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# Mechanism of Interaction of Substituents in Bicycloalkane Compounds

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**Abstract**—The mechanism of interaction of substituents in the 4-substituted bicyclo[2.2.2]oct-1-ylfluorides and bicyclo[2.2.1]hept-1-ylfluorides based on the inductive effect and the positive charge effect was studied.

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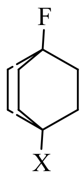
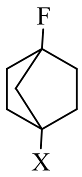
In this work we investigated the mechanism of interaction between the substituents X [X = $NO_2$, CN, COOMe, COOH, F, Cl, $NH_2$, $Sn(Me)_3$] and F in the 4-substituted bicyclo[2.2.2]oct-1-ylfluorides **I** and bicyclo[2.2.1]hept-1-ylfluorides **II**.



**I**



**II**

1,4-Disubstituted bicycloalkanes, being the geometrically rigid aliphatic systems in which the substituents and the reaction center (side chain) are located in the spatially remote positions, are good model systems for studying the nature of the substituents interaction without the stereochemical and π-resonance effects.

It has been shown previously that in the aromatic compounds such as $XC_6H_4Y$ the influence of the polar substituent X on the Y group is defined, along with its inductive and resonance effects, by the so-called positive charge effect [1, 2]. The influence of the latter is as follows. Let the $C^1$ atom in the benzene ring be attached to the Y group (Y = CN, $CF_3$, COOH, etc.) and be positively charged. The acceptor substituent X in the *para*-position to the Y group increases the positive charge on the $C^1$ atom. According to the positive charge effect, this leads to the negative charge transfer to the Y group. The influence of the donor substituent X is completely opposite: it decreases the positive charge on the atom $C^1$, the charge transfer occurs from the Y group to $C^1$. Due to the positive charge effect, there is an opposite (contrary to the expectations) change in the electron density on the α-atom of the Y moiety (for example, on the C atom of CN group), which is manifested in the reverse chemical shifts of the atoms. Such shifts are observed for many atoms $Y_\alpha$ = C, N, P, S, etc. [3].

Another formulation of the positive charge effect is also used. For example, in a series of the structurally similar molecules ABC, in which the electronegativity of the atoms A and C is greater than that of B (i. e., B is a positively charged atom), there is an increase in the electronegativity of the A atom. In this case, the negative charge on the C atom is increased regardless of the inductive effect of the A atom.

The reverse chemical shifts of the fluorine signals are observed for compounds **I**. The chemical shifts $\delta_F$ (ppm) for compounds **I** and **II** with respect to the parent compounds (X = H) are given below. The negative value indicates an upfield shift of the fluorine signal [4–6].

| X | $NO_2$ | CN | $CF_3$ | COOH | F | Cl | $NH_2$ | $N^+(Me)_3$ | $Sn(Me)_3$ |
|---|---|---|---|---|---|---|---|---|---|
| $\delta_F$ (**I**) | –9.89 | –5.40 | –6.05 | –5.68 | –10.32 | –8.14 | –7.51 | –11.14 | +3.83 |
| $\delta_F$ (**II**) | 7.91 | 2.41 | – | 4.94 | 10.08 | 6.84 | 10.56 | – | –2.67 |

As can be seen, the value of $\delta_F$ in compounds **I** increases, therewith the upfield shift depends on the electronegativity ($\chi$) of the X substituent. In compound **II** the trend in the shift of the fluorine signal is reversed. Apparently, the mechanism of the substituents interaction in these systems can be described similarly to the case of aromatic compounds [1], but without the resonance effect of X.

The substituents interaction in the bicycloalkane compounds was studied in several works [7, 8]. The main problem discussed in these studies was the mechanism of the influence transfer. Two mechanisms are possible: the transfer through space (the field effect, $\sigma_F$) and the transfer through the σ-bonds (the σ-inductive effect, $\sigma_X$). The first effect depends on the dipole moment of the X substituent, and the second, on its electronegativity. There is a possibility of hyperconjugation of the orbitals in the transfer of the inductive effect ($\sigma_X$) of the X substituent to the fluorine atoms [7, 8], even if they are attached to a saturated carbon skeleton, such as is present in compounds **I** and **II**. According to [5], besides the polar field effect ($\sigma_F$) causing the C–F σ-bond polarization, in this case an effect of the long-range action occurs, which has a similar influence on this bond. In compound **I** this effect is transferred through a three-bond electronic delocalization mechanism (σ-resonance or σ–σ-hyperconjugation effect). The delocalizetion mechanism predominates in the inductive interaction between the groups X and F, since the $C^1$–$C^4$ distance in compound **I** is too large (2.59 Å) [5].

The total chemical shift of the $^{19}F$ nuclei for compounds **I** and **II** reflects mainly the change of the σ-electron density on the fluorine atom. According to [4, 5], the decrease in the electron density causes the negative (upfield) shift of the fluorine signal. The latter assumption seems to be wrong because it contradicts the existing theory of the $^{19}F$ chemical shifts [9].

The diametrically opposite trend in the chemical shifts $\delta_F$ of compounds **I** and **II** is due to the different nature of the σ-electron delocalization in these compounds: trough three (**I**) and two bonds (**II**).

The mechanism of the interaction between the X and F substituents in compound **I** considered below is based on the inductive effect of the X substituent in its traditional representation as an effect, whose influence expands over no more than two bonds from the substituent [10], and on the positive charge effect, which is directly connected with changing the positive charge on the $C^1$ atom under the influence of the X substituent.

The quantum-chemical *ab initio* calculations (RHF/MP2/MINI-4//RHF/MP2/MINI-4) [11] were carried out. The scale factors of the valence orbitals of all atoms of the compound were optimized by the minimum energy criterion. The optimization was stopped at a step $E < 0.0001$ a.u. The atomic charges ($Q$, a.u.) for the different X substituents in compound **I** are presented below. The numbering of carbon atoms in these compounds is obvious from the text (see above).

| X | $Q$(F) | $Q$($C^1$) | $Q$($C^2$,$C^6$,$C^7$) | $Q$($C^3$,$C^5$,$C^8$) | $Q$($C^4$) | $Q$(Cl) |
|---|---|---|---|---|---|---|
| H | –0.3924 | 0.3340 | –0.3020 | –0.2637 | –0.1405 | – |
| Cl | –0.3940 | 0.3450 | –0.2977 | –0.2788 | 0.0857 | –0.2086 |
| F | –0.4022 | 0.3515 | –0.2918 | –0.2918 | 0.3515 | – |

If in compound **I** X = F, the electron density on the $C^2$, $C^6$, and $C^7$ carbon atoms decreases due to the induction effect of the X substituent resulting in increasing the atoms electronegativity and the positive charge on the $C^1$ atom. According to the positive charge effect, the latter causes an increase in the electron density on the F atom and upfield shift of the fluorine signal. In the case of other X substituents ($\chi_X < \chi_F$), for example X = Cl, the fluorine signal is shifted upfield, but less significantly than in the case of F. Also, there are less significant changes in the electron density on the $C^1$ and fluorine atoms (see the calculation results for X = Cl). If X is a donor substituent, such as $SnMe_3$, it reduces the positive charge on the $C^1$ atom and the negative charge on the fluorine atom, shifting the $^{19}F$ signal downfield.

The data on the $^{13}C$ chemical shifts for the $C^1$ atom of compound **I** do not coincide with the results of our calculations indicating the increase in the positive charge of this atom with increasing $\chi_X$: In the experiment the shielding of the $C^1$ atom is observed [5]. Perhaps, in this case the theoretical studies are right which indicate that the decrease in the σ-electron density on the $sp^3$-hybridizated carbon atom is accompanied by the upfield shift of the $^{13}C$ signal [12].

Next, consider compound **II**, where the effect of the X substituent on the fluorine chemical shift has the opposite character as compared with compound **I**.

| X | $Q$(F) | $Q$($C^1$) | $Q$($C^2$,$C^6$) | $Q$($C^3$,$C^5$) | $Q$($C^4$) | $Q$($C^7$) |
|---|---|---|---|---|---|---|
| H | –0.3911 | 0.3479 | –0.2978 | –0.2808 | –0.1310 | –0.2971 |
| F | –0.3761 | 0.3249 | –0.2861 | –0.2861 | 0.3249 | –0.3140 |

The replacement of the hydrogen by the fluorine atom at $C^4$ leads to an increase in the positive charge of the carbon atom. According to the positive charge effect, it causes an increase in the negative charge on the $C^3$, $C^5$, $C^7$, and $C^4$ atoms. The electron density on the $C^2$ and $C^6$ atoms decreases as a result of the induction effect of the fluorine atom. The positive charge of the $C^1$ atom is reduced due to the simultaneous effect of the $C^2$, $C^6$ and $C^7$ atoms. Also the negative charge on the fluorine atom bound to the $C^1$ atom decreases, and the $^{19}$F nuclei resonate in the weak field. The donor X substituent causes a reverse effect: the $^{19}$F nuclei resonate in the strong field.

Thus, the proposed model of the substituents interaction in the 4-substituted bicyclo[2.2.2]oct-1-yl-fluorides **I** and bicyclo[2.2.1]hept-1-ylfluorides **II** based on the inductive effect of the X substituent and the positive charge effect appears to be able to rationalize the trends in the chemical shifts of the fluorine atom under the substituents influence.

The quantum-chemical calculations were performed using a GAMESS software [13].

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