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ORIGINAL PAPER

DFT investigation of the thermodynamics and mechanism of electrophilic chlorination and iodination of arenes

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Abstract Quantum chemical calculations at the B3LYP/6-311G* level have been carried out in order to investigate the reaction mechanisms of the iodination of benzene and its monosubstituted derivatives with ICl, I^+, I_3^+ and reagents containing N–I and O–I bonds as the iodinating agents. The results are compared with those obtained for chlorination by Cl^+ and Cl_2, both in the gas phase and in methanol solution using the PCM solvent model. We have also used the MP2/DGDZVP level of theory and the IEFPCM model to perform comparisons in a few cases. The thermodynamic parameters for the reactions have been calculated, the structures of the intermediate products (π- and σ-complexes) and transition states have been optimized, and the profiles of the free energy surfaces have been constructed.

Keywords Iodination · Chlorination · π-Complex · σ-Complex transition state · DFT

Introduction

Aryl iodides are valuable precursors in organic synthesis, especially during carbon–carbon, carbon–nitrogen or carbon–oxygen bond formation [1]. In addition, they are important because of their use in medicine, either as drugs or as radioactively labeled diagnostic markers and X-ray diagnostic agents [1–6]. Despite this, the mechanisms of electrophilic iodination reactions have been insufficiently explored. For example, there are no systematic experimental data concerning the reactivities of the substrates and reagents in iodination reactions or the structures of electrophilic iodinating molecular species.

It is well known that electrophilic aromatic iodination often gives worse preparative results than the corresponding chlorination or bromination. The number of aromatic substrates that can be iodized is limited in comparison with the substrates that undergo chlorination or bromination. However, there is still no generally accepted viewpoint on the causes of the difficulties and limitations of electrophilic iodination reactions, and the literature suggests divergent points of view on these problems.

Thus, the smaller electrophilicity of iodine compared with chlorine and bromine is often mentioned, although the structure of the true electrophilic intermediate during iodination remains unknown. For example, using DFT calculations, we have already shown that the electrophilicities of some iodinated intermediates such as the hypoiodite RO-I or *N*-iodimides may be even higher than those of the corresponding derivatives of chlorine and bromine [7].

Another possible reason for the problems with electrophilic iodination is their reversibility (i.e., the protodeiodination of aryl iodides) compared with the irreversible nature of the chlorination and bromination. However, there is very little quantitative experimental data on the reversibility of electrophilic iodination.

Published DFT calculations show that the iodination of arenes using I_2 and ICl is indeed more reversible than

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chlorination, but this has been established for only a limited number of examples [8]. Thus, understanding the factors limiting the electrophilic iodination requires a detailed comparative analysis of all stages of the iodination and chlorination of aromatic substrates.

In previous papers [7–9], the relative electrophilic abilities of iodinating agents with X–I (X=Cl, O, N) bonds were established by quantum-chemical calculations, the thermodynamic functions for the electrophilic iodination reactions of monocyclic and polycyclic arenes were evaluated, and the mechanisms for the iodination of free-radical alkanes were investigated. The purpose of the present paper is to provide a quantitative description of the mechanisms of iodination of aromatic compounds, the reactivities of substrates and reagents, and the profiles of free-energy surfaces.

Computational details

We have defined, for the first time, the characteristics of all stationary points and transition states on the potential energy surfaces of iodination reactions using density functional theory (DFT). The analysis of the bonding was performed using the NBO approach. Since aromatic chlorination and iodination are two limiting cases, we take the opportunity to compare the two processes. The calculations employed the nonlocal hybrid, three-parameter B3LYP [10–12] functional in conjunction with 6-311G* sets for the atoms N, C, O, F, and S. For the iodine atom, a relativistic core potential was used for the 46 core electrons, while a 10s9p5d basis set was selected for the valence electrons [12]. This potential is standard and gave good results for such halogen complexes [7–9]. For the calculations in methanol solution, the model of the polarized continuum (PCM) based on the optimized structures in the gas phase without optimization in the solution was used [13]. The structures and thermodynamic parameters of the reactions of benzene with the cationic electrophilic reagents Cl^+ and I^+ in the gas phase and methanol solution at the MP2/DGDZVP level of theory and using the IEFPCM model also were calculated. All calculations were carried out using the GAUSSIAN 03 W program package [14]. Energy calculations were corrected for zero-point vibrational energy and reduced to normal conditions (298.15 K, 1 atm) using thermal corrections to the enthalpy and free energy. For reactants, products, and intermediate π- and σ-complexes, stationary character was confirmed by the absence of imaginary vibration frequencies, while the transition states were characterized by the presence of only one imaginary frequency. In addition, all transition states were analyzed by the IRC method.

Benzene and various monosubstituted benzenes (**1a–f**) were chosen as the substrates. The iodinating agents chosen were compounds that have I–X bonds as well as their protonated $I–XH^+$ forms, the iodine monocation I^+ in the triplet electronic configuration, and the singlet I_3^+ cation, the characteristics of which have been provided previously [7]. For the purposes of comparison, chlorination of the same set of substrates using both molecular chlorine and the triplet Cl^+ cation as chlorinating agents was examined.

Results and discussion

Thermodynamic characteristics of iodination and chlorination

The calculated changes in the thermodynamic functions for the halogenation reactions of benzene and the monosubstituted benzenes **1a–f** (reactions 1, 1a, 2, see below) either in the gas phase (ΔH, ΔG) or in methanol solution (ΔG_s) are given in Table 1.

$$C_6H_5R + I - X \rightleftharpoons IC_6H_4R + HX \tag{1}$$

$$C_6H_5R + I - XH^+ \rightleftharpoons IC_6H_4R + H_2X^+ \tag{1a}$$

$$C_6H_5R + Cl_2 \rightleftharpoons ClC_6H_4R + HCl \tag{2}$$

Here, R=H (**a**), Me (**b**), *t*-Bu (**c**), OH (**d**), NH_2 (**e**), NO_2 (**f**), while I–X=ClI, HOI, MeOI, CH_3COOI, CF_3COOI, CF_3SO_2OI, $HOSO_2OI$, *N*-iodosuccinimide (NIS), *N*-iodosaccharin (NISAC), I^+, or I_3^+.

The accuracy of the calculations is supported by the good agreement between the calculated and experimental data for the chlorination reactions, and also by the known ability of reagents such as ICl, NIS, and NISAC to iodinate benzene. Thus, the ΔH for the chlorination of benzene by Cl_2 is −32.0 kcal mol^{-1} in the liquid phase [15], and the ΔH for the isomerization of *ortho*-chlorobenzene into the *para*-isomer is −5.1 kcal mol^{-1} [16], which agree with the corresponding calculated data (Table 1). This indicates that our calculations using the hybrid functional DFT give sufficiently reliable results that are close to the experimental values. Compounds with hypoiodite character (X–O–I) are often postulated as iodinating agents [17], but without well-defined experimental evidence. In this context, the results given in Table 1 serve as proof that hypoiodites act as electrophilic iodination reagents.

It was previously shown [7] that the electrophilic activities of iodinating reagents I–X (expressed in terms of both charge and orbital parameters) increase according to the following series: $I–Cl < CH_3OI < HOI < NIS < CH_3COOI < CF_3COOI < NISAC < HOSO_2OI < CF_3SO_2OI$. As can be seen

Table 1 Thermodynamic parameters for the halogenation of benzene in **1a**–**f** with X–I and Cl_2 in the gas phase (ΔH, ΔG) and methanol solution (ΔG_s) (the PCM model), calculated at the B3LYP/6-311G+level of theory (values in kcal mol^{-1})

Reaction	ΔH	ΔG	ΔG_s
$C_6H_6+HOI \rightarrow C_6H_5I+H_2O$ (1)	−18.8	−17.7	−21.7
$C_6H_6+H_2O^+I \rightarrow C_6H_5I+H_3O^+$ (2)	−13.6	−12.9	−43.0
$C_6H_6+CH_3OI \rightarrow C_6H_5I+CH_3OH$ (3)	−16.5	−16.4	−21.6
$C_6H_6+CH_3OH^+I \rightarrow C_6H_5I+CH_3OH_2^+$ (4)	−16.2	−16.0	−48.79
$C_6H_6+CH_3COOI \rightarrow C_6H_5I+CH_3COOH$ (5)	−19.3	−18.9	−26.14
$C_6H_6+CH_3C(OH^+)OI \rightarrow C_6H_5I+CH_3C(OH^+)OH$ (6)	−11.8	−10.4	−34.45
$C_6H_6+CF_3COOI \rightarrow C_6H_5I+CF_3COOH$ (7)	−19.9	−19.7	−27.82
$C_6H_6+CF_3C(OH^+)OI \rightarrow C_6H_5I+CF_3C(OH^+)OH$ (8)	−5.7	−5.7	−30.11
$C_6H_6+CF_3SO_2OI \rightarrow C_6H_5I+CF_3SO_2OH$ (9)	−21.0	−20.8	−30.62
$C_6H_6+CF_3SO(OH^+)OI \rightarrow C_6H_5I+CF_3SO(OH^+)OH$ (10)	−13.2	−12.8	−32.32
$C_6H_6+IOSO_2OH \rightarrow C_6H_5I+H_2SO_4$ (11)	−20.8	−20.6	−29.46
$C_6H_6+IOSOO(H^+)OH \rightarrow C_6H_5I+HOSO(HO^+)OH$ (12)	−14.6	−14.1	−31.13
$C_6H_6+ClI \rightarrow C_6H_5I+HCl$ (13)	−5.1	−4.4	−7.08
$C_6H_6+ClH^+I \rightarrow C_6H_5I+H_2Cl^+$ (14)	5.9	6.6	−3.65
C_6H_6+NIS→C_6H_5I+succinimide (15)	−16.1	−15.9	−21.6
C_6H_6+NIS-H^+ → C_6H_5I + succinimide-H^+ (16)	−11.9	−11.9	−30.0
C_6H_6+NISAC→C_6H_5I+saccharine (17)	−17.1	−17.2	−22.2
C_6H_6+NISAC-H^+ → C_6H_5I+saccharine-H^+ (18)	−15.2	−15.1	−28.9
$C_6H_6+I_3^+ \rightarrow C_6H_5I+I_2H^+$ (19)	19.0	19.5	14.6
$C_6H_6+I_2H^+ \rightarrow C_6H_5I+IH_2^+$ (20)	15.6	16.6	12.5
$C_6H_5Me+ICl \rightarrow$ p-$IC_6H_5Me+HCl$ (21)	−5.3	−4.6	−4.3
$C_6H_5Me+ICl \rightarrow$ *o*-$IC_6H_5Me+HCl$ (22)	−4.8	−3.1	−4.0
C_6H_5*t*-Bu+ICl→*p*-IC_6H_5*t*-Bu+HCl (23)	−5.4	−4.7	−4.9
C_6H_5*t*-Bu+ICl→*o*-IC_6H_5*t*-Bu+HCl (24)	2.4	3.8	3.61
$C_6H_5NH_2+ICl \rightarrow$ *p*-$IC_6H_5NH_2+HCl$ (25)	−5.4	−4.7	−5.0
$C_6H_5NH_2+ICl \rightarrow$ *o*-$IC_6H_5NH_2+HCl$ (26)	−5.8	−4.9	−4.1
$C_6H_5OH+ICl \rightarrow$ *p*-$IC_6H_5OH+HCl$ (27)	−4.8	−4.1	−2.9
$C_6H_5OH+ICl \rightarrow$ *o*-$IC_6H_5OH+HCl$ (28)	−6.5	−5.6	−3.2
$C_6H_5NO_2+ICl \rightarrow$ *m*-$IC_6H_5NO_2+HCl$ (29)	−3.4	−2.7	−2.7
$C_6H_6+Cl_2 \rightarrow C_6H_5Cl+HCl$ (30)	−29.7	−29.2	−32.1[a]
$C_6H_5Me+Cl_2 \rightarrow$ *p*-$ClC_6H_5Me+HCl$ (31)	−29.7	−29.3	−29.0
$C_6H_5Me+Cl_2 \rightarrow$ *o*-$ClC_6H_5Me+HCl$ (32)	−29.9	−28.5	−29.9
C_6H_5*t*-Bu+Cl_2→*p*-ClC_6H_5*t*-Bu+HCl (33)	−29.9	−29.4	−30.2[b]
C_6H_5*t*-Bu+Cl_2→*o*-ClC_6H_5*t*-Bu+HCl (34)	−24.8	−23.7	−24.4[b]
$C_6H_5NH_2+Cl_2 \rightarrow$ *p*-$ClC_6H_5NH_2+HCl$ (35)	−29.6	−29.2	−26.7
$C_6H_5NH_2+Cl_2 \rightarrow$ *o*-$ClC_6H_5NH_2+HCl$ (36)	−30.2	−29.6	−26.6
$C_6H_5OH+Cl_2 \rightarrow$ *o*-$ClC_6H_5OH+HCl$ (37)	−30.3	−29.7	−22.7
$C_6H_5OH+Cl_2 \rightarrow$ *p*-$ClC_6H_5OH+HCl$ (38)	−29.1	−28.7	−24.3
$C_6H_5NO_2+Cl_2 \rightarrow$ *m*-$ClC_6H_5NO_2+HCl$ (39)	−27.8	−27.3	−28.8

[a] Experimental value of ΔH for chlorination [15] in the liquid phase is −32.0 kcal mol^{-1}

[b] ΔH for isomerization [16] of the *ortho*-**1c** into the *para* isomer is −5.1 kcal mol^{-1}

from Table 1, there is no correlation between the investigated electrophilic activities of the reagents and thermodynamic parameters (ΔH, ΔG, ΔG_s) for the iodination of benzene, as the values of ΔH for iodination by NIS and NISAC are less than expected. At the same time, for the limited group of hypoiodite reagents X–O–I, the enthalpy of the iodination reaction increases with increasing reagent electrophilicity [7], as well as with the strength of the corresponding X–OH acid.

According to our calculations, increasing the polarity of the medium should lead to an increase in the iodination equilibrium constant, especially in acidic media when the iodinating reagent is XH^+–I. This is a consequence of the nonspecific solvation of XH_2^+ products with energies that are~20–30 kcal mol^{-1} higher than those of the XH^+–I reagents. Moreover, protonating the iodinating agents in a nonpolar medium slightly decreases the reaction enthalpy, leading to positive values of ΔH and ΔG for $IClH^+$ (Eqs. 13 and 14, Table 1); the reason for this is the thermodynamic instability of the protonated form H_2Cl^+ as the reaction product. Benzene iodination by I_3^+ in the gaseous phase and in solution (Eq. 19 in Table 1) is clearly thermodynamically unfavorable and attracts attention. This intermediate was regarded as a valid iodinating agent for arenes in sulfuric acid solution [18, 19]. The reason for the theoretical impossibility of direct benzene iodination by I_3^+ in an aprotic medium is the extremely low stability of the I_2H^+ species (Eq. 19 in Table 1). However, an examination of the thermodynamics of iodination in the presence of a stronger proton acceptor than iodine, for example methanol, shows that the process is quite feasible thermodynamically, especially in the liquid phase:

$$C_6H_6 + I_3^+ + CH_3OH \rightleftharpoons C_6H_5I + I_2 + CH_3O^+H_2 \tag{3}$$

ΔH=−11.6; ΔG=−9.4; ΔG_s=−55.2 kcal mol^{-1}

Calculating the thermodynamics of iodination via the same scheme in the presence of an even weaker proton acceptor (sulfuric acid) also shows that this reaction is feasible in a relatively polar medium (methanol):

$$C_6H_6 + I_3^+ + H_2SO_4 \rightleftharpoons C_6H_5I + I_2 + SO_2(OH^+)OH \tag{4}$$

ΔH=2.2; ΔG=4.5; ΔG_s=−19.6 kcal mol^{-1}

To quantitatively assess the reactivities of aromatic substrates, we calculated the thermodynamic functions for the iodination and chlorination of the benzene in **1a–f** by ICl and Cl_2 (Table 1). The chlorination reactions are found to be much more exothermic than the iodination reactions (on average by 25 kcal mol^{-1}). Increasing the polarity of the medium leads to a small drop in the exothermicity of each halogenation reaction (except for the chlorination of nitrobenzene), but the effect of this solvent is more noticeable for iodination. The nature of substrate (**1a–f**) influences the thermodynamic parameters of the halogenation in an irregular and minor way; i.e., thermodynamic parameters of the reactions with ICl do not correlate with the donor or acceptor properties of R substitutes. Moreover, the calculated thermodynamic parameters of iodinated isomeric benzenes do not correspond to the known *ortho*-/*para*- and *meta*-orienting effects of R substituents. Thus, the calculations show that, according to the Gibbs free energy changes, *meta*-iodo derivatives of toluene, phenol and aniline are more stable than the corresponding *para* isomers by 0.06, 0.14 and 0.17 kcal mol^{-1}, respectively, and *para*-iodonitrobenzene is more stable than the *meta* isomer by 0.49 kcal mol^{-1}. Therefore, the calculations confirm that the electrophilic iodination reactions of the substituted benzene series are not thermodynamically controlled. At the same time, there is an approximately linear correlation (r=0.980; S=0.6) between the ΔH values for the chlorination and iodination of compounds **1a–f** in the gas phase, indicating the absence of any specific differences between the two halogenation reactions in the gas phase. In these and the subsequent correlation equations, r is a correlation coefficient and S is the standard curve fit error.

π-Complex structure and stability

In general, the calculations predict that halogenation involves the following stages (Eq. 5) that are expected for electrophilic aromatic substitution reactions:

$$\mathrm{ArH} + \underset{\pi-\mathrm{complex1}}{\mathrm{XY}} \rightleftharpoons \underset{\mathrm{TS1}}{[\mathrm{Ar.XY}]^{\#}} \rightleftharpoons \underset{\sigma-\mathrm{complex}}{\mathrm{ArXH^+Y^-}} \rightleftharpoons \underset{\mathrm{TS2}}{[\mathrm{ArX.HY}]^{\#}} \rightleftharpoons \mathrm{ArX} + \mathrm{HY}. \tag{5}$$

However, the first stationary point encountered in the interactions of the studied arenes with charged electrophiles such as I^+ and IOH_2^+ is the corresponding σ-complex, while the uncharged reagents I_2, Cl_2, ICl, HOI, MeOI, CF_3COOI and NIS and the ion I_3^+ can give π-complexes. For benzene and some other arenes with halogens and ICl, the latter complexes are known and have been studied using both experimental [20–22] and theoretical methods [23, 24], whereas π-complexes with the remaining acceptors discussed here are unknown.

Some calculated geometric and electronic characteristics of the π-complexes of **1a** (benzene) with different acceptors, as well as the thermodynamic parameters for their formation in the gas phase (ΔH, ΔG) and in methanol (ΔG_s), are given in Table 2.

The satisfactory correspondence of the calculated thermodynamic parameters with the known experimental data for the complexes with I_2, Cl_2, ICl [20–22] confirm the calculation's adequacy. The experimental enthalpies of π-complex formation are −1.87 and −2.54 kcal mol^{-1} for I_2 and ICl complexes, which are close to the corresponding calculated data (Table 2). On the one hand, the calculated structures of π-complexes of benzene are of the same type and are characterized by the conservation of the planar aromatic system and an angle between the X–Y molecular axis and the ring plane of less than 90° (C_s symmetry). On the other hand, these complexes are divided into two classes. I_2, Cl_2, ICl, CF_3COOI, NIS and I_3^+ coordinate mainly with one carbon atom of the benzene ring, while the hypoiodites IOH and IOMe are arranged in such a way that the I...C^i distances between two adjacent carbon atoms are almost the same (Fig. 1a, b), but this second type of complex has a noticeably lower stability than the first type.

Among the calculated electronic characteristics, parameters such as the atomic charges q^i and the Wiberg indices

Table 2 Parameters of the π-complexes of benzene **1a** with electron acceptors X–Y, calculated at the B3LYP/6-311 G* level. Parameters include: the distance between X and the closest aromatic carbon atoms (d X...C^i), elongation of the X–Y bond (Δd), natural charge of the carbon atom that interacts with X–Y q(C^i), the Wiberg indices (W), and enthalpy and Gibbs free energy of complex formation in the gas phase (ΔH^{compl}, ΔG^{compl}) and in methanol solution (ΔG_s^{compl})

Parameters	X–Y							
	I_2	ICl	Cl_2	IOH	IOMe	CF_3COOI	NIS	I_3^+
d X–C^i (Å)	3.326	3.129	2.970	3.466 C^{1}3.527 C^2	3.420 C^{1}3.468 C^2	3.013	3.3993.512	3.045
Δd X–Y (Å)	0.021	0.035	0.031	0.006	0.004	0.030	0.010	0.043
q C^i	−0.271 C^1	−0.323 C^1	−0.280 C^1	−0.240 C^1–0.224 C^2	−0.239 C^1–0.228 C^2	−0.361	−0.264 C^1–0.205 C^2	−0.296
$W_{X–Y}$	0.9691	0.8861	0.9619	0.8586	0.8239	0.6346	0.5352	0.8691 I^2–I^{1}0.8826 I^2–I^3
$W_{X–C}{}^i$	0.0341	0.0621	0.0411	0.0217 C^{1}0.0192 C^2	0.0242 C^{1}0.0218 C^2	0.0881	0.0239 C^{1}0.0147 C^2	0.0884
ΔH^{compl} (kcal mol^{-1})	−1.72	−3.60	−1.66	−1.41	−1.19	−4.50	−0.90	−14.02
ΔG^{compl} (kcal mol^{-1})	6.53	5.94	6.85	6.67	7.59	5.60	6.07	−5.53
$\Delta G^{compl}{}_s$ (kcal mol^{-1})	−4.09	−5.91	−2.24	−0.85	0.42	−6.64	−1.74	−10.47

for X...C^i bonds (Table 2) show a trend that corresponds with that of the thermodynamic properties. As a result, we have obtained the following correlations between the enthalpy of π-interaction, atomic charge, and the Wiberg indices:

$$\Delta H^{compl} = 0.005 - 52 W_{X-C}{}^{i} \qquad (r = 0.980;\ s = 0.3;\ n = 7) \tag{6}$$

$$\Delta H^{compl} = 5 + 27\,q\,C^{i} \qquad (r = 0.972;\ s = 0.3;\ n = 7). \tag{7}$$

In accordance with the theory of donor–acceptor interactions, there is a good linear correlation between ΔH^{compl} from Table 2 and E_{LUMO} (taken from [7]):

$$\Delta H^{compl} = 4.1 + 1.8 E_{LUMO} \qquad (r = 0.997; s = 0.4; n = 6). \tag{8}$$

Complexes of arenes with halogens were first discovered by Hilderbrand as far back as 1941, and investigations of these compounds laid the foundations for the donor–acceptor interaction theory [20]. However, the question of whether arene π-complexes are true intermediates in electrophilic substitution reactions, and in particular halogenations, is still a matter for debate (for example, see [25]). One of the main ways to establish the role of arene π-complexes in electrophilic substitution reactions would be to answer the question: do the orienting effects of substituents become apparent at the stage of complexation with electrophiles? We have investigated this possibility while studying the formation of π-complexes between the substituted benzenes **1b**,**d**–**f** and ICl by varying the initial acceptor position relative to different ring atoms. The optimized structures predict that the most stable complexes are formed by the coordination of ICl at the *ortho* and *para* positions of aniline **1e** and phenol **1d**, as well as at the *meta* position in nitrobenzene **1f** (Table 3). Coordination at other positions leads to less stable complexes or structures which are not stationary. In the case of toluene **1b**, the stationary point corresponds to the complex in which coordination takes place at the *para* position of the ring. Conversely, the *ortho*-oriented complex is the least stable and has an imaginary vibrational frequency. In general, the structures of the π-complexes that are calculated to be the most stable show that acceptors are coordinated to the substituted benzenes, in agreement with the rules of electrophilic substitution. This serves as an additional argument for the idea of π-complexes as true halogenated intermediates: they lie on the reaction path.

In the series of π-complexes of substituted benzenes (**1a**, **b**,**d**–**f**) with ICl investigated here, an expected increase in

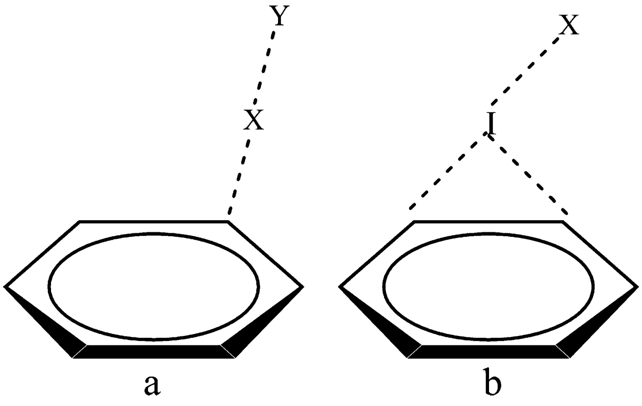

Fig. 1 Schematic structures of the π-complexes of benzene with I_2, Cl_2, ICl, CF_3COOI, NIS, I_3^+ (**a**), and IOH and IOMe (**b**)

stability is observed upon increasing the electron-donor ability of the aromatic substrate, and a satisfactory linear correlation is observed for *para*- and *meta*-coordinated complexes between ΔH^{compl} and $\sigma_{p,m}$ of the substituent (r =0.984). According to our calculations, increasing the polarity of the medium should lead to a noticeable increase in the stabilities of all of the investigated complexes (Tables 2, 3).

σ-Complex structure and stability

The geometric and electronic characteristics of the σ-complexes $C_6H_6X^+$ [X=Cl (**2a**), I (**2b**)], according to our calculations, are given in Fig. 2 and Table 4. Regarding the bond distances and the angles shown in Fig. 2, the calculated geometrical parameters of the $RC_6H_5{}^+Cl$ σ-complexes are found to be sufficiently close to the well-known crystallographic characteristics of the tetramethyltoluene chloroarene σ-complex [26], and the structure of the complex **2a** is similar to that calculated earlier [27] at the MP2/6-31+G* level of theory.

Despite some similarities between the structures of the planar cyclic fragments of intermediates **2a** and **2b** (typical Weiland complexes), there are significant differences between them. In the **2a** complex, the chlorine atom is located closer to the ring plane than the iodine atom is in **2b**. Also, the hydrogen atom of the C^1–H bond deviates more from the plane, and the C^1–H bond is longer than in the **2b** complex (compare angles β and γ and the C^1–H bond distances in the Table 4). Thus, the structure of the **2a** σ-complex is more like the product than the **2b** complex is; i.e., it has more "late" character.

We have also optimized the geometries of the σ-complexes $RC_6H_5{}^+X$ (R=Me, *t*-Bu, NH_2, OH, NO_2; X=Cl, I) of the substituted benzenes **1b**–**f** with R substituents located at positions *ortho*, *para*, and *meta* to the X halogen atoms, and calculated their thermodynamic properties in the gas phase and in methanol solution. These intermediates show electronic characteristics and trends upon changing the halogen atom that are similar to those found for the **2a** and **2b** complexes (Table 4). As expected, σ-complexes that obeyed the rules of electrophilic substitution turned out to be the most stable.

The enthalpies and free energy changes (ΔH^{σ}, ΔG^{σ}) for the more stable isomers of the σ-complexes formed in reactions (9, 10), in which Cl_2 and ICl are the halogenating agents, were calculated both in the gas phase and in methanol solution, based on the assumption that the reaction products exist separately (Table 5):

$$RC_6H_5\ Cl_2 \rightleftharpoons RC_6H_5{}^+Cl + Cl^- \tag{9}$$

$$RC_6H_5 + ICl \rightleftharpoons RC_6H_5{}^+I + Cl^-. \tag{10}$$

Table 3 Parameters of the π-complexes of the aromatic hydrocarbons **1b**–**f** with ICl, calculated at the B3LYP/6-311G* level of theory

Parameters	Molecules **1b,d–f**					
	$C_6H_4CH_3$ [a] (**1b**)	C_6H_4OH [a] (**1d**)	C_6H_4OH [b] (**1d**)	$C_6H_4NH_2$ [a] (**1e**)	$C_6H_4NH_2$ [b] (**1e**)	$C_6H_4NO_2$ [c] (**1f**)
d X–C^i, Å	3.076	3.026	3.033	2.944	2.911	3.241
Δd X–Y (Å)	0.042	0.052	0.046	0.074	0.073	0.018
q(I)	0.190	0.182	0.191	0.172	0.175	0.189
$q(C^i)$	-0.341	−0.365	−0.398	−0.396	−0.456	−0.305
W_{X-Y}	0.8699	0.8490	0.8611	0.8059	0.8066	0.9214
W_{X-C^i}	0.0744	0.0912	0.0853	0.1231	0.1325	0.0404
ΔH^{compl} (kcal mol^{-1})	−3.61	−4.22	−3.52	−6.00	−5.89	−0.79
ΔG^{compl} (kcal mol^{-1})	3.51	4.05	4.89	2.53	3.07	6.32
$\Delta G^{compl}{}_s$ (kcal mol^{-1})	−4.40	−5.00	−3.87	−8.12	−6.89	−2.24

ICl coordinates to the next position on the aromatic ring: [a] *para*-; [b] *ortho*-; [c] *meta*-

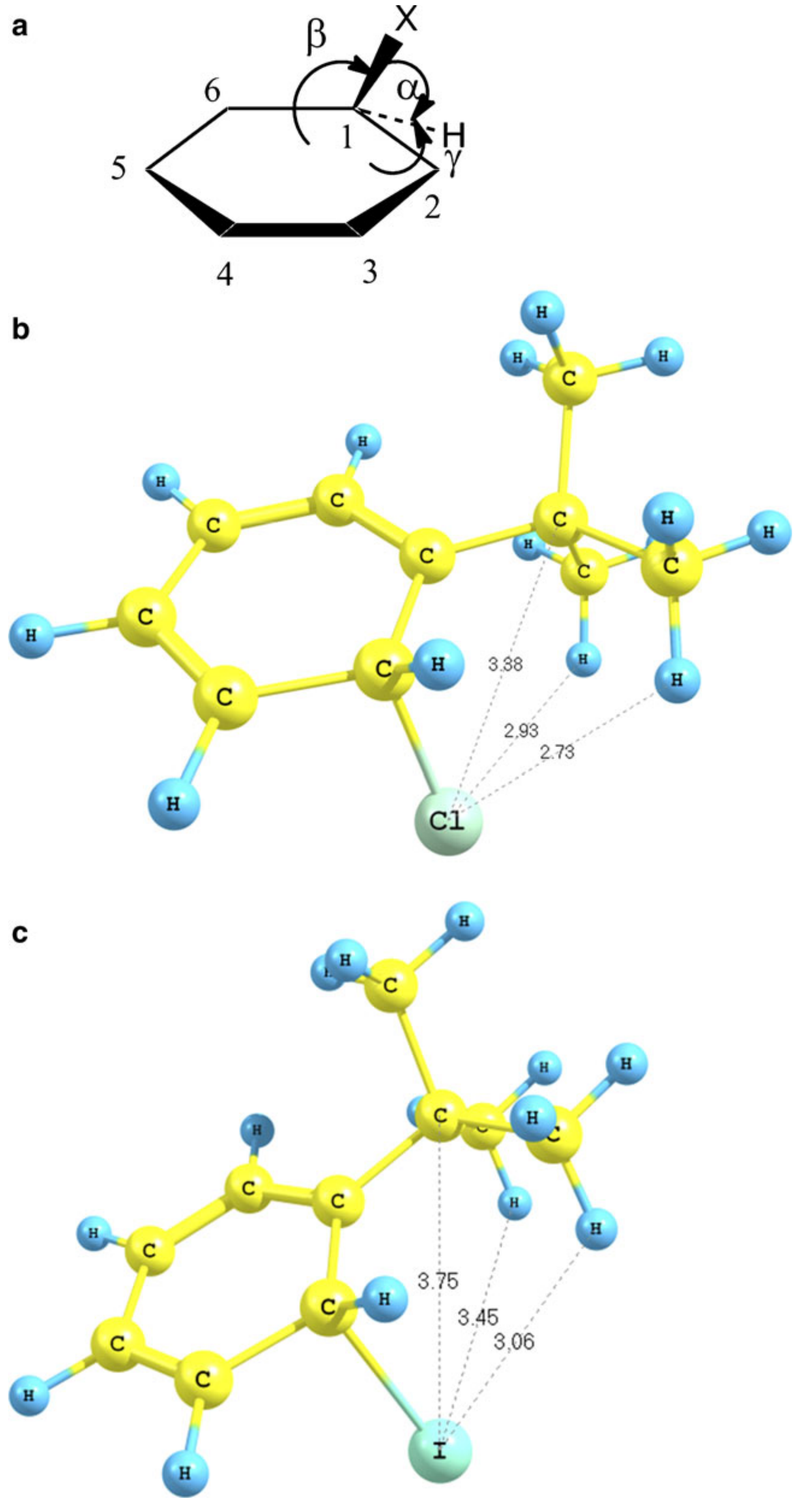

Fig. 2 Schematic structures of the σ-complexes of **a** $C_6H_6X^+$ (X=Cl **2a**, I **2b**) and the σ-complexes of **b** *ortho-tert-*$BuC_6H_5^+Cl$ and **c** *ortho-tert-*$BuC_6H_5^+I$

The calculated data show that the product enthalpies of the chlorination reactions are lower by 9–17 kcal mol^{-1} than those for the iodination reactions, which is consistent with the well-known higher rates of arene electrophilic chlorination. The enthalpies and free energies of the reaction naturally decrease as the electron-donating ability of the R substituent increases. There are also satisfactory correlations of the calculated enthalpies of formation of

Table 4 Geometric and electron parameters of the σ-complexes $RC_6H_5^+X$ and **3a, b** complexes

R	X	Bond length (Å)					α	β	γ	q(X)	q(C^1)	Wiberg indices, W	
		1–2, 1–6	2–3, 5–6	3–4, 4–5	C^1–X	C^1–H						C^1–X	C^1–H
H	Cl	1.477	1.367	1.412	1.800	1.114	104.6	141.6	105.7	0.105	−0.495	0.9998	0.7738
	I	1.460	1.372	1.408	2.275	1.089	99.9	108.4	144.4	0.319	−0.568	0.7530	0.8595
o-Me	Cl	1.494, 1.481	1.323, 1.359	1.399, 1.417	1.800	1.112	104.5	145.2	102.2	0.087	−0.506	1.0061	0.7809
	I	1.475, 1.466	1.383, 1.367	1.400, 1.410	2.266	1.089	100.6	107.9	145.4	0.302	−0.600	0.7738	0.8668
p-Me	Cl	1.481	1.358	1.426	1.815	1.104	104.6	131.6	114.8	0.088	−0.483	0.9787	0.8114
	I	1.462	1.365	1.421	2.264	1.089	99.9	110.8	141.2	0.285	−0.564	0.7790	0.8590
o-*t*-Bu	Cl	1.505, 1.486	1.385, 1.355	1.397, 1.419	1.836	1.096	104.7	118.9	129.3	0.085	−0.552	0.9530	0.8394
	I	1.476, 1.468	1.391, 1.364	1.395, 1.412	2.279	1.087	100.3	105.8	148.4	0.293	−0.0649	0.7628	0.8685
p-*t*-Bu	Cl	1.479	1.355	1.433	1.816	1.104	104.5	131.9	114.6	0.078	−0.481	0.9780	0.8137
	I	1.462	1.362	1.428	2.262	1.090	100.0	110.4	141.7	0.271	−0.562	0.7836	0.8606
o-NH_2	Cl	1.512, 1.494	1.418, 1.344	1.367, 1.441	1.807	1.102	104.7	146.1	103.1	0.056	−0.498	1.0074	0.8261
	I	1.494, 1.479	1.416, 1.349	1.369, 1.435	2.241	1.089	102.1	105.7	140.1	0.247	−0.629	0.8430	0.8768
p-NH_2	Cl	1.488	1.344	1.444	1.826	1.096	104.4	124.4	122.0	0.059	−0.469	0.9657	0.8451
	I	1.472	1.350	1.440	2.246	1.090	100.2	114.1	136.8	0.222	−0.548	0.8273	0.8629
o-OH	Cl	1.503, 1.490	1.397, 1.349	1.379, 1.434	1.801	1.106	105.1	145.3	100.3	0.075	−0.518	1.012	0.8064
	I	1.478, 1.472	1.395, 1.359	1.385, 1.422	2.245	1.089	101.9	105.2	141.6	0.298	−0.587	0.8073	0.8628
p-OH	Cl	1.486	1.350	1.433	1.820	1.099	104.7	126.8	119.5	0.083	−0.478	0.9721	0.8309
	I	1.468	1.357	1.427	2.253	1.090	100.2	112.9	138.6	0.264	−0.558	0.8047	0.8586
m-NO_2	Cl	1.477, 1.478	1.360, 1.369	1.408, 1.408	1.800	1.114	104.7	140.0	107.1	0.128	−0.510	0.9993	0.7709
	I	1.458, 1.460	1.367, 1.375	1.403, 1.404	2.278	1.089	100.2	107.5	145.3	0.357	−0.583	0.7383	0.8571
3a	Cl	1.486, 1.487	1.394, 1.381	1.414, 1.430	2.003, 3.107[a]	1.092	99.3	95.4	149.1	0.001	−0.454	0.8051, 0.2079[a]	0.8744
3b	I	1.485, 1.487	1.394, 1.381	1.415, 1.432	2.301, 3.140[a]	1.090	98.9	93.8	150.7	0.195	−0.528	0.7424, 0.1625[a]	0.8706

[a] Interatomic distance and the Wiberg indices of the C^2 …Cl bond

Table 5 Thermodynamic parameters of the $[RC_6H_5^+X]$ $[Cl^-]$ σ-complexes obtained from the reactions of arenes **1a**–**f** with Cl_2 and ICl in the gas phase (ΔH^σ, ΔG^σ) and in methanol solution (ΔG_s^σ) kcal mol^{-1}

Parameter	X	H	*p*-NH_2	*o*-NH_2	*p*-OH	*o*-OH	*p*-Me	*o*-Me	*p*-*t*-Bu	*o*-*t*-Bu	*m*-NO_2
ΔH^σ	Cl	128.37	94.22	98.22	111.12	113.74	118.92	120.04	115.99	120.10	145.16
	I	139.71	109.97	115.22	125.13	128.60	131.69	133.42	129.32	132.87	154.77
ΔG^σ	Cl	130.33	96.67	100.74	113.35	116.22	120.44	122.98	117.79	122.22	146.96
	I	142.01	112.81	118.06	127.77	131.37	134.29	136.29	131.43	135.74	156.97
ΔG_s^σ	Cl	−7.32	−33.87	−29.21	−17.47	−12.50	−14.46	−12.64	−16.40	−0.70	5.46
	I	12.98	−19.39	−14.45	−3.48	0.03	4.81	7.12	2.73	10.01	24.99

$RC_6H_5^+X$ (X=Cl, I) σ-complexes in the gas phase with Hammet's $\sigma_{p,m}$ constants (Eqs. 11, 12) and, as expected for electrophilic substitution, the best correlations are observed when σ^+ constants are used (Eqs. 13, 14):

$$\Delta H^{\mathrm{R}} / \Delta H^{\mathrm{H}} = 0.95 + 0.26\,\sigma_{p,m} \quad r = 0.962, S = 0.04\,(X = Cl) \tag{11}$$

$$\Delta H^R / \Delta H^H = 0.96 + 0.21\sigma_{p,m} \quad r = 0.973, S = 0.03\,(X = I) \tag{12}$$

$$\Delta H^R / \Delta H^H = 0.99 + 0.20{\sigma^+}_{p,m} \quad r = 0.970, S = 0.04\,(X = Cl) \tag{13}$$

$$\Delta H^R / \Delta H^H = 0.99 + 0.17{\sigma^+}_{p,m} \quad r = 0.980, S = 0.02\,(X = I) \tag{14}$$

Ortho-substituted $RC_6H_5^+X$ σ-complexes turn out to be less stable than *para*- for all **1b**–**e** arenes, which mainly reflects the influence of steric factors. Nevertheless, in comparison with chlorination, the reduced significance of the "*ortho* effect" in the iodination of **1c** (*tert*-butyl benzene) is surprising. This leads to a paradoxical conclusion: for the largest substituent R (*tert*-butyl), steric factors become less apparent when the size of the halogen atom X increases. However, this paradox can be resolved if the abovementioned differences between σ-complexes formed during the chlorination and iodination reactions are taken into account. In $RC_6H_5^+Cl$ σ-complexes, the halogen is strongly bound, and lies closer to the ring plane. In such a position, despite the reduced size of the chlorine atom, the R...X repulsive interaction is more significant when R is the voluminous *tert*-Bu group. Indeed, as seen from Fig. 2b, c, which show the calculated structures of the sigma complexes of *ortho*-*tert*-$BuC_6H_5^+Cl$ and *ortho*-*tert*-$BuC_6H_5^+I$, respectively, the chlorine atom has more close contacts with the *tert*-butyl group (2.73, 2.93, and 3.38 Å) than the iodine atom does (3.06, 3.45, 3.75 Å).

Since the charged products in reactions (9, 10) are much better solvated by the polar solvent than the reagents, a polar medium should naturally lead to a decrease in free energy compared to the gas phase. However, the solvent influence is so strong that, for highly reactive substrates (aniline, phenol) and for all chlorination reactions, the ΔG_s^σ values become negative. Although negative activation energies are known for some electrophilic substitution reactions (see, for example, [28, 29] and references cited therein), the determined absolute values of ΔG_s^σ still seem to be too negative (as is well known, spontaneous benzene chlorination by chlorine does not occur in the absence of a catalyst). The reason for this is the use of a model which assumes the isolated existence of $[RC_6H_5^+X]_s$ σ-complexes and the counterion $[Cl^-]_s$ in solution. In such a model, the increased energy of the nonspecific solvation of the small chloride ion (−75.6 kcal mol^{-1}) leads to an large decrease in the energies of the reaction products for reactions (9) and (10). Thus, the negative values of the ΔG_s^σ quantities show that, in reality, halogenated σ-complexes should bind to counterions in solution; i.e., $[RC_6H_5^+X\ Cl^-]_s$ is surrounded by the common solvation sphere.

For the reactions of benzene with Cl_2 and ICl, we have calculated stationary points corresponding to the σ-complexes $C_6H_6^+X\ldots Cl^-$ [X=Cl (**3a**), I (**3b**)] "bound" to the counterion. Their structure is shown in Fig. 3, and geometrical and electronic parameters are given in Table 4.

The geometric parameters of these complexes lead to the transition states TS1 and TS2 (see below) and to the hypothetical products of the addition of Cl_2 or ICl to a benzene double bond. The structure of the chlorine and benzene σ-complex **3a** is similar but not identical to the earlier one calculated at the B3LYP/6-311+G* level of theory [30] (contrary to statements made in [30], this structure does not correspond to a potential energy minimum, because it has one imaginary frequency, −75 cm^{-1}). Comparison of the C^1–X and C^1–H bond distances and the Wiberg indices for the complexes **2a**,**b** and **3a**,**b** (Table 4) shows a weaker bond to the ring with halogens in the latter complexes.

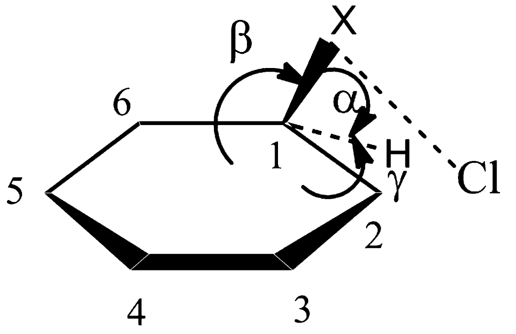

Fig. 3 Schematic structure of the σ-complexes of Cl_2 and ICl with benzene (X=Cl **3a**; I **3b**)

The calculated changes in enthalpy and the free energies of formation for the σ-complexes **3a**,**b** when the reactions are performed in the gas phase and in methanol are as follows:

$$C_6H_6 + Cl_2 \rightleftharpoons C_6H_6{}^{+}Cl...Cl^{-}(\mathbf{3a}) \tag{15}$$

$\Delta H^{\sigma}=37.1$; $\Delta G^{\sigma}=45.08$; $\Delta G_{s}{}^{\sigma}=24.2$ kcal mol^{-1}

$$C_6H_6 + ICl \rightleftharpoons C_6H_6{}^{+}I....Cl^{-}(\mathbf{3b}) \tag{16}$$

$\Delta H^{\sigma}=49.6$; $\Delta G^{\sigma}=58.5$; $\Delta G_{s}{}^{\sigma}=36.5$ kcal mol^{-1}

The solvation energies of the **3a**,**b** complexes in methanol are −16.0 and −17.0 kcal mol^{-1}, which is considerably lower than the excessive solvation energies of the isolated complexes and chloride ion noted earlier.

On the whole, the calculated values of ΔH^{σ}, ΔG^{σ}, and $\Delta G_{s}{}^{\sigma}$ for the chlorination and iodination of benzene based on Eqs. 15 and 16 agree much better with the activation energies of real halogenation reactions than with the corresponding values obtained from the model of the isolated σ-complexes (Eqs. 9, 10 and Table 5).

Transition state and free energy surface profiles

A search for transition states in the chlorination and iodination reactions of benzene **1a** was carried out along several reaction paths starting from π- and σ-complexes, from reagents (benzene and an electrophile), and from the products (chloro- and iodobenzenes and HCl). Cl_2, ICl and the triplet monocations Cl^{+} and I^{+} were regarded as the electrophiles. Only structures with a single imaginary vibrational frequency were investigated by the IRC method to confirm that they are true transition states. These transition states were created from reagents and products during the early stages of the forward and backward reactions, respectively. As a result, two types of transition state have been characterized (as sketched in Fig. 4): "early" (TS1) and "late" (TS2).

In Table 6, we give the calculated distance between X and the closest ring carbon (X–C^{i}) for TS1 and TS2, the degree of bond shortening relative to the free molecule X–Y (ΔL X–Y), the angle between the ring plane and the axis of the bonds X–Y (α) and C–H (β), the effective charges qI, qC^{i} on the interacting atoms, the Wiberg indices of the C–X bonds, and the enthalpy and free energy changes in the gas phase ($\Delta H^{\#}$, $\Delta G^{\#}$) and in methanol ($\Delta G_{s}{}^{\#}$). It is characteristic that in a charged transition state TS1 (Fig. 4a), iodine cations and especially chlorine cations are almost equally strongly bound to the ring atoms C^{1} and C^{2}, and in an electroneutral TS1, weaker electrophiles are coordinated with a single carbon atom (Fig. 4b). The "early" TS1 is characterized by the substitution of the

Fig. 4 Schematic structures of the "early" (TS1) (**a**, **b**) and "late" (TS2) (**c**, **d**) transition states. X=Cl, I (**a**, **c**); X=Y=Cl (**b**); X = I, Y=Cl (**d**)

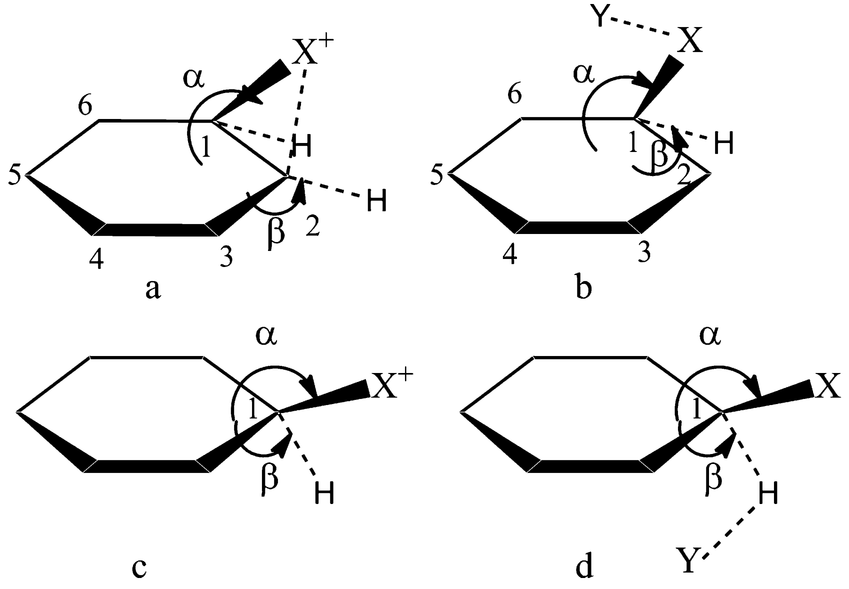

Table 6 Parameters for the transition states TS1 and TS2 during the reaction of benzene **1a** with Cl^+, I^+, Cl_2, and ICl (for a guide to the notation, see the main text)

Parameters	TS1				TS2			
	X=Cl^+	X=I^+	X=Y=Cl	X=I, Y=Cl	X=Cl^+	X=I^+	X=Y=Cl	X=I, Y=Cl
d X–C^i, (Å)	2.047 (1.983) C^1, C^2	2.427 (2.364) C^1 2.457 (2.480) C^2	1.919	2.387	1.929 (1.873)	2.282 (2.247)	1.805	2.214
d C^i–H (Å)	1.083 (1.091) C^1, C^2	1.084 (1.092) C^1, C^2	1.089	1.085	1.467 (1.417)	1.365 (1.626)	1.158	1.267
Δ*d* X–Y (Å)			0.899^a	1.060^a			0.760^6	0.549^6
α	106.9 (104.0)	85.1 (87.3)	106.6	102.4	177.1 (176.7)	174.3 (175.0)	145.02	134.5
β	161.8 (159.8)	159.8 (158.2) C^1–H 161.6 (165.8) C^2–H	145.7	178.7	131.3 (129.1)	127.7 (130.0)	97.2	105.1
q(X)	0.222 (0.151)	0.392 (0.312)	0.065	0.204	0.248 (0.184)	0.379 (0.337)	−0.016	0.125
q(C^i)	−0.290 C^1,C^2 (−0.222)	−0.363 (−0.346)C^1 −0.326 (−0.215) C^2	−0.480	−0.534	−0.441 (−0.341)	−0.445 (−0.308)	−0.420	−0.474
W X–C^i	0.623 C^1,C^2	0.552 C^1 0.508 C^2	0.800	0.618	0.824	0.776	0.985	0.889
W C^1–H	0.896 C^1,C^2	0.895 C^1 0.893 C^2	0.877	0.888	0.264 0.546 H–Cl	0.484 0.365 H–I	0.625	0.496
$\Delta H^{\#}$ (kcal mol^{-1})	−124.8	−63.4	37.4	49.6	−104.7	−34.9	18.3	37.8
$\Delta G^{\#}$ (kcal mol^{-1})	−115.3 (−155)	−54.0 (−93)	46.7	59.0	−95.8 (−134)	−26.5 (−65)	28.6	48.0
$\Delta G_s{}^{\#}$ (kcal mol^{-1})	−106.2 (−67)	−52.9 (−75)	25.0	31.4	−78.3 (−51)	−20.7 (46)	11.6	29.9

[a] Elongation of the Cl–Cl and I–Cl bonds in TS1 in comparison with free Cl_2 and ICl

[b] Elongation of the H–Cl bond in TS2 in comparison with free HCl

leaving protons for electrophiles during the path from the reagents to σ-complexes, while the "late" TS2 is characterized by the inverse process of halogen substitution for a proton (protodehalogenation) (Eq. 5). Accordingly, the TS2 states are closer in structure to the halogenated products (relatively "strong" C^1–X bonds and weak C^1–H bonds, and an almost planar conformation of the ring and X atoms), while the TS1 states are closer to σ-complexes, which is reflected in the values of the X–C^i and C^i–H bond distances, the dihedral angles *α* and *β*, and the Wiberg indices of the corresponding bonds (Table 6).

The energy level schemes calculated for the reactions of benzene with Cl^+ and I^+ are given in Fig. 5. In the first stage of the interaction of benzene with Cl^+ or I^+, the absence of energy barriers is predetermined by the extremely low stability of the cations and the correspondingly large energy gaps when σ-complexes form. A similar situation occurs in the reaction of benzene with nitronium cation [28]. In both cases, the highest energetic barrier in both the gas phase and solution occurs at the transition from σ-complexes **2a**,**b** to TS2; i.e., the calculations predict the limiting deprotonation of σ-complexes. This contradicts the known mechanisms of electrophilic benzene halogenation and, in particular, the absence of kinetic isotope effects. However, the calculations were carried out without taking into account the influence of external nucleophiles, which in one form or another are always present in real halogenation reactions and facilitate the deprotonation of σ-complexes.

This discrepancy between the calculated and experimental limiting stages independently confirms that in real electrophilic chlorination and iodination reactions the decomposition of σ-complexes should occur spontaneously; external nucleophiles should assist proton removal. Transition states corresponding to the latter process should have a noticeably lower energy than that found for TS2. Paradoxically, the lower calculated activation energy for iodination compared to that of chlorination is due to the higher stability of the σ-complex of **2a** in comparison with that of **2b** (Fig. 5). The possible role played by chlorine and iodine monocations in electrophilic halogenation reactions has been a matter of discussion for a long time [7].

The calculations show that if the monocations Cl^+ and I^+ take part in chlorination and iodination reactions of arenes as kinetically independent particles, the principal characteristics of these reactions should significantly differ from those observed experimentally.

Similar results were obtained by us at the MP2/DGDZVP level of theory when using the IEFPCM model. It was shown by us [9] that the use of the all-electron basis DGDZVP set yields thermodynamic parameters for the iodination reaction that are very close to the experimental values. The IEFPCM method describes the solvation of the

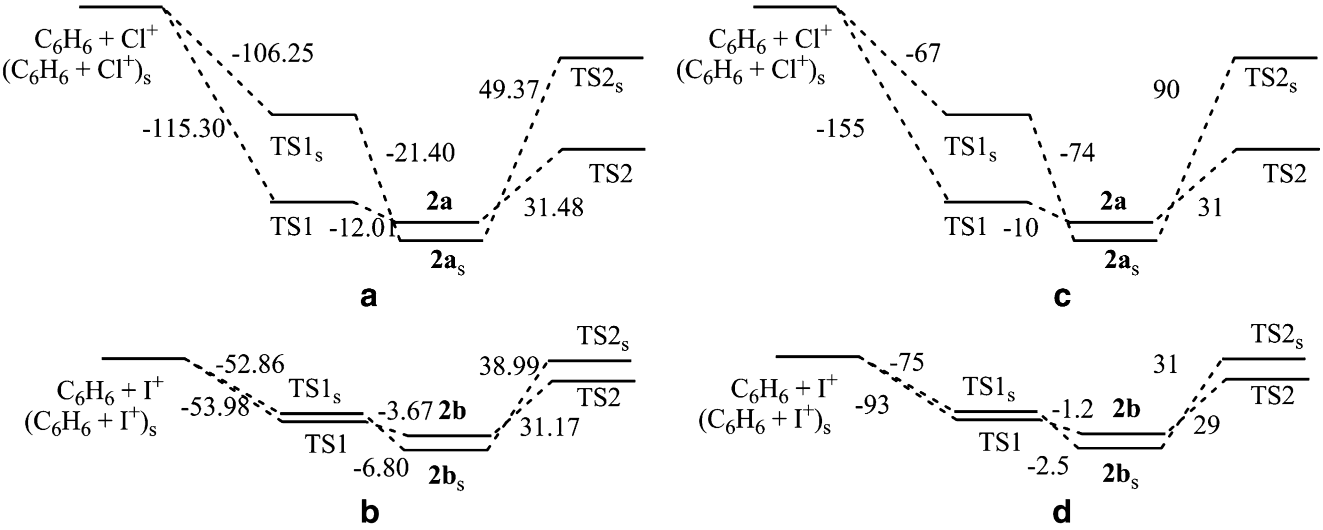

Fig. 5 Energy profiles of the ΔG reaction of benzene with the cationic electrophilic reagents Cl^+ and I^+ in the gas phase and in methanol solution, calculated at the B3LYP/6-311G* level and with the PCM model (**a**, **b**), and calculated at the MP2/DGDZVP level of theory and with the IEFPCM model (**c**, **d**) (kcal mol^{-1})

charged particles well. In Table 6, the results at this level of calculation are shown in parentheses, and in Fig. 5c, d the energy profiles for the reactions of the monocations Cl^+ and I^+ with benzene are represented. From these data, it is clear that, despite quantitative differences, the results and the profiles of the reactions are qualitatively close to those calculated at the B3LYP/6-311G(d) level.

Other, more realistic profiles of the free energy surfaces for the chlorination and iodination of benzene with Cl_2 and ICl are shown in Fig. 6. In these cases, TS1 possesses the highest free energy, and the activation energy for chlorination is reduced in comparison with that for iodination.

In terms of free energies, the σ-complexes **3a**,**b** are very close to the corresponding TS1 states, and their subsequent decomposition takes place without an energy barrier. A quantitatively similar conclusion for the benzene chlorination reaction has already been made [30] on the basis of the B3LYP/6-311+G* method, while in [31] it was concluded that a small energy barrier (~3.5 kcal mol^{-1}) exists between the σ-complex and the TS2 *para*-iodination of anisole by iodine monochloride. A sharp decrease in the energy of TS2 occurs in the reactions of benzene with Cl_2 and ICl relative to those for the reactions with Cl^+ and I^+, respectively (see Fig. 4); the reason for this is the

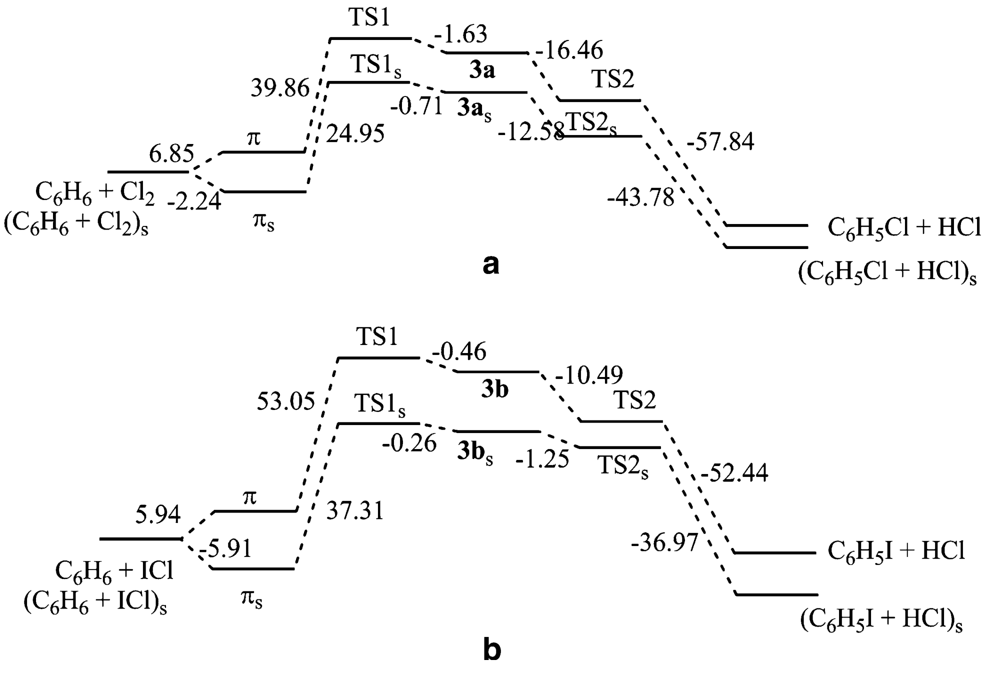

Fig. 6 Energy profiles for the reactions of benzene with Cl_2 (**a**) and ICl (**b**) in the gas phase (ΔG) and in methanol solution (ΔG_s) (kcal mol^{-1})

participation of the leaving chloride ion in the deprotonation of the corresponding σ-complexes.

Conclusions

We first carried out a quantum-chemical comparative analysis of all stages of the electrophilic chlorination and iodination of the arenes of interest. Structural and electronic parameters and thermodynamic characteristics of the halogenating agents and reaction intermediates in the gas phase and methanol were found. The parameters for the reactivities of the halogenating agents and the number of monosubstituted benzenes were calculated. The calculations show reduced reactivity of arenes in iodination reactions in comparison with chlorination and bromination reactions, due to both kinetic and thermodynamic factors, which were quantitatively determined.

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