integral (Mulliken formula).[22] This repulsion should be enhanced with increasing atomic number for atoms X belonging to the same group of the Periodic Table (for example: O---S---Se or CL---Br---I). This is probably due to the more diffuse character of 3p and 3s orbitals with respect to the 2p and 2s orbitals. This effect is shown for the compound investigated in scheme XV. The more diffuse 3p sulfur orbital (see [23]) overlap with orbitals of the alkoxy group oxygen. Apparently, the effect of "hockey sticks" should affect a geometry change in these molecules, particularly in the comparative distances l_1 and l_2 (scheme XV) and a rotameric configuration about the bond C—OR. We also notice that using the effect

TABLE 1. NMR SPECTRA OF 2R 1,4-OXATHIANES

No.	R in I	Solvent	Chem shift (± 0·05 ppm)	Form of signal H_x	$(J_{AX} + J_{BX})$ Hz (± 0·2 Hz)	Percentage conformer I Series C	Series A	Series B
III	-Me	CCl_4	4·20	triplet[a]	8·8	55	85[c] 80[d]	68
		MeCN	4·45	quadruplet	8·7	56	80[c] 67[d]	73
IV	—Et	CCl_4	4·45	triplet	9·0	53	80[b] 78[d] 68[e]	70
		MeCN	4·55	badly resolved quadruplet	9·2	50	65[h] 62[d]	73
V	—Bu-n	CCl_4	4·40	triplet	9·0	53	89[c] 82[h]	66
		MeCN	4·50	badly resolved quadruplet	9·0	53	86[c] 63[h]	69
VI	—Bu-tert	CCl_4	4·60	quadruplet	9·5	47	82[c] 70[d] 62[e]	44
VII	—Pr-n	CCl_4	4·85	triplet	10·4	36	61[f] 64[g]	
		MeCN	4·95	badly resolved quadruplet	10·2	39	68[f] 47[g]	
VIII	—Bu-n	CCl_4	5·05	triplet	10·6	34		
		MeCN	5·15	badly resolved quadruplet	10·7	33		
IX	—$SCMe_2Et$	CCl_4	5·0	triplet	10·6	34	66[i]	
X	—$SCH_2C_6H_5$	CCl_4	4·70	triplet	10·2	39		
		CH_3CN	4·80	triplet	10·3	38		
XI	—SC_6H_5	CCl_4	5·2	quadruplet	9·5	44	74[c]	
		CH_3CN	5·3	quadruplet	9·3	47	68[c]	
XII	$—\mathrm{S}\underset{\underset{\mathrm{S}}{\Vert}}{\mathrm{P}}(\mathrm{Me})_2$	CCl_4	5·55	doublet of quadruplets	8·2	62		
		CH_3CN	5·65	badly resolved doublet of quadruplets	7·9	66		
XIII	$—\mathrm{S}\underset{\underset{\mathrm{S}}{\Vert}}{\mathrm{P}}(\mathrm{Et})_2$	CCl_4	5·60	doublet of quadruplets	8·3	61		
		CH_3CN	5·7	badly resolved doublet of quadruplets	7·9	66		

[a] In the 100 mHz spectrum—quadruplet. [b] Ref. 9 [c] Ref. 3 [d] Ref. 5 [e] Ref. 6 [f] for —SC_2H_5, Ref. 3 [g] for —SCH_3, Ref. 5 [h] Ref. 7 [i] for —$SC(CH_3)_3$, Ref. 5

TABLE 2

Compound	Yield	B.p. (P, mm Hg)	d_4^{20}	n_D^{20}	MR_D Found	MR_D Calc.	Found % C	Found % H	Found % P	Formula	Calculated % C	Calculated % H	Calculated % P
V	70	96·0–96·5(6)	1·0362	1·4800	48·30	48·15	54·40	9·16		$C_8H_{16}O_2S$	54·49	9·16	
VI	40	93·0(11)	1·0427	1·4830	48·20	48·15	54·35	9·10		$C_8H_{16}O_2S$	54·49	9·16	
VII	50	101·0(3)	1·1143	1·5370	49·98	50·11	47·64	7·89		$C_7H_{14}OS_2$	47·59	7·91	
VIII	50	86(1)	1·0775	1·5305	54·54	54·72	49·82	8·28		$C_8H_{16}OS_2$	49·95	8·31	
IX	50	115(3)	1·0600	1·5225	59·35	59·34	53·12	8·97		$C_9H_{18}OS_2$	52·37	8·79	
X	35	104–105[a] (1·4 × 10^{-3})	1·2155	1·6040	64·09	64·22	58·82	6·22		$C_{11}H_{14}OS_2$	58·36	6·23	
XI	30	120(1)	1·2115	1·6200	59·40	59·60	56·34	5·50		$C_{10}H_{12}OS_2$	56·56	5·69	
XII	75	(60·5)[b]					27·87	5·09	11·67	$C_6H_{13}O_3S_3P$	27·67	5·03	11·88
XIII	90	106–107[a] (2·0 × 10^{-2}	1·2580	1·5559	73·70	73·49	33·25	6·08	10·53	$C_8H_{17}O_3S_3P$	33·31	5·94	10·74

[a] Bath temp [b] M.p.

of "hockey sticks" one may explain an abnormal conformational behavior of the benzodioxan carboxylic acid derivatives (XVI). As found in our work[24] and also by British authors,[25] the axial conformation is predominant for compounds XVI. However, in our opinion, this example cannot be interpreted as the common anomeric effect since the latter was not observed for 2-formyl- and 2-methoxycarbonyltetrahydropyrans XVII.[24, 25] Besides, the value ΔG_{COOR} for 2-substituted tetrahydropyran is equal to 1·6 kcal/mole[28] as opposed to 1·1 kcal/mole for cyclohexane derivatives. Thus the specific conformational behavior of XVI is due to a transition from dihydropyran system to that of 1,4-dioxan. The stability of the axial conformation can be explained by a reverse effect of "hockey sticks", which is evident from XVIII. We may point out that the reverse "anomeric" effect has been experimentally confirmed.[29]

In conclusion one may notice that the effect of "hockey sticks" may explain the above mentioned higher sensitivity of the conformational equilibrium towards the bulk of substituent in the alkoxy group in series 1,4-dioxan in comparison to alkoxytetrahydropyrans.[9, 27] Rotameric conformation XVb in which the group R is oriented outside the ring should be more stable.[7] This makes possible a repulsion of an $y = O$ atom from the alkoxy group oxygen similar to XVb. However, the R being less bulky, the group OR would be in a more favorable rotameric conformation to diminish repulsion. When R is bulky, the lability of the OR group is restricted and one may observe an unfavorable orientation of $-OR$ with respect to $y = O$.

EXPERIMENTAL

The PMR spectra of 30% soln were taken on the RS-60 and JNM-C-60H instruments with hexamethyldisiloxan as the internal standard.

III and IV were prepared by cyclization of the respective dialkyl-(2-oxyethylthio)-acetals in presence of hydrogen chloride.[30] The 2-alkoxy- and 2-alkylthioderivatives of 1,4-oxathian were obtained also in presence of hydrogen chloride by the following method: a catalytic quantity of ether saturated with HCl was added to a mixture of 1,4-oxathien and 50% excess of the corresponding alcohol or mercaptan. The mixture was then heated on a bath at 90° for 3–4 hr, neutralized with dry K_2CO_3 and distilled *in vacuo*. Constants of the compounds obtained are listed in Table 2. XII and XIII were synthesized by the following procedure: An equimolar mixture of 1,4-oxathien and dialkyldithiophosphoric acid were stirred at room temp. for 3–4 hr and then distilled in a high vacuum (0·02 mm Hg).

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