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Retrieval and Analysis of Transition States in Electrophilic Substitution Reactions of the Carborane(12) Series

S. P. Knyazev and E. G. Gordeev

Lomonosov Moscow State Academy of Fine Chemical Technology, pr. Vernadskogo 86, Moscow, 119571, Russia
e-mail: mp2sdtq@gmail.com

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Abstract—The transition states of the reaction of electrophilic substitution in a series of *ortho*-, *meta*-, and *para*-carboranes were found by calculations in the B3PW91/6-31G(d,p) and B3LYP/6-31G(d,p) approximations. The key role of catalyst was demonstrated in the reactions of halogenation and alkylation. The reaction selectivity of electrophilic alkylation by CH_3Br in the presence of $AlCl_3$ should be lower than that of the chlorination reaction.

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The dicarba-*closo*-dodecaboranes(12), as aromatic systems [1], are characterized by the reactions of hydrogen substitution not affecting the integrity of the stable icosahedral cage.

In experimental studies of the electrophilic halogenation reaction of carboranes(12) [2] it was found that the first replaced are the hydrogen atoms at the boron atoms most distant from the carbon atom in the molecular framework. However, despite the vast factual material, an information about the mechanism of catalytic reactions of electrophilic halogenation in a series of carboranes(12) is almost lacking.

The reaction of electrophilic alkylation of the carboranes(12) despite the similarity of its mechanism with that of halogenation, differs considerably from the latter. For example, it has been shown experimentally in [3] that in the reaction of *o*-carborane with C_2H_5Br at 25°C four hydrogen atoms are the most easily replaced by the ethyl groups. Carrying out the reaction at the boiling point of C_2H_5Br makes it possible to replace eight hydrogen atoms by the ethyl groups in the mole-cule of the *o*-carborane [3], that is, alkylation affects more positions in the carborane framework than halogenation. The alkylation reaction results in a mixture of isomers [3–5] suggesting that this process is less selective than halogenation.

A fruitful way of understanding the observed patterns of chemical reactions is finding a relationship between electronic structure of the isolated carborane(12) molecule and its chemical properties. Just this approach has been used to explain the direction of electrophylic substitution in the *ortho*- and *meta*-carboranes on the basis of the framework atomic charges [6]. Similar studies involving a wider range of electronic parameters were described in [7]. Despite the occurrence in many cases of clear correlation between the electronic parameters (particularly the parameters of the frontier molecular orbitals) of the molecules of carboranes(12) and chemical properties of these compounds, this approach obviously has fundamental limitations, since it ignores the influence of the other components of the reaction (in the first place, catalyst) and prevents estimation of the kinetic factor of the reaction, which in this case is a very important one.

From the chemical viewpoint, the description of the reaction of electrophilic substitution in the framework of the theory of activated complex is more complete. Therefore we carried out retrieving of the transition states in the reaction of proton transfer in the B3PW91/6-31G(d,p) approximation [8], electrophilic chlorination and alkylation [B3LYP/6-31G(d,p)] both without a catalyst, and with involvement of $AlCl_3$.

Thermodynamic factor in the reaction of electrophilic substitution in the series of carborane (12). The electrophilic chlorination can be represented by reaction (1):

$$C_2B_{10}H_{12} + Cl_2 \overset{kt}{\rightleftarrows} C_2B_{10}H_{11}Cl + HCl. \quad (1)$$

Thermodynamic parameters of the reaction (1) (see the table) indicate that the equilibrium is shifted completely to the reaction products.

For the chlorination reaction the significant negative values of thermodynamic parameters are expectable, given the high energy of the B–Cl bond. However, thermodynamic parameters of the reaction remain almost the same for any position in the molecules of *o*- and *m*-carboranes and the isomers. Similar trends are found in the thermodynamics of the alkylation reaction. For example, the ΔG value of *o*-carborane methylation in position 9 (12) and 3 (6) is –7.8 and –9.0 kcal mol^{-1}, respectively, that is, the difference between the two extreme positions is negligible.

Thus, changes in the reactivity of carboranes(12) in the reaction of electrophilic substitution should be governed not by the thermodynamic, but by the kinetic factor, that is, by the energy of the transition state.

Electrophilic substitution without a catalyst. A simplest electrophilic substitution reaction is a proton transfer: the interaction of carboranes (12) with hydrogen chloride in a protic solvent medium is an exchange of protons between the carborane and HCl molecules. In this process the electrophile is the HCl molecule.

The molecular structure of the reaction site (that is, the atomic groups that are directly involved in the reaction) in all the transition states considered in this paper (Fig. 1) was obtained by the analysis of the topology of the total electron density distribution function [9] in the framework of the Bader's *atoms in molecules* theory [10]. According to the topological approach, for the binding interaction of two atoms the existence between the atoms of a critical point of type (3; –1) of the total electron density distribution function is essential.

The reaction (1) parameters calculated by the B3LYP/6-31G(d,p) method

Position	ΔE, kcal mol^{-1}	ΔH, kcal mol^{-1}	ΔG, kcal mol^{-1}
o-Carborane			
9(12)	–53.2	–54.1	–54.1
8(10)	–52.6	–53.5	–53.5
4(5, 7, 11)	–52.3	–53.3	–53.3
3(6)	–52.6	–53.7	–53.7
m-Carborane			
9(10)	–52.6	–53.4	–53.0
5(12)	–53.0	–54.0	–53.5
4(6, 8, 11)	–52.5	–53.4	–53.0
2(3)	–52.0	–52.9	–52.5
p-Carborane			
Any at B atom	–52.4	–53.2	–54.1

To analyze the reactivity of carboranes in the proton transfer we found several types of transition states (TS). The simplest is the bimolecular TS (Fig. 1a) formed with the involvement of only the carborane and hydrogen chloride molecules. It should be noted that in the bimolecular TS the bonding paths of the reaction site form a cruciform rather than circular structure, with a bonding path between the exchanging hydrogen atoms H^1 and H^2. Therewith, the boron and chlorine atoms are not bound with the hydrogen atoms, but with the bonding point (3; –1) which lies between the atoms H^1 and H^2. Potential barriers $\Delta E^{\neq}$ for the bimolecular TS [B3PW91/6-31G(d,p), kcal mol^{-1}] are for *o*-carborane 51.7, 52.8, 54.3, 57.6, 69.3 in position 9 (12), 8 (10), 4 (5, 7, 11), 3 (6) and 1 (2) (C atoms), respectively (the energy of the source reagent is taken as a sum of total energies of isolated carborane and HCl molecules). As seen, the lowest barrier in this series has the proton transfer in the positions 9 and 12, whereas the exchange of protons between HCl and the CH group of *ortho*-carborane kinetically is the most difficult. Thus, even the simplest model of the transition state on a qualitative level reproduces adequately the experimental behavior of the changes in the reactivity of various groups of atoms in a molecule of *ortho*-carborane. However, the obtained absolute values of the potential barriers for bimolecular TS are too high.

In practice, the reaction of proton transfer takes place in the environment of the protic solvents like methanol. Since methanol is capable of forming associates with a molecule of HCl, then the MeOH–HCl complex can be considered as a single kinetic unit, that is, the formation of trimolecular TS (Fig. 1b) does not require a triple collision of molecules, as the MeOH–HCl complex approaches carborane molecule as a whole. The introduction to the structure of the transition state of a methanol molecule (Fig. 1b) leads to a significant reduction in the reaction barrier (as energy of the initial reagent the sum of total energies

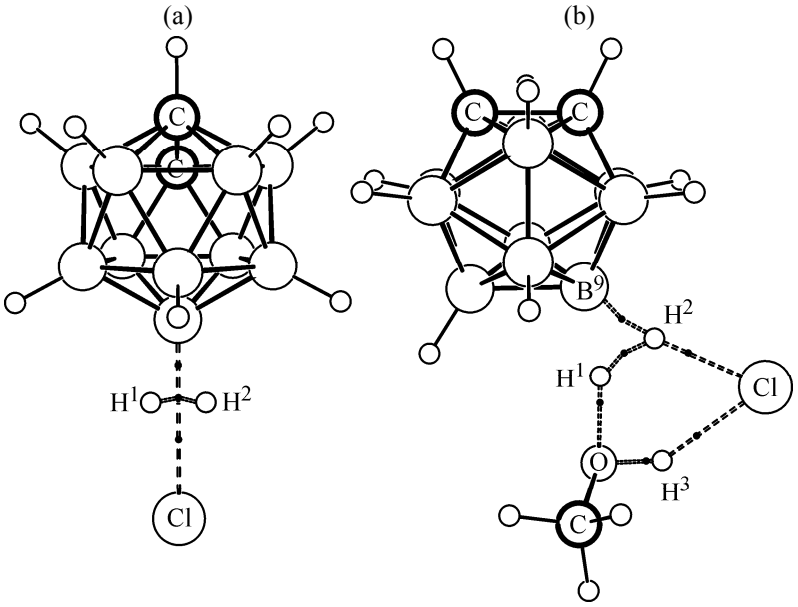

Fig. 1. The molecular structure of bimolecular (1698.3*i* cm^{-1}) (a) and trimolecular (1076.5*i* cm^{-1}) (b) transition states of proton transfer in position B^9 of *o*-carborane calculated by the B3PW91/6-31G(d,p) method. Black dots indicate the position of critical points (3; –1), the binding paths (dotted line) are indicated schematically.

of isolated molecules of carborane and an associate of CH_3OH with HCl is taken) [B3PW91/6-31G(d,p), kcal mol^{-1}]: $\Delta E^{\neq}$ of *o*-carborane is 37.5, 37.5, 37.7, 38.0, 41.2 in positions 9 (12), 8 (10), 4 (5, 7, 11), 3 (6), and 1 (2), respectively; of *m*-carborane, 38.3, 38.0, 38.6, 40.7, 43.2 in positions 9 (10), 5 (12), 4 (6,8,11) 2 (3), and 1 (7), respectively, of *p*-carborane, 39.2 for any BH group, and 44.3 for the CH groups. In the TS shown in Fig. 1b the reaction coordinate is the transfer of the proton H^1 (which has been originally associated with the boron atom 9) to the oxygen atom of a molecule of methanol, therewith the atom H^3 "belonging" to the methanol transfers to the chlorine, and atom H^2 is separated from the chlorine atom and moves to the atom B^9. Thus, the path of this reaction is a circular proton exchange between the three molecules.

Two methanol molecules can associate with a molecule of HCl. The adding one more MeOH molecule to the TS structure leads to a marked reduction in the potential barrier. For example, for the *ortho*-carborane $\Delta E^{\neq}$ is 33.8, 33.8, 33.1, 33.00, 37.0 kcal mol^{-1} in position 9 (12), 8 (10), 4 (5, 7, 11), 3 (6), and 1 (2), respectively.

We can conclude that the selectivity of this process with respect to the various positions in the framework of the carborane(12) should be small for all the considered models of the transition states of the proton transfer reactions. The most pronounced selectivity for *ortho*-carborane is obtained in a bimolecular TS. Trimolecular TS leads to a lesser selectivity, and adding one more molecule of alcohol completely smooths the differences between the positions in the framework. Perhaps the use of other models of the transition states of the process or accounting for the additional factors of environmental influence can lead to higher differences in the potential barriers of this reaction.

The transition states of reactions of electrophilic halogenation and alkylation have other structure than the TS of the proton transfer reaction. To illustrate the crucial role of catalyst in alkylation and electrophilic halogenation at the boron atom of carboranes(12), we initially found the transition states of these reactions without a catalyst.

To calculate the potential barrier of the chlorination reaction, the energy of reactants (the initial system) was assumed to be equal to a sum of the total energies of isolated molecules of carborane(12) and chlorine, and to calculate the potential barrier of the reaction of methylation the sum of the total energies of isolated molecules of carborane(12) and CH_3Br was taken.

For the reaction site of the transition state in the chlorination reaction (Fig. 2a) the binding points are between pairs of atoms: B^9–H, H–Cl^1, and Cl^1–Cl^2 (in Fig. 2, they are connected by dotted lines). A similar distribution of binding critical points is typical also for

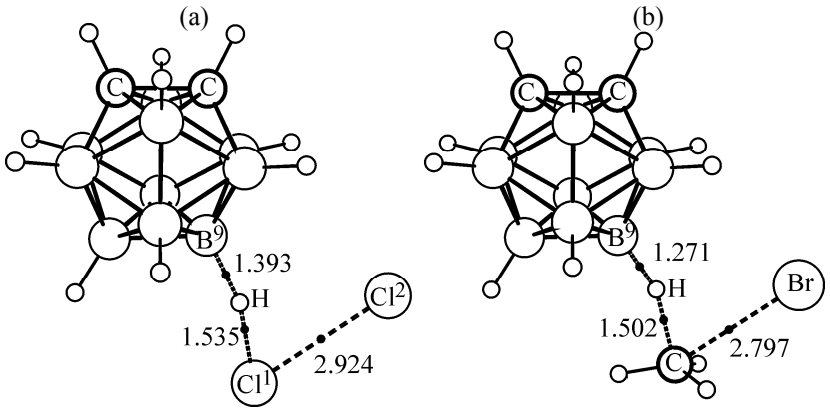

Fig. 2. The molecular structure of transition states in the reactions of electrophilic chlorination (563.7*i* cm^{-1}) (a) and methylation (432.7*i* cm^{-1}) (b) without catalyst, calculated by the B3LYP/6-31G(d,p) method. Interatomic distancesare given in Å.

the transition state of the alkylation reaction (Fig. 2b), in which the carbon atom of the methyl group is bound simultaneously with the replaced hydrogen atom and the bromine atom. Thus, under this approach the reaction site of the TS of chlorination and alkylation reactions is not a closed cyclic structure, typical of most "classical" transition states. Each of the found transition states have one imaginary frequency in the vibrational spectrum, corresponding to vibrations along the reaction coordinate.

As showed our calculations of the reaction path (IRC-computing), the transformation of the transition state into the reaction product in the case of chlorination occurs as follows. Initially, the replaced hydrogen atom forms an HCl "molecule" with Cl^1 atom, but this molecule then disintegrates, and the H atom is transferred to the atom Cl^2, and the Cl^1 atom freed from the H atom is attached to the B^9 atom of the framework. Therefore the HCl^2 rather than HCl^1 molecule is one of the leaving reaction products, in contrast to that might seem from the structure of the transition state.

The same way of the transformation of the transition state in the product is characteristic of the case of the alkylation reaction: the leaving hydrogen atom is initially bonded with the carbon atom of the methyl group, and then it migrates to the atom Br, forming a molecule of HBr, while the methyl group is attached to the atom B^9.

As expected, the potential barriers of the chlorination reaction without the catalyst are high. For example, for the chlorination reaction the potential barriers are $\Delta E^{\neq}$ = 60.2, 61.3, and 66.6 kcal mol^{-1} for *o*-carborane (in position 9 or 12), *m*-carborane (in position 9 or 10), and *p*-carborane respectively.

For the non-catalytic methylation the barriers are slightly higher than for chlorination [B3LYP/6-31G(d,p), kcal mol^{-1}] for *o*-carborane 66.8, 67.0, 63.7, and 62.9 in position 9 (12), 8 (10), 4 (5, 7, 11), and 3 (6), respectively, for *m*-carborane 68.1, 64.2, 65.4, and 69.0 in position 9 (10), 5 (12), 4 (6, 8, 11), and 2 (3), respectively, for *p*-carborane 71.8. As in the case of chlorination, the highest value of the potential barrier is in *p*-carborane, which is consistent with its smallest chemical activity among the considered three isomers. The slight decrease in the potential barrier for *o*-carborane in going from the positions 9 (12) to 3 (6) is due to the fact that upon the approach of the reaction site to the carbon atom, the bromine atom begins to participate in binding to the "acidic" hydrogen atoms C–H of the carborane molecule, and this additional binding to the positions 4 (5, 7, 11) and 3 (6) leads to lowering the transition states energy and as a consequence, to a slight decrease in potential barriers.

If the alkylating agent is not CH_3Br, but CH_3Cl, the structure of the transition state is quite similar; however, the potential barrier slightly increases. For example, for *o*-carborane the barriers to the alkylation with CH_3Cl are $\Delta E^{\neq}$ = 71.2, 71.3, 68.6, and 68.4 kcal mol^{-1} for the positions 9 (12), 8 (10), 4 (5 ,7, 11), and 3 (6), respectively. This increase in the potential barriers at replacing CH_3Br by CH_3Cl is fully consistent with the experimental data, since the C–Br bond undergoes dissociation easier than the C–Cl bond.

Electrophilic substitution with a catalyst. In electrophilic halogenation of carboranes(12) a catalyst is used acting as a Lewis acid, like aluminum chloride.

It is known from the experiments that the substitution of hydrogen by halogen atoms occurs primarily at the boron atoms maximally distant from the framework carbon, that is, in the positions 9 (12), 8 (10) in *o*-carborane and 9 (10), 5 (12) in *m*-carborane [2].

Simplified reaction of the catalytic chlorination of carboranes(12) is given by Eq. (2).

$$\underbrace{C_2B_{10}H_{12} + 1/2Al_2Cl_6 + Cl_2}_{\mathbf{I}} \rightleftarrows \underbrace{C_2B_{10}H_{12} + Cl_2\cdots AlCl_3}_{\mathbf{II}} \rightleftarrows [TS]^{\neq} \rightleftarrows \underbrace{C_2B_{10}H_{11}Cl + HCl\cdots AlCl_3}_{\mathbf{III}} \rightleftarrows \underbrace{C_2B_{10}H_{11}Cl + 1/2Al_2Cl_6 + HCl}_{\mathbf{IV}}, \quad (2)$$

where **I** is the initial system consisting of isolated molecules of carborane, dimer Al_2Cl_6, and Cl_2 molecules; **II** is the intermediate system containing intermolecular complex of $AlCl_3$ with Cl_2; $[TS]^{\neq}$ is the transition state of the reaction; **III** is the intermediate system containing isolated molecule of chlorinated carborane and intermolecular complex of $AlCl_3$ with HCl; **IV** is the final system containing isolated molecule of $C_2B_{10}H_{11}Cl$, Al_2Cl_6, and HCl.

The equilibrium between systems **I** and **II** is expressed by Eq. (3).

$$1/2Al_2Cl_6 + Cl_2 \rightleftarrows Cl_2\cdots AlCl_3. \quad (3)$$

The ΔE for reaction (3) in the B3LYP/6-31G(d,p) approximation is 8.0 kcal mol^{-1}, that is, the equilibrium is shifted toward the formation of the dimer Al_2Cl_6, and, hence, the intermolecular complex $Cl_2\cdots AlCl_3$ is a thermodynamically unstable intermediate system.

Similarly, the equilibrium between systems **III** and **IV** is represented by reaction (4).

$$HCl\cdots AlCl_3 \rightleftarrows 1/2Al_2Cl_6 + HCl. \quad (4)$$

For reaction (4), ΔE = –5.6 kcal mol^{-1}, that is, the equilibrium is shifted toward the formation of the dimer Al_2Cl_6, which is recovered in the reaction course and re-enters the substitution reaction as a catalyst.

According to the analysis of the topology of the total electron density, the catalytic transition state of the chlorination (Fig. 3a), like in the reaction without a catalyst, does not have the cyclic structure of the reaction site. The route of conversion the transition state (Fig. 3a) into the reaction products is similar to that in the reaction performed without $AlCl_3$. Based on the calculation of the reaction coordinate we found that initially the leaving hydrogen atom forms a molecule of HCl^1, and after that the HCl^1 molecule turns by its hydrogen atom to atom Cl^2, and at this turn the atom Cl^1 remains almost immovable, playing the role of a "pivot" for the turning hydrogen atom. Then the hydrogen atom is detached from the Cl^1 and forms HCl^2 molecule, while the atom Cl^1 is attached to the atom B^9.

In accordance with Eq. (2) the potential barrier of the reaction is equal to the energy difference between $[TS]^{\neq}$ and the system **I** [B3LYP/6-31G(d,p), kcal mol^{-1}]: for *o*-carborane 8.0, 8.5, 9.3, and 12.0 in position 9 (12), 8 (10), 4 (5, 7, 11), and 3 (6), respectively, for *m*-carborane 10.2, 9.6, 11.3, and 17.6 in position 9 (10), 5 (12), 4 (6, 8, 11), and 2 (3), respectively, for *p*-carborane 13.5. For *o*-carborane the potential barrier increases monotonically during the transition from the positions of 9 (12) to 3 (6), which agrees with the experimental data indicating that the first to be replaced are the hydrogen atoms in positions 9 (12). For *m*-carborane this pattern is expressed not so clearly in this approximation, but, as in the case of *o*-carborane, the maximum potential barrier to the substitution reactions corresponds to the positions closest to the carbon atoms, namely, 2 (3). In the least reactive *p*-carborane the potential barrier is among the largest ones.

In this paper we investigated the possibility of involving other acids as a catalyst, in particular, the molecules of HCl [Eq. (5)].

$$C_2B_{10}H_{12} + Cl_2 + HCl \rightleftarrows [TS]^{\neq} \rightleftarrows C_2B_{10}H_{11}Cl + 2HCl. \quad (5)$$

The molecular structure of TS in reaction (5) (Fig. 3b) by the topology of the distribution function of total electron density, is similar on the whole to that of TS with $AlCl_3$. The potential barrier of reaction (5) is $\Delta E^{\neq}$ = 22.9, 25.0, 26.7 kcal mol^{-1} for *o*-carborane [positions 9 (12)], *m*-carborane [positions 9 (10)] and *p*-carborane, respectively, which is consistent with decreasing activity of carboranes(12) in this series. Thus, HCl also has the ability to reduce the potential barrier of the reaction of electrophilic substitution, although not as significant as $AlCl_3$.

It should be noted that the presence of donor

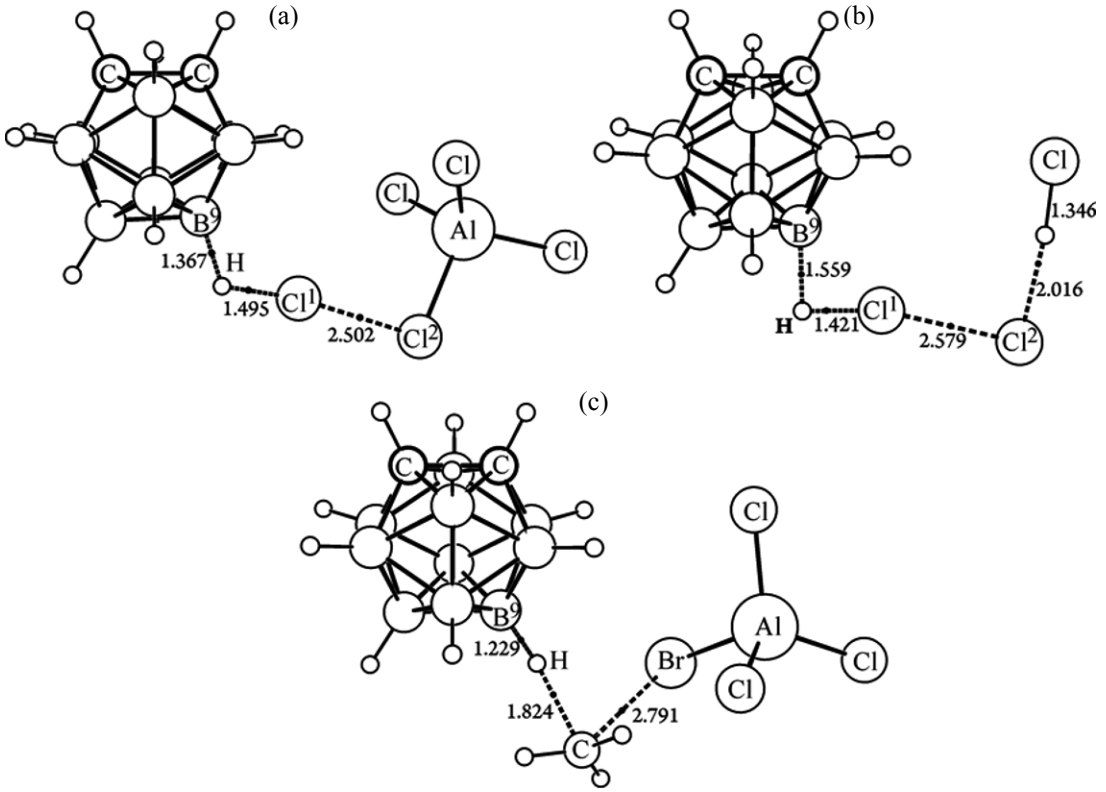

Fig. 3. The molecular structures of the transition states of electrophilic reactions: chlorination with $AlCl_3$ (147*i* cm^{-1}) (a), chlorination with HCl (528*i* cm^{-1}) (b), methylation with $AlCl_3$ (454*i* cm^{-1}) (c) at the B^9 position of the molecule of *ortho*-carborane, calculated by the B3LYP/6-31G(d,p) method.

substituents at the boron atoms leads to a decrease in the reaction barrier, while the acceptor substituents increase it. The assumed model of the transition state (Fig. 3a) is well consistent with this experimental findings. For example, the potential barrier $\Delta E^{\neq}$ of the chlorination of 9-methyl-*ortho*-carborane at position 12 catalyzed by $AlCl_3$ is 6.9 kcal mol^{-1} (for the unsubstituted *o*-carborane, this value is equal to 8.0 kcal mol^{-1}), whereas for the 9-chloro-*ortho*-carborane the barrier is 10.1 kcal mol^{-1}.

The potential barriers to the methylation calculated according to Eq. (6) do not change as significantly as in the chlorination. For different positions in the framework and for different isomers the following values were obtained [B3LYP/6-31G(d,p) kcal mol^{-1}]: for *o*-carborane 37.6, 38.0, 36.6, and 38.5 in position 9 (12), 8 (10), 4 (5, 7, 11), and 3 (6), respectively, for *m*-carborane 39.3, 37.5, 38.7, and 42.5 in position 9 (10), 5 (12), 4 (6, 8, 11), and 2 (3), respectively, for *p*-carborane 39.8.

$$C_2B_{10}H_{12} + 1/2Al_2Cl_6 + CH_3Br \rightleftarrows [TS]^{\neq}$$
$$\rightleftarrows C_2B_{10}H_{11}(CH_3) + 1/2Al_2Cl_6 + HBr. \quad (6)$$

The molecular structure of the transition state of methylation reaction (Fig. 3c) and the route of its transformation in the products are similar to those found for the chlorination.

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