Extending Limits of Chlorine Kinetic Isotope Effects

Katarzyna Świderek[†] and Piotr Paneth*,[‡]

[†]Departamento de Quimica Fisica, Universitat de Valencia, 46100 Burjasot (Valencia), Spain

[‡]Institute of Applied Radiation Chemistry, Faculty of Chemistry, Lodz University of Technology, Zeromskiego 116, 90-924 Lodz, Poland

Ⓢ *Supporting Information*

ABSTRACT: Chlorine kinetic isotope effects exceeding semiclassical limits were observed in enzyme-catalyzed reactions, but their source has not been yet identified. Herein we show that unusually large chlorine kinetic isotope effects are associated with reactions in which chlorine is the central atom that is being passed between two heavy atoms. The origin of these large values is the ratio of imaginary frequencies for light-to-heavy species (the so-called temperature-independent factor).
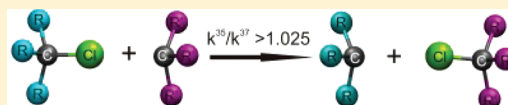
INTRODUCTION

Chlorine kinetic isotope effects (KIEs) proved very useful in elucidating mechanisms of chemical reactions, especially those elimination and substitution reactions in which chloride is the leaving group.[1] Since chlorine is a relatively heavy element, the expected range of chlorine KIEs is not very broad, but available precision of chlorine isotopic ratio measurements[2] secures their usefulness in mechanistic studies of chemical and enzyme-catalyzed reactions.[1,3,4]

Mechanistic interpretation of a Cl-KIE value relies on the generally accepted range, initially introduced by Streitwieser and co-workers, who evaluated the maximum value of Cl-KIE to be equal to 1.013.[5] This threshold has been shown experimentally to be too low, as Cl-KIEs in the range 1.015−1.017 have been found for biotic reduction of perchlorate.[6,7] On the basis of simple BEBOVIB[8] calculations, Paneth extended the maximum value to 1.019,[9] which coincides very well with the value extrapolated from results obtained at the quantum DFT level for a simple S_N2 reaction.[10] In most cases, however, typical values in the range of 1.006−1.009 for the chlorine being the leaving group[11] and around 1.0 for the chlorine being the incoming group in a substitution reaction may be expected. Results presented in Table 1 for the simple identity reaction 1 support these expectations. Furthermore, they show that for this reaction the effect of solvent on Cl-KIE is negligible, at least within the polarized continuum model.

$$Cl^- + H_3CCl \rightarrow CH_3Cl + Cl^- \qquad (1)$$

Table 1. Chlorine KIEs for Incoming and Leaving Chlorines on the Identity S_N2 Reaction 1 Calculated Using the 6-31+G(d,p) Basis Set

theory level	leaving Cl$^-$	incoming Cl$^-$
M05-2X[12]	1.0085	0.9995
MP2[13]	1.0087	0.9994
SMD[14]/MP2	1.0084	0.9995
MP4[15]	1.0084	0.9995

Using BEBOVIB methodology, Sims and co-workers[16] predicted Cl-KIE as large as 1.0256 for ionization of *tert*-butyl chloride proceeding by the S_N1 mechanism. They identified the main source of this high value to be the ratio of imaginary frequencies (called the temperature-independent factor, TIF) of light-to-heavy species (1.0172). The value of this Cl-KIE is, however, in significant disagreement with the experimental value of about 1.011.[17] The correct value was obtained when solvation of the forming free chloride anion has been included in calculations. This has been achieved by changing and coupling individual force constants rather than including explicitly solvent molecules. For the purpose of this paper, we have carried out calculations at the DFT level[18] recommended for Cl-KIEs calculations.[19] While we were unable to find the transition state for *tert*-butyl chloride, we succeeded for the ionization of highly sterically hindered 3-*tert*-butyl-3-chloro-2,2,4,4-tetramethylpentane:

$$^tBu_3CCl \rightarrow {}^tBu_3C^+ + Cl^- \qquad (2)$$

This reaction used eight water molecules immediate to the chlorine atom treated quantum-mechanically and a sphere of about 130 water molecules described by the AMBER force field[20] within the ONIOM protocol (for details, see the Supporting Information).[21] In agreement with Sims' results, we have arrived at the Cl-KIE value lower by over 1% for this aqueous solution model compared to the gas-phase calculations.

Chlorinated compounds are currently dominating environmental pollutants.[22] In the quest for detoxification methods, chlorine KIEs are again becoming one of the very best kinetic tools for studying mechanisms of biotic and abiotic transformations of chlorinated compounds.[23] This caused a renaissance of studies of Cl-KIEs on reactions of environmental interest. Among these, we have found one communication very surprising: Reddy et al. reported large chlorine KIE of about

1.012 for Fe(III)−heme−chloroperoxidase-catalyzed chlorination of trimethoxybenzene (TMB).[24] Cl-KIE for the analogous abiotic reaction between TMB and hypochlorite is much smaller, 1.0037. The mechanism of the reaction leading to the unusually large Cl-KIE remains unclear. This fact prompted us to evaluate chlorine kinetic isotope effects on reactions for which these isotope effects have been neglected thus far, i.e., reactions in which chlorine is being transferred between two heavy atoms.

In this paper, we present calculations on five reactions that cover a wide range of energetic pathways and kinds of the transferred species. Equations 3−5 illustrate chlorine transfer reactions between CCl_4 and carbanions that are characterized by very late, very early, and symmetric transition states, respectively, as illustrated in Figure 1.[25]

$$\text{(3)}$$

$$\text{(4)}$$

$$\text{(5)}$$
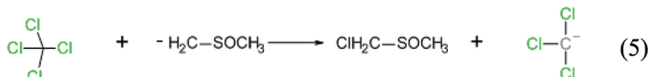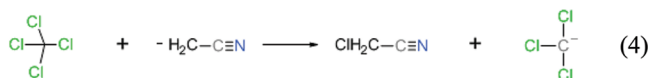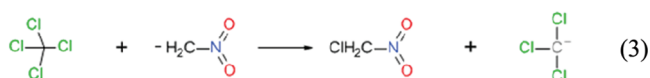
Equation 6 represents a reaction that shares with those described above one reactant, CCl_4, but proceeds via a radical mechanism.

$$\text{(6)}$$
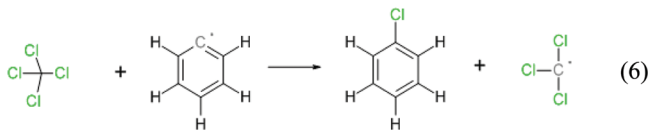
Finally, in reaction 7 between trichlorohialuric acid and trifluoroborobenzene anion the species being transferred

$$\text{(7)}$$
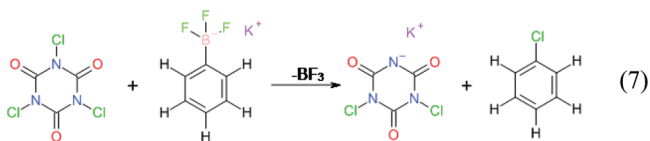
formally bears a positive charge.[26] The common feature of reactions 3−7 is transfer of chlorine between two heavy atoms, a process for which Cl-KIEs have not been determined thus far. We speculate that in such processes chlorine is shielded from the solvent which results in a very large values of Cl-KIEs. Should this assumption prove correct it might explain very large values observed experimentally in reactions of chlorination with hypochlorite anion.[24]

■ RESULTS AND DISCUSSION

In typical nucleophilic substitution (both S_N1 and S_N2) reactions the chlorine leaving group exposure to solvent or active site residues[27] increases with the reaction progress. On the contrary, during reactions 3 − 7 shielding from solvent molecules of the transferred Cl increases with the progress from the reactant to the transition state and thus neglect of explicit hydrogen bonding may result in slight underestimation of chlorine KIEs. Thus it seems safe to resort to a continuum
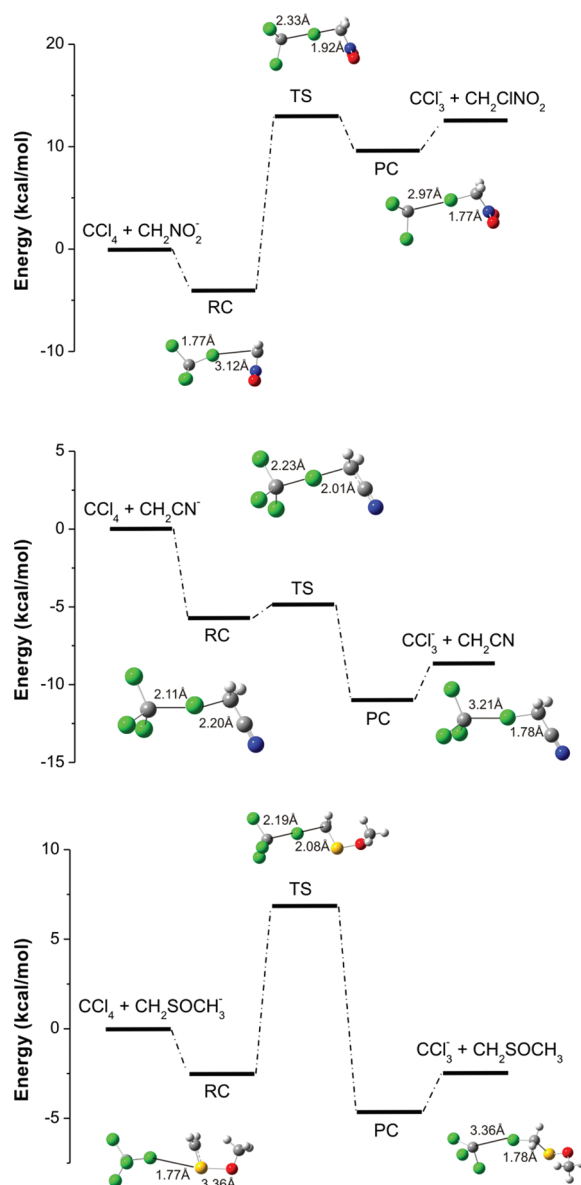
Figure 1. Free Gibbs energy profiles of reactions 3−5, top to bottom, respectively.

solvent model of aqueous solution. We have used PCM[28] with electrostatics described by the SMD model, as implemented in Gaussian 09 package.[29] All calculations were carried out at the correlated MP2 level expressed in standard 6-31+G(d,p) basis set, which was shown to perform well at the correlated MP2 as well as DFT levels.[30]

Reactions 3−5 share a common mechanism but exhibit three different energy profiles covering most important mechanistic situations depicted in Figure 1; reaction 3 is strongly endothermic with a very late transition state, reaction 4 is very early, with the transition state close to reactants, while reaction 5 is symmetrical. Reaction 6 shares with those mentioned above one of the reactants, CCl_4, but the nature of this reaction is different since the acceptor is radical. It exhibits a moderate barrier of about 9 kcal/mol but is strongly exothermic. Subsequent reaction 7 proceeds in a manner very similar to that of reaction 6, but the mechanism is ionic. In Table 2 are collected main geometric features of all stationary

Table 2. Selected Distances (Å) and CHelpG Partial Atomic Charges[31] (au) for Reactants, Transition States, And Products of Reactions 3−7

	RC	TS	PC
reaction 3			
$d(C1-Cl3)$	1.77	2.36	3.36
$d(C6-Cl3)$	3.10	1.90	1.75
$\angle(C1-Cl3-C6)$	162.2	180.0	172.3
partial charge			
Cl3	0.081	−0.275	−0.236
C1	−0.059	0.286	−0.151
C6	−0.645	0.099	0.214
reaction 4			
$d(C1-Cl3)$	2.11	2.24	3.45
$d(C6-Cl3)$	2.19	2.01	1.78
$\angle(C1-Cl3-C6)$	179.4	179.0	169.8
partial charge			
Cl3	−0.174	−0.276	−0.233
C1	0.168	0.256	−0.149
C6	−0.194	0.098	0.322
reaction 5			
$d(C1-Cl3)$	1.77	2.19	3.83
$d(C6-Cl3)$	3.21	2.08	1.78
$\angle(C1-Cl3-C6)$	170.3	177.3	175.9
partial charge			
Cl3	−0.042	−0.332	−0.193
C1	0.076	0.386	0.015
C6	−0.147	0.021	−0.155
reaction 6			
$d(C1-Cl3)$	1.77	1.88	3.24
$d(C6-Cl3)$	2.99	2.21	1.75
$\angle(C1-Cl3-C6)$	169.5	164.0	159.9
partial charge			
Cl3	−0.033	−0.104	−0.257
C1	−0.011	0.076	0.246
C6	0.007	0.021	0.255
reaction 7			
$d(N2-Cl10)$	1.72	2.15	4.06
$d(C19-Cl10)$	3.01	2.79	1.75
$\angle(N2-Cl10-C19)$	174.3	150.9	174.3
partial charge			
Cl10	0.024	−0.023	−0.265
N2	−0.458	−0.576	−0.972
C19	−0.237	−0.067	0.210
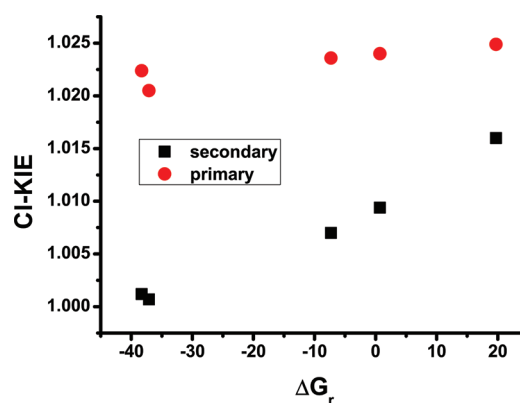
Figure 2. Correlation of Cl-KIEs with the Gibbs free energy of reactions (kcal/mol).

points, while the first two rows of Table 3 summarize the energetics of these reactions.

Reaction 4 shows interesting features. First, in the reacting complex, RC, the bond between the carbon atom and the chlorine that is being transferred is strongly weakened, leading to the C−Cl distance of 2.11 Å, compared to 1.77 Å in the remaining complexes that comprise CCl_4 as well as in free CCl_4. As a consequence, the change in the C−Cl distance on going from the reacting complex to the transition state is very small, only about 0.08 Å. Interestingly, it has very little influence on the final value of the primary chlorine kinetic isotope effect. This is because, as can be inferred from the last three rows of Table 3, the main contribution to Cl-KIE comes from the temperature independent factor (TIF); i.e., the ratio of imaginary frequencies in the transition state for light (^{35}Cl) and heavy (^{37}Cl) species. This is also true for the other studied reactions. Thus, it seems that regardless of the mechanism, reactions that proceed with chlorine transfer between heavy atoms exhibit very large chlorine kinetic isotope effects.

Elevated TIF values, in comparison to typical S_N2 reactions in which chlorine is either an incoming or a leaving group, come from the fact that this quantity increases with the increase of masses of atoms on both sides of the central atom, reaching the maximum value of about 1.028 in the case of chlorine 35/37 isotopes.[32] In the studied reactions, this value oscillates around 1.019, indicating that reactions characterized by even larger Cl-KIEs might be expected. On the other hand, it should be kept in mind that in calculations that involve a continuum solvent model imaginary frequency depends on the dielectric

Table 3. Gibbs Free Energies of Activation and Reaction (kcal/mol), Imaginary Frequencies (cm^{-1}), and selected Kinetic Isotope Effects and Their Components for Reactions 3−7

reaction property	eq 3	eq 4	eq 5	eq 6	eq 7
$\Delta G^\ddagger$	26.3	0.4	13.7	8.9	16.1
ΔG_r	19.7	−7.3	0.7	−37.1	−38.3
$i\nu^\ddagger$	251.4	251.2	292.9	305.4	366.4
^{13}C (acceptor)	1.0061	1.0005	1.0136	1.0023	1.0255
^{13}C (donor)	1.0285	1.0066	1.0196	1.0071	
^{15}N (donor)					1.0094
^{37}Cl$_3$ (secondary KIE)	1.0160	1.0070	1.0094	1.0028	
^{37}Cl$_2$ (secondary KIE)					1.0012
^{37}Cl (primary KIE)	1.0246	1.0236	1.0240	1.0205	1.0224
TIF	1.0198	1.0207	1.0197	1.0163	1.0166
TDF	1.0047	1.0028	1.0042	1.0041	1.0057

constant which in turn depends on the temperature. More studies of PCM as well as explicit solvent models are evidently needed to fully understand the source and magnitude of TIF for these reactions.

In the case of typical S_N2 reactions like reaction 1, we have argued[10] that only the temperature-dependent factor, TDF, correlates with the C−Cl bond order in the transition state. Present results show similar dependence of both primary and secondary Cl-KIEs on C−Cl bond length in the transition state. Interestingly, the dependence holds for both forming and breaking C−Cl bonds. The dependence of Cl-KIE on the breaking bond distance in the transition state is qualitatively the same as the dependence of the Gibbs free energy of reaction that is illustrated in Figure 2; secondary Cl-KIE increases strongly when the reaction becomes endothermic, while primary Cl-KIE shows the same trend but the increase is much smaller.

The main goal of this contribution was to find processes that may exhibit very large chlorine KIEs that exceed thus far accepted limits and that could be invoked to explain large Cl-KIEs on halogenation reactions observed experimentally. We have shown that such isotope effects can be associated with reactions in which chlorine is passed between two heavy atoms and is shielded from interactions with solvent molecules. Such reactions are proposed as a rate-determining step in enzymatic chlorination where a transiently formed hypochlorite anion is the source of chlorine that forms a new C−Cl bond.

Probably the most striking result of our studies is, however, the possibility of finding secondary chlorine KIEs that can be as large as typical primary Cl-KIEs in most reactions studied thus far (see Table 3). Such isotope effects, of over 1.005 per atom, have been found for reaction 3. These findings strengthen our call for caution[11,33] in interpreting experimental values of the chlorine isotopic fractionation, especially when compound-specific isotopic analysis (CSIA), the method of choice in environmental studies that averages isotopic composition of all atoms of a given element in a molecule, is employed.

ASSOCIATED CONTENT

Ⓢ Supporting Information

Structures and energies of stationary points of reactions 2−7 optimized at the PCM(SMD)/MP2/6-31+G(d,p) theory level. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
*E-mail: paneth@p.lodz.pl.
Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENTS

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