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HOMOALLYLIC INTERACTION OF THE DOUBLE BOND WITH SUBSTITUENTS

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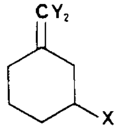
***Ab initio* calculations were carried out on systems with a geometrically constrained relationship between a double bond and a homoallylic substituent X, as in YC=CCCX. The axial–equatorial equilibria in 3-substituted methylenecyclohexanes and 4-substituted cyclohexenes are determined largely by the homoallylic interaction between X and the double bond. The homoallyic substituent was chosen to be OCH_3, and the nature of the double bond was varied by changing Y (H, CH_3, F, Cl, CN). NMR experiments previously had found very significant dependences of the axial–equatorial equilibrium on the nature of the X and Y substituents. Electrostatic calculations, based on Mulliken charges, reproduce the experimental (NMR) substituent effects on the axial–equatorial equilibrium and suffice to explain all the observations.**

Electronic interactions between a double bond and attached substituents (C=C—Y) are well understood in terms of conjugation (if the group has π orbitals) and induction (if it is polar). When the double bond is insulated from the substituent by a saturated carbon, either allylically (C=C—C—X) or homoallylically (C=C—C—C—X), the situation is less clear. Conformational aspects of the allylic case are dominated by the $A^{1,3}$ nonbonded interaction.[1] The homoallylic interaction has been less studied. There may be orbital interactions, possibly through the bond chain or partially through space. Contributing electrostatic phenomena can include the σ inductive effect and higher order effects such as the dipole–dipole interaction. In this paper, the letter Y will be used for vinylic substituents (Y—C=C) and X for homoallylic substituents (C=C—C—C—X).

We have been studying the homoallylic interactions of the double bond by NMR spectroscopy and UV photoelectron spectroscopy.[3] We have focused on the exocyclic (**1**) and endocylic (**2**) six-membered ring systems, in which the homoallylic substituent X may be varied and the properties of the double bond may be altered by the choice of Y. In each case, the ring may exist in two conformations, in which the substituent X is either axial or equatorial. The spatial arrangement and hence the interaction between the substituent and the double bond are different in the two conformations. The relative amounts of the conformations provide a measure of this interaction, which depends on the nature of X, Y and the solvent.



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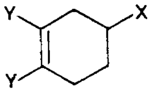

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Almost all our NMR observations could be explained in terms of an electrostatic interaction between the substituent X and the double bond. For the *exo*-methylene case (**1**, Y = H), a higher electronegativity of X increased the equatorial conformer at the expense of the axial conformer,[3] as would be expected from a repulsive dipole–dipole interaction between the C—X bond and the C=CH_2 double bond. A change to a more polar solvent reduced these interactions. Reduction of the polarity of the double bond by substitution with an electron-donating group (**1**, Y = Me) essentially nullified the interaction.[2,3] Similar observations in the endocyclic series also were consistent with an electrostatic interaction that controlled the conformational equilibrium between axial and equatorial X in **2**.[2]

One set of observations appeared to be inconsistent with the electrostatic interaction.[3] Just as a reduction in the polarity of the double bond through substitution with an electron-donating group (Y = CH_3) reduced the observed homoallylic interaction, we thought that an increase in the polarity through substitution with an electron-withdrawing group should increase the interac-

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tion. Consequently, we prepared **1** with Y = Cl, Br and CN. Surprisingly, with Cl and Br, the homoallylic interaction was reduced, as demonstrated by increased proportions of the axial conformer. Thus Cl and Br had the same effect as CH_3. We considered the possibility that the inductive effect of Cl and Br was reduced or even reversed by resonance donation from the halogen lone pairs, but the available dipole moment data indicated that the groups were electron withdrawing.[2] Consequently, we were forced to invoke an alternative mechanism, an attractive, through-space $n-\pi^*$ interaction. We concluded that an 'electrostatic explanation alone cannot explain all these observations,' but noted that the attractive $n-\pi^*$ interaction was 'only a hypothesis ... no experiments have been carried out to test its validity.'[2]

The experiments were hampered in part by insolubility of **1** with Y = CN at low temperatures and lack of success in preparing **1** with X = F. Consequently, we had recourse to *ab initio* calculations in order to assess the importance of electrostatic interactions. We carried out calculations on both the exocyclic (**1**) and endocyclic (**2**) systems with X = OCH_3 and Y = F, Cl or CN. We found that orbital interactions are not necessary to explain the results for the polar homoallylic substituents X, but that a unified electrostatic interaction between X and the Y-substituted double bond is sufficient to explain all the NMR observations.

RESULTS

Mulliken populations were calculated on a Harris version of the SCF–MO GAUSSIAN 82 program at the restricted Hartree–Fock level.[4] Initial geometries obtained with the molecular mechanics program MM2 were optimized with the *ab initio* program. Because of the large size of the molecules, only the minimal basis set STO-3G was used. Table 1 gives Mulliken populations for the *exo*-methylene cases: atom 1 is the *exo* carbon, atom 2 is the unsaturated carbon in the ring and atoms 3 and 3′ are the atoms attached to atom 1. Some differences between these quantities are given in Table 2, indicating the electron imbalance between

Table 1. Mulliken populations for methylenecyclohexanes (**1**)

X	Y	C-1[a]	C-2[b]	3,3′[c]
H	H	6·140	5·986	
eq-OCH_3	H	6·138	5·988	
ax-OCH_3	H	6·135	5·982	
H	CH_3	5·995	6·002	6·169
eq-OCH_3	CH_3	5·993	6·004	6·169
ax-OCH_3	CH_3	5·989	6·000	6·168
H	F	5·748	6·045	9·134
eq-OCH_3	F	5·746	6·046	9·132
ax-OCH_3	F	5·741	6·041	9·132
H	Cl	5·965	5·960	17·102
eq-OCH_3	Cl	5·945	5·964	17·113
ax-OCH_3	Cl	5·940	5·959	17·113
H	CN	6·027	5·916	5·92, 7·181[d]
eq-OCH_3	CN	6·024	5·919	5·922, 7·179[d]
ax-OCH_3	CN	6·021	5·912	5·919, 7·182[d]

[a] The external unsaturated carbon.
[b] The ring unsaturated carbon atom.
[c] The atom attached to C-1.
[d] For C and N of C≡N respectively.

Table 2. Differences in Mulliken populations for methylenecyclohexanes (**1**)

X	Y	[(C-1) − (C-2)][a]	[C-1(H − OCH_3)][b]	[C-2(H − OCH_3)][c]
H	H	0·154		
eq-OCH_3	H	0·150	−0·002	0·002
ax-OCH_3	H	0·153	−0·005	−0·004
H	CH_3	−0·007		
eq-OCH_3	CH_3	−0·011	−0·002	0·004
ax-OCH_3	CH_3	−0·011	−0·006	−0·002
H	F	−0·297		
eq-OCH_3	F	−0·300	−0·002	0·001
ax-OCH_3	F	−0·300	−0·007	−0·004
H	Cl	−0·005		
eq-OCH_3	Cl	−0·019	−0·020	0·004
ax-OCH_3	Cl	−0·035	−0·025	−0·001
H	CN	0·111		
eq-OCH_3	CN	0·105	−0·003	0·003
ax-OCH_3	CN	0·109	−0·006	−0·004

[a] Difference between the exocyclic (C-1) and ring (C-2) unsaturated carbon atoms.
[b] Difference at C-1 between X = H and X = OCH_3.
[c] Difference at C-2 between X = H and X = OCH_3.

Table 3. Intramolecular electrostatic interaction energies (kcal mol^{-1}) for 3-methoxymethylenecyclohexanes (**1**, $X = OCH_3$)

Y	E(equatorial)	E(axial)	ΔE
H	1·22	2·02	0·79
CH_3	−0·04	−0·21	−0·17
F	−1·99	−3·53	−1·54
Cl	−0·76	−1·44	−0·68
CN	−0·65	−1·24	−0·60

Table 4. Intramolecular electrostatic interaction energies (kcal mol^{-1}) for 4-methoxycyclohexenes (**2**, $X = OCH_3$)

Y	E(equatorial)	E(axial)	ΔE
H	1·37	2·01	0·64
CH_3	0·02	−0·09	−0·11
F	−2·07	−2·91	−0·84
Cl	−0·78	−1·37	−0·59
CN	−0·55	−1·01	−0·46

carbons 1 and 2 (column 3) and the effect of introducing methoxyl as the homoallylic substituent (columns 4 and 5).

Electrostatic interactions between atoms were calculated by the classical coulombic expression

$$E = \sum_i \sum_j \frac{q_i q_j}{r_{ij}} \qquad (1)$$

where q is the Mulliken charge on atoms separated by a distance r. Table 3 gives the magnitude of the composite of these interactions for the atoms of the double bond (C-1 and C-2), the oxygen atom ($X = OCH_3$) and the ring carbon to which X is attached. Other atoms did not contribute, either because the charge q is too small or the distance r is too large. The total electrostatic interactions for the equatorial and axial conformers are given in the second and third columns, respectively. The axial–equatorial differences are given in the last column, as a measure of the conformational free energy difference. These calculations were repeated for the endocyclic system **2**, with a similar set of substituents on the double bond (Table 4).

DISCUSSION

Because of the use of the minimal basis set and nonspatial charges, we prefer to look at qualitative or semiquantitative trends rather than absolute values of Mulliken populations and charges. From Tables 1 and 2 it may be seen that the exocyclic carbon (C-1) of the methylenecyclohexane system **1** (Y = H) is negative (higher Mulliken population) with respect to the unsaturated ring carbon (C-2), as is expected for this pattern of substitution, $R_2C^{\delta+}-C^{\delta-}H_2$. Introduction of the 3-methoxy group has little effect on this polarity. The difference in electron density between C-1 and C-2 (third column in Table 2) is about 0·15 electron at this level of calculation.

The assumption in the NMR investigation of the isopropylidene system[2] (**1**, $Y = CH_3$) was that the nearly equal substitution of C-1 and C-2 ($R_2C{=}CMe_2$) rendered the double bond essentially nonpolar. As seen from Tables 1 and 2, this assumption is confirmed. There is almost no polarity to the bond; if anything there is a slight reversal, $R_2C^{\delta-}-C^{\delta+}Me_2$, but only 0·007–0·011 electron.

The effect of Y = F is to raise the Mulliken population on the ring carbon and lower it on the exocyclic carbon, $R_2C^{\delta-}-C^{\delta+}F_2$. This result may reflect resonance donation from fluorine, $^-C-C{=}F^+$, and the poor ability of fluorine to stabilize an α-carbanion because of four-electron repulsion.

Chlorine has a similar but much reduced effect, so that the polarity of the double bond is almost zero. Hence, in this system, the effect of Cl is nearly identical with that of CH_3. The reason probably is that π donation by Cl tends to cancel σ withdrawal, as we originally suspected but could not confirm from the dipole moment literature.[2] Hence the calculations are in complete accord with the NMR results and render unnecessary a special explanation for the chlorine system, and likewise presumably for the bromine system. NMR experiments were not carried out with the F system. The cyano system retains the original polarity, $R_2C^{\delta+}-C^{\delta-}(CN)_2$, somewhat reduced, but again there are no NMR experiments for comparison.

From the calculations, we have two clear predictions. For **1** with Y = F, there should be decreased repulsion between the double bond and $X = OCH_3$ with a resulting increase in the proportion of the axial conformer over that with Y = H and even that with Y = Cl. For **1** with Y = CN there should be a small decrease in the repulsion, with an increase in the axial conformer that is smaller than for Y = Cl or CH_3.

Table 2 contains some further comparisons. Introduction of the 3-methoxy group results in small changes in Mulliken populations (last two columns). There is a slight reduction at the exomethylene carbon (C-1) for both equatorial and axial methoxyl. At the ring carbon (C-2), equatorial methoxyl invariably raises the Mulliken populations while axial methoxyl lowers it.

The calculated Mulliken populations are in agreement with ^{13}C chemical shift changes that occur on introduction of the methoxy group (see the archival version of Ref. 2). As seen in Table 2 (last two columns), introduction of equatorial methoxyl lowers the Mulliken population at the *exo*-methylene carbon (C-1) and raises it at the ring carbon (C-2) (in solution there is little axial conformer for Y = H, so comparisons cannot be made). Similarly, the *exo*-methylene carbon is deshielded and the ring carbon is shielded on introduction of methoxyl.

The dynamic NMR data for $Y = H$ and CH_3 were successfully explained in terms of a dipole–dipole electrostatic interaction.[1,2] The cases $Y = Cl$ and Br, however, were thought to be anomalous because they were expected to have reverse polarity from that of $Y = CH_3$. From the above results, we have seen that the Cl case has Mulliken populations that are very similar to those for $Y = CH_3$. Thus the NMR experiments and the calculations are in agreement for all substituents.

The calculations can give further insight into the mechanism of the interaction between the X substituent and the double bond. The relative magnitude of the electrostatic interactions may be assessed by application of equation (1) to the Mulliken charges. Table 3 gives the calculated magnitude of composite coulombic interactions (E) for each conformer. The difference ΔE between these quantities should be a measure of the axial–equatorial equilibrium constant and hence of ΔG°(ax – eq).

Several interesting conclusions may be drawn from the data in Table 3. In the *exo*-methylene case ($Y = H$), there is repulsion between the methoxy group in both the axial and equatorial positions (E is positive), but the repulsion is clearly larger for the axial conformation. The net electrostatic interaction therefore favors the equatorial conformer (ΔE is positive), as observed.[1] For all other Y substituents the electrostatic interactions are attractive (E is negative), as observed.[1] The effect for $Y = CH_3$ is almost zero, also as observed. Thus the electrostatic interaction indeed operates in the same direction for $Y = CH_3$ and Cl and favors the axial conformer.[2] The effect is proportional to electronegativity, in the ascending order CH_3, CN, Cl, F. The parallelism between the NMR observations and the electrostatic calculations is clearly seen in Figure 1. The electrostatic calculations are simplistic, in that the charges were placed on the atoms and the resulting dipolar interactions calculated, but the trends clearly reproduce the experimental results.

These results show that all the experimental observations may be explained in terms of electrostatic interactions that operate through space. Although other effects (through-bond induction, orbital) may be important in absolute terms, they tend to influence the axial and equatorial forms equally and hence do not result in a change in the equilibrium constant.

We also carried out experiments on 4-substituted cyclohexenes (**2**).[5] For $X = CN$, we examined both the unsubstituted ($Y = H$) and dimethyl-substituted ($Y = CH_3$) double bond. We now have performed the same electrostatic calculations for the cyclohexenes **2** ($Y = H$ or CH_3) as were described above for the methylenecyclohexanes **1**. The results of these calculations are given in Table 4, in which calculations also are reported for $Y = F$, Cl or CN, systems that were not accessible synthetically. The sets of results in Tables 3 and 4 are very similar, except that the interactions for the cyclohexenes are smaller than those for the methylenecyclohexanes, as observed by NMR.[5] Thus the interaction is repulsive for $Y = H$, essentially zero for CH_3 and attractive for F, Cl and CN. The electrostatic interaction favors the equatorial conformer when $Y = H$ and the axial conformer for the remaining Y entities. The major difference between the two data sets is that the interactions in the cyclohexenes are smaller than those in the methylenecyclohexanes. The axial 4-methoxy group is actually closer to the double bond in the cyclohexene than is the axial 3-methoxy group in the methylenecyclohexane. The changes in the calculated Mulliken populations and electrostatic interactions, however, are smaller for the cyclohexenes, in agreement with the NMR observations.[5] In these interactions, both directionality and distance are important, and for the case of the cyclohexenes the directionality of the interaction between the double bond and the substituent is unfavorable.

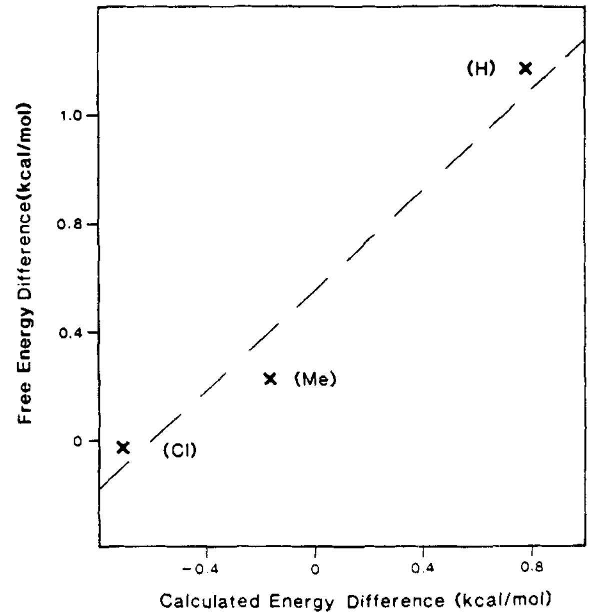

Figure 1. Experimental free energy difference vs the calculated electrostatic energy difference for 3-methoxy-*exo*-disubstituted-methylenecyclohexanes (**1**: $X = OCH_3$ and $Y = H$, CH_3 or Cl)

CONCLUSIONS

The stereochemical component of the homoallylic interaction between a double bond and a substituent may be explained in terms of a dipolar electrostatic mechanism.

This conclusion was based on experimental NMR observations and on *ab initio* calculations for the axial and equatorial 3-methoxymethylenecyclohexanes and 4-methoxycyclohexenes. Inductive and orbital interactions are important, but they tend to affect the axial and equatorial conformations to similar extents. The electrostatic interaction invariably affects the two conformations differently (Tables 3 and 4). The calculations agree with experiment on all points: (i) the Mulliken populations parallel the observed results (Tables 1 and 2); (ii) electrostatic interactions calculated by equation (1) from Mulliken charges (Tables 3 and 4) parallel the NMR populations (Figure 1); (iii) the chemical shift changes on introduction of equatorial $X = OCH_3$ parallel the changes in Mulliken populations; and (iv) the calculated electrostatic interactions are smaller for 4-X-cyclohexene (**2**) than for 3-X-methylenecyclohexane (**1**), in parallel with the NMR observations (Tables 3 and 4).

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