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THE INFLUENCE OF REMOTE SUBSTITUENTS ON THE REACTIVITY OF THE CYCLOHEXENE DOUBLE BOND

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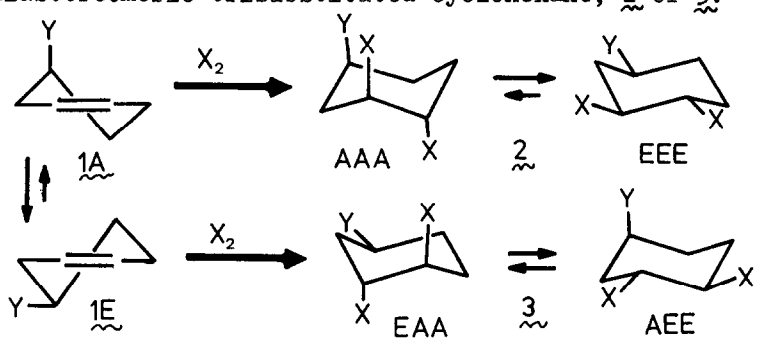
Abstract. The rate of addition of chlorine to the axial conformer of 4-RO--cyclohexenes is faster than for addition to the equatorial conformer. The deactivation of the double bond by an equatorial electronegative substituent via orbital interactions is proposed to account for this effect.

The polar effects of remote substituents can in some cases be transmitted over long distances [1-4]. For example a sharp decrease in rate of electrophilic additions has been clearly demonstrated for 4-substituted cyclohexenes 1 with electronegative substituents [2,3]. One of the general theories concerning the problem of such "long-range" interaction, based on MO considerations [4], predicts that deactivation of the double bond in 1 ought to be much greater for an equatorial conformer, 1E, than for an axial conformer, 1A. In the present paper we report experimental observations supporting this prediction [5].

The halogenation of cyclohexenes 1 (Y = OCD_3, $OOCCH_3$, $OOCCF_3$) was chosen as a model reaction. In this process conformers 1A or 1E produce corresponding diastereomeric trisubstituted cyclohexane, 2 or 3.



2 and 3

a X = Cl, Y = OCD_3
b X = Cl, Y = $OOCCH_3$
c X = Cl, Y = $OOCCF_3$
d X = Br, Y = OCD_3
e X = Br, Y = $OOCCH_3$
f X = Br, Y = $OOCCF_3$

We have carried out an exhaustive halogenation of compounds 1 (dry $CHCl_3$; gradual addition of gaseous Cl_2 at -50-60°C or Br_2 at 0°C) and determined the proportions of isomeric products 2 and 3 by integration of signals for the methine protons H_x and H_y in the ^1H NMR spectra. These data are presented in Table 1. The ^1H NMR and TLC data indicate the absence of noticeable amounts of side products on bromination and only a minor (5-10%) content of byproducts from the chlorination.

Table 1. The ratio of the products from the reaction of 1 with X_2. *

Y	X = Cl		X = Br	
	2	3	2	3
OCD_3	60	40	35	65
$OOCCH_3$	55	45	40	60
$OOCCF_3$	60	40	40	60

*Averages of two measurements. Integration data are reproduciable within ±5.

Table 2. Chemical shifts (p.p.m. from int.TMS) and band widths (Hz). *

	CCl_4		$(CD_3)_2CO$	
	δ	W	δ	W
2b				
H_1	3.83	22.5±0.4	4.00	25.4±0.2
H_2	3.90	22.5±0.4	4.10	25.7±0.2
H_4	4.71	27.2±0.3	4.77	30.5±0.2
3b				
H_1	4.09	15.0±0.3	4.16	20.7±0.4
H_2	4.25	15.3±0.3	4.28	21.2±0.3
H_4	5.02	23.8±0.2	5.05	17.3±0.4

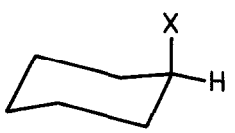
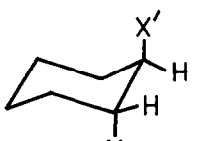
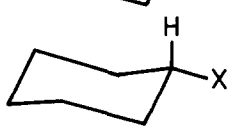
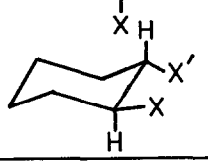
*Recorded on a Bruker WH 360 instrument for 5 mol % solutions.

Assignment of signals in the ^1H NMR spectra to 2 or 3 was made in accordance with their integral intensities and with double resonance data. The isomers 3a, 3d and 3f were isolated by column chromatography on silica-gel (eluent CCl_4, $CHCl_3$ or $CHCl_3$-pentane), and their spectra confirmed the assignment. It is of interest that the signals of compound 2 are always shifted upfield from the corresponding signals of 3.

In going from 3 to 2 one may expect an anisotropic influence of Y on the chemical shift of H_2 to be changed more considerably than that on the chemical shift of H_1. Indeed, one of these signals (downfield) changes its position more strongly than another. So we assigned it to H_2.

Configurations and conformations of 2 and 3 were determined by use of bandwidth of the $H_{x,y}$ signals, $W = \sum J_{HH}$. The W values were measured as a distance between centres of terminal peaks of multiplet. The ^1H NMR data for 2b and 3b (Table 2) exemplify these results. Comparison of these data with that for individual cyclohexane conformers (Table 3) enables us to determine whether the corresponding substituent is axial or equatorial one.

Table 3. Limiting W values (Hz).

Model compounds	X	W	Model compounds	X	W
	OAc	10.8 [6]		Hlg	7-10.6 [8,9]
	OCH_3	10.9 [7]			
	OAc	31.3 [6]		Hlg	23-26.2 [8,9]
	OCH_3	30.2 [7]			

The bandwidths for one type of isomer indicate that all substituents are predominantly equatorial, and this is assigned the structure 2. In polar solvent all multiplets $H_{x,y}$ become broader, and that means an increase of the content of the EEE-conformer. It is of interest that the conformational equilibrium 2AAA ⇄ 2EEE is not anancomeric at least in nonpolar solvent. There is a considerable population of the conformer with three axial groups in equilibrium inspite of the unfavourable position of all substituents and a syn-axial interaction X···Y. Conformers of 2f in CCl_4 possess almost equal stability.

For isomer 3 two situations are observed: (i) both substituents X are predominantly axial and Y is predominantly equatorial, or (ii) both X groups are predominantly equatorial and Y is predominantly axial. In polar solvents the signals H_x become broader and the signal H_y becomes narrower indicating that the EEA-conformer becomes more stable.

Conformational properties of compounds 2 and 3 are now under active study.

The main result of this work is the prevalence of isomer 2 over isomer 3 from chlorination of 1 (Table 1). It means that the rate of chlorination of axial 1A is greater than that of equatorial 1E. We believe that this fact gives evidence of deactivation of the remote double bond by the polar influence of an equatorial substituent as a factor determining the relative reactivity of conformers. Other alternatives seem to be much less probable. Indeed, the preferential addition of Cl_2 to the axial conformer 1A can not be explained by conformational properties of cyclohexenes 1, because the equatorial conformer 1E predominates in the equilibrium 1A ⇄ 1E [10,11]. On the other hand a preliminary coordination ("specific directing effect", see [13]) of type RO···X_2 in the conformer 1A, which could be proposed as a reason for axial attack, in our case seems to be improbable (cf. [9]). Moreover the axial substituent Y should hinder to some extent the approach of X_2 to the double bond in 1A. Perhaps the smaller proportion of isomer 2 from bromination as compared with chlorination is a result of this hinderance. Thus, the only reasonable explanation of the effect is the deactivation of the double bond by the electronegative equatorial substituent via orbital interactions [4].

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