QUANTITATIVE DESCRIPTION OF DISTRIBUTION OF ISOMERS FORMED IN REACTIONS OF SUBSTITUTED BENZENES WITH ELECTROPHILIC REAGENTS

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Despite the large number of papers on the investigation of the reactions of aromatic compounds with electrophilic reagents, factors which determine the ratio between the isomers formed still remain very unclear. As examples, we can cite the difficulties in explaining the ratio between the ortho and para substituents in monosubstituted benzenes and the role of an ipso-attack in the reactions of polysubstituted aromatic compounds.

Many data in this field can be given a simple explanation if we assume (see [1]) that the reaction of an electrophile with an aromatic substrate leads, first, to the formation of a set of i, $j-\pi$ -complexes, in which the electrophile is bound to different pairs of neighboring carbon atoms (or to $C^{i} \\ \cdots \\ C^{j}$ bonds) of the aromatic ring. Each i, $j-\pi$ -complex is further transformed into isomeric i- and $j-\sigma$ -complexes. If we assume that at the first stage the direction of the reaction is controlled by charge and orbital factors, and at the second stage by the thermodynamic factor, the following relationship for the competing formation of the i- and $m-\sigma$ -complexes by routes i(i, j) and m(m, n) can be written

$$\lg \frac{k_{i(i,j)}}{k_{m(m,n)}} = a \left[(q_i + q_j) - (q_m + q_n) \right] + b \sum_{k=1}^{k} \left[\frac{(c_i + c_j)_k^2 - (c_m + c_n)_k^2}{E_k - E_e} \right] + d \left(L_i^+ - L_m^+ \right)$$
(1)

where q_i is the charge on atom C^i ($q_i > 0$ corresponds to positive charge); $(c_i)_k$ is the coefficient of the i-th atomic orbital in the k-th occupied molecular orbital of an aromatic substrate with energy E_k ; E_e is the energy of lowest vacant orbital of the electrophile; L_i^+ is the localization energy of electron pair for the i-th position of substrate; a, b, and d are constants, whose values depend on the nature of the electrophile and the reaction conditions.

Taking into account, to a first approximation, only the highest occupied molecular orbital (HOMO) of the aromatic substrate, neglecting in considering the position selectivity the difference in the E_{HOMO} of different substrates, and substituting L_i^+ by $\rho \Sigma \sigma^+$, we can write relationship (1) in a simpler form (2)

$$\lg \frac{k_{i(i,j)}}{k_{m(m,n)}} = A \left[(q_i + q_j) - (q_m + q_n) \right] + B \left[(c_i + c_j)^2 - (c_m + c_n)^2 \right] + D \left[\Sigma \sigma^+(i) - \Sigma \sigma^+(m) \right]$$
(2)

The values of q_i and c_i used in this investigation were calculated by the CNDO/2 method. The values of σ_p^+ and σ_m^+ constants of the different substituents are known; the σ_0^+ constants of +I and +M substituents were determined from the equilibrium ratios between the substituted benzenonium ions (for CH₃, F, Cl, OH, OCH₃, $\sigma_0^+ = -0.25$, +0.06, +0.18, -0.80, -0.67 [2, 3]); σ_0^+ for -M substituents were assumed to be equal to σ_p^+ ; moreover, $\sigma_{ipso-CH_3}^+ = +0.10$ [2].

One of the attempts usually mentioned in the literature to explain the ratio between the ortho and para orientation in the reactions of monosubstituted benzenes with electrophilic reagents has been described in [4]. The authors of this paper concluded that in the case of chlorination and nitration reactions there is no noticeable specific ortho effect of the substituent (for example, steric), but they did not succeed in finding a quantitative description of the ratio between the isomers formed. The data of [4] on the chlorination of monosubstituted benzenes are listed in Table 1; in parentheses, results are given of the calculation according to Eq. (2), using the values of A = -8.6, B = +8.9, and D = -5.0 (to find these constants, it is sufficient to have the experimental information on the distribution of isomers for two compounds). It can easily be seen that the calculation according to Eq. (2) reproduces well the experimentally observed ratio between the isomers.

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Subst i tuent	ortho	meta	para	
CH₃ Cl OCH₃ NO₂ CN	74,7 (75,9) 36,4 (36,1) 34,9 (29,6) 17,6 (19,9) 23,2 (24)	$\begin{array}{c} 2,2(1,4) \\ 1,3(2,2) \\ 0(0) \\ 80,9(79,1) \\ 73,9(76) \end{array}$	$ \begin{vmatrix} 23,1(22,7), \\ 62,3(61,7) \\ 65,1(70,4) \\ 1,5(0) \\ 2,9(0) \end{vmatrix} $	<u></u>

TABLE 1. Distribution of Isomers during Chlorination of Monosubstituted Benzenes [4] ($Cl_2 + HClO_4$, 25°C)

Similar results were obtained for many other electrophilic substitution reactions.

As an example, we shall consider in somewhat greater detail the proposed approach to describe the electrophilic hydroxylation of substituted benzenes by the action of H_2O_2 in HSO_3F-SO_2ClF at $-78^{\circ}C$ [5].

The HOMO of toluene has b_1 symmetry, and, therefore, hydroxylation of this compound should proceed by routes shown in scheme (3), and there are reasons for believing that the oxybenzenonium ions of type I undergo a rearrangement by 1,2-shift of the CH₃ group [5].

Also the hydroxylation of fluorobenzene (HOMO of b_1 type) proceeds by similar routes, but in this case the high electronegativity of the fluorine atom excludes the possible formation of the ipso- σ -complex. By using the experimental data on the ratio between the ortho, meta, and para isomers formed from toluene (71: 6:23) and fluorobenzene (24:3:73), we can readily determine the parameters of Eq. (2) (A = -3.8, B = +5.8, D = -2.4). At the same time, we find that 12% of ortho-cresol is formed from toluene by route 1 (1,2) with a shift of the CH₃ group, and 88% by route 2 (1,2). An experiment carried out using toluene-1-¹³C confirmed this result of calculated analysis.

In the case of p-xylene, the formation of only one π -complex is possible [scheme (4)], and, therefore, the ratio between the 2,4- and 2,5-dimethylphenols is completely determined by the thermodynamic term of Eq. (2): the predicted ratio is 35:65, and the experimentally observed [5] is 36:64.



(3)

In contrast to toluene and p-xylene, pentamethylbenzene has HOMO with a_2 symmetry, and, therefore, the reaction should preferentially proceed by routes 1 (1,2) - 2 (1,2) [scheme (5)], and, as the calculation shows, using the above values of A, B, and D, with the products being obtained in a ratio of 27:73,



In a study of the behavior of pentamethylbenzene under the hydroxylation reaction conditions, 12% of pentamethylphenol has been isolated from the reaction mixture, as well as 21% of 3,4,5,6,6-, 33% of 2,3, 4,6,6-, and 34% of 2,3,5,6,6-pentamethyl-2,4-cyclohexadienones, which well agrees (33:67) with the predicted value for routes 1 (1,2) and 2 (1,2).

The last example makes it possible to understand why the reaction of pentamethylbenzene with NO_2^+ leads to a preferential formation of 2-nitro-1,2,3,4,5-pentamethylbenzenonium ion [6], and not to the addition of nitronium cation into the unsubstituted position.

In conclusion, we should note that it is interesting to compare the above approach with the recently proposed calculation scheme, similar in character [7], in which, however, the possible role of the thermodynamic factor is not taken into account.

CONCLUSIONS

If we take into account the charge and orbital control at the stage of formation of the π -complexes and thermodynamic control at the stage of their transformation into the σ -complexes, it is possible to quantitative-ly describe the distribution of the isomers formed in the reactions of benzene derivatives with electrophilic agents.

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