J. Chem. Theory Comput. **2009,** *5,* 33–36

33

JCTC Journal of Chemical Theory and Computation

A DFT Study of the Kinetic Isotope Effects on the Competing S_N2 and E2 Reactions between Hypochlorite Anion and Ethyl Chloride

Anna Pabis, Piotr Paluch, Joanna Szala, and Piotr Paneth*

Faculty of Chemistry, Technical University of Lodz, Zeromskiego 116, 90-924 Lodz, Poland

Abstract: Kinetic isotope effects (KIEs) on the two alternative reactions, S_N2 and E2, between hypochlorite anion and ethyl chloride in water have been studied theoretically using B3LYP and M06−2X functionals. It has been found that the latter one yields more correct geometries and energetics. Although, in the qualitative sense, KIEs obtained using both DFT functionals are in agreement, interpretation of some of them, like ^{18}O-KIE in the present case, leads to different mechanistic conclusions.

Introduction

The competition between S_N2 (bimolecular nucleophilic substitution) and E2 (bimolecular elimination) reaction pathways in the gas and condensed phases has been intensively investigated over past few years.[1] Both mechanisms are of significant importance in organic chemistry. In environmental chemistry frequently only analysis of the remaining reactant is possible, and therefore means allowing distinguishing between the two mechanisms received much attention. One of the ways to differentiate these two types of reactions is to evaluate kinetic isotope effects (KIEs); secondary deuterium KIEs are expected at room temperature to be normal (larger than unity) for the E2 mechanism and inverse (smaller than unity) for the S_N2 mechanism.

The above-mentioned competition has been examined both theoretically and experimentally. Available theoretical studies are mostly concerned with reactions occurring in the gas phase, rarely introducing explicit solvent models that allow considering solvation effects. To the best of our knowledge no studies on E2 vs S_N2 competition in condensed phases that involve implicit (continuum) solvent model have been reported. Experimental studies of the gas-phase reactions, on the other hand, remain rather involved due to the instrumentation requirements and the fact that both reactions lead to the same ionic product, which makes the analysis quite troublesome.

In recent work, Hu and Truhlar[2] have evaluated the reaction rate constants and deuterium kinetic isotope effects on the reaction between ClO^- and C_2H_5Cl for both S_N2 (eq 1) and E2 (eq 2) pathways in the gas phase, using dual−level generalized transition state theory and statistical calculations based on high-level, correlated electronic calculations. They have used MP2 theory level and modified aug-cc-pVDZ basis set.

$$ClO^- + C_2H_5Cl \rightarrow C_2H_5OCl + Cl^- \qquad (1)$$

$$ClO^- + C_2H_5Cl \rightarrow ClOH + C_2H_4 + Cl^- \qquad (2)$$

Villano et al.[3] have recently shown that experimental results differ substantially from the theoretical predictions. This discrepancy prompted us to extend studies of these model reactions. Because of the shortage of the theoretical studies in the condensed phase we have elected to model reactions in solution by using implicit model of water. There are two additional reasons for undertaking these studies. The first one is computational; DFT methods proved very efficient in predicting mechanisms of chemical reactions and are used nowadays routinely. In organic chemistry the B3LYP functional is being considered the most robust and versatile. However, in recent years a plethora of new functionals has been developed with a promise of much better performance. One of the most recent of these is the family of M0x functionals introduced by Truhlar and co-workers.[4] In this contribution we compare results obtained with B3LYP and a number of M0x functionals. Second, hypochloride is an important species in chemical, biochemical, and atmospheric studies, but its reactivity is yet not fully understood. It is used as a bleaching agent[5] and as a disinfectant.[6] It is also a postulated intermediate in many enzymatic halogenation/dehalogenation processes,[7] yet its isotopic fate remains puzzling.[8] Thus it is of great interest to fully characterize main mechanisms that involve this reactant.

Methods and Results

Calculations were carried out at the DFT level of theory using the standard 6−31+G(d,p) basis set.[9] The polarizable continuum solvent model[10] (PCM) with parameters for water was used. UFF[11] radii of all atoms, including hydrogen atoms, were used in the cavity building. 1 molar concentration was assumed as the standard state. The following functionals were employed: B3LYP,[12] M05,[13] M05−2X,[13] M06,[14] and M06−2X.[14] In the reference calculations the MP2[15] level with the aug-cc-pVDZ basis set[16] was used. The *Gaussian03* electronic structure

Table 1. Comparison of the Selected Geometrical Parameters of the S_N2 Transition State

	gas						water					
	MP2	B3LYP	M05	M05−2X	M06	M06−2X	MP2	B3LYP	M05	M05−2X	M06	M06−2X
Cl_9-O	1.707	1.726	1.676	1.689	1.696	1.691	1.710	1.729	1.680	1.691	1.699	1.692
$O-C_5$	2.097	2.198	2.138	2.118	2.149	2.101	2.105	2.216	2.704	2.134	2.186	2.115
$C-C$	1.510	1.501	1.491	1.503	1.491	1.504	1.508	1.497	1.486	1.499	1.487	1.501
C_5-Cl_{10}	2.168	2.235	2.278	2.205	2.227	2.198	2.197	2.256	2.282	2.229	2.242	2.219
C_5-O-Cl_9	108.1	114.3	115.0	109.8	111.1	109.6	106.3	111.8	111.8	108.1	108.3	108.6
$H_2-C_1-H_4$	108.1	108.3	108.3	108.3	108.0	108.1	108.9	109.2	109.3	109.2	108.9	109.0
$O-C_5-C_1$	89.0	88.3	89.6	89.7	89.2	89.5	91.4	91.3	92.4	92.2	92.3	91.6
$C_5-C_1-H_3$	109.1	108.3	89.6	108.3	108.7	108.6	109.1	108.4	108.2	108.4	108.8	108.6
$Cl_{10}-C_5-C_1$	99.0	100.8	99.6	99.0	99.3	98.9	99.2	101.2	100.8	99.4	100.1	99.3
$H_7-C_5-H_6$	117.4	117.0	117.3	117.4	116.7	117.3	117.6	117.2	117.2	117.7	116.8	117.6
rms(bonds)	-	0.055	0.055	0.021	0.037	0.016	-	0.057	0.27	0.021	0.043	0.014
rms(angles)	-	2.7	8.5	0.82	1.3	0.68	-	2.4	2.4	0.87	1.0	0.97

Table 2. Comparison of the Selected Geometrical Parameters of the E2 Transition State

	gas						water					
	MP2	B3LYP	M05	M05−2X	M06	M06−2X	MP2	B3LYP	M05	M05−2X	M06	M06−2X
Cl_9-O	1.713	1.725	1.681	1.689	1.696	1.691	1.713	1.721	1.673	1.688	1.687	1.690
$O-C_1$	2.636	2.627	2.619	2.631	2.625	2.627	2.638	2.655	2.671	2.636	2.661	2.626
$O-H_3$	1.226	1.281	1.209	1.237	1.246	1.217	1.299	1.376	1.426	1.310	1.408	1.286
H_3-C_1	1.412	1.353	1.416	1.395	1.379	1.411	1.341	1.281	1.245	1.326	1.254	1.341
H_2-C_1	1.099	1.093	1.092	1.089	1.095	1.092	1.097	1.092	1.090	1.088	1.092	1.091
$C-C$	1.436	1.425	1.426	1.425	1.429	1.433	1.424	1.415	1.407	1.414	1.407	1.419
C_5-Cl_{10}	2.108	2.212	2.115	2.146	2.104	2.094	2.197	2.350	2.426	2.250	2.406	2.201
C_1-H_3-O	175.6	171.9	171.8	176.9	177.9	177.1	176.8	174.8	179.1	177.5	177.4	177.4
H_3-O-Cl_9	102.9	106.4	108.0	103.8	103.5	104.3	101.2	103.3	101.4	102.2	98.9	103.3
$H_2-C_1-H_4$	112.6	111.9	111.9	112.6	111.4	111.8	113.8	113.2	113.9	113.8	113.5	113.3
$C_5-C_1-H_3$	102.8	105.3	105.9	103.3	105.2	104.1	99.9	102.2	100.5	100.3	101.2	101.2
$Cl_{10}-C_5-C_1$	116.0	115.7	116.4	115.2	115.4	115.8	113.8	113.0	112.0	112.9	110.9	113.4
$H_6-C_5-H_7$	112.6	113.4	112.3	113.2	112.1	112.3	114.2	115.0	115.6	114.8	115.3	114.1
rms(bonds)	-	0.050	0.016	0.020	0.017	0.011	-	0.069	0.11	0.024	0.096	0.011
rms(angles)	-	2.4	2.9	0.79	1.5	1.1	-	1.6	1.3	0.69	1.7	1.1

program[17] alone or with the MN-GSM module[18] was used. All stationary points were fully optimized using default convergence criteria. Vibrational analysis was performed for each stationary point. All minima and transition states (TSs) were confirmed to have zero and exactly one imaginary frequency, respectively, and Hessians from these calculations were used in calculations of KIEs by the conventional transition state theory using the Isoeff program.[19]

Selected geometric parameters of the optimized transition states are collected in Tables 1 and 2 for the S_N2 and E2 mechanisms, respectively. Complete transition state structures (together with Gibbs free energies and imaginary frequencies) optimized in the reaction field of the implicit solvent are collected in the Supporting Information. Atom numbering is presented in the left panel of Figure 1, which illustrates the transition state for the gas-phase S_N2 reaction. The right panel illustrates the structure of the corresponding transition state of the E2 reaction. Table 3 summarizes nongeometrical results obtained for these theory levels; energetics, Mulliken partial atomic charges, dipole moments, imaginary frequencies, and KIEs are collected.

Discussion

Previously reported results have been compared to MP2 calculations in which the aug-cc-pVDZ basis set has been modified.[2] Since not all geometric features of these structures are available, we have repeated MP2 calculations using the full aug-cc-pVDZ basis set. These results are collected in Tables 1

and 2 under the MP2 heading and are used in the following discussion as the reference level for the DFT calculations in which the standard 6−31+G(d,p) basis set has been used. The last two lines in these tables list the root-mean-square deviation of the listed bond lengths and valence angles from those obtained at the reference level. As can be seen generally M0x functionals, and especially the M0x-2X functionals, yield much better geometric results than those obtained using B3LYP. We note that the overall best performance is obtained with the M06−2X functional, and therefore we have used it in the following calculations.

From the mechanistic point of view results listed in Tables 1 and 2 indicate that the presence of the solvent leads to the looser transition state of reaction (1); both $O-C_5$ and C_5-Cl_{10} bond lengths are longer than in the gas phase calculations. These bond lengths are significantly shorter in M06−2X calculations than in B3LYP suggesting that this latter theory level overestimates bond lengths at transition states. The large value of the C_5-Cl_{10} bond indicated a late transition state. In the case of the E2 mechanism inclusion of the solvent results in elongation of the $O-H_3$ bond and shortening of the H_3-C_1 bond indicating that the transition state in the gas phase is later than in the aqueous solution. Again this change is exaggerated in B3LYP calculations.

In agreement with literature reports,[20] B3LYP underestimates the height of the activation barrier. This is corrected in M06−2X calculations. The cost of calculations using this latter functional is about 30% higher than when B3LYP is used both in energy
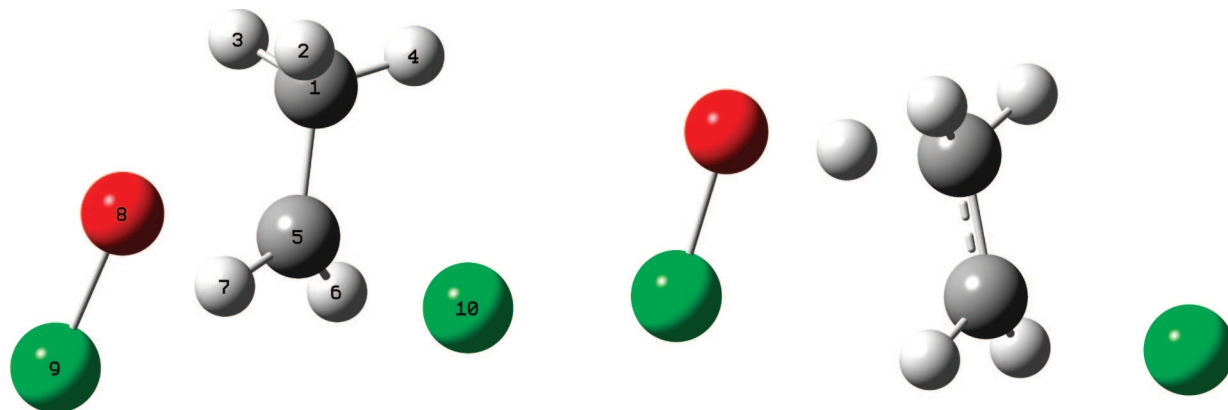
Letter

J. Chem. Theory Comput., Vol. 5, No. 1, 2009 **35**

Figure 1. Gas-phase structures of the S_N2 (left) and E2 (right) transition states for reactions between hypochlorite and ethyl chloride at 300 K.

Table 3. Calculated KIEs, Partial Atomic charges (q), Dipole Moments (μ), Imaginary Frequencies (ν), and Gibbs Free Energies for the Reactions between Hypochlorite and Ethyl Chloride in Water at 300 K

	S_N2		E2	
	M06−2X	B3LYP	M06−2X	B3LYP
Cl_9	0.9989	0.9998	0.9983	0.9988
Cl_{10}	1.0071	1.0066	1.0055	1.0059
O	0.992	0.998	0.978	0.987
CD_3	0.97	1.00	5.71	5.13
CD_2	1.03	1.01	1.16	1.19
C_5	1.0563	1.0455	1.0150	1.0126
C_1	0.9996	1.0013	1.0100	1.0059
qCl_9	−0.06	−0.08	−0.05	−0.09
qCl_{10}	−0.60	−0.60	−0.43	−0.48
qO	−0.71	−0.70	−0.56	−0.55
qH_3	0.20	0.19	0.34	0.33
μ [D]	1.49	1.54	1.71	1.85
νi [cm^{-1}]	577.4	426.3	1245.3	856.2
$\Delta G^{\ddagger}$ [kcal/mol]	11.0	9.2	17.9	15.5
ΔG_r [kcal/mol]	−31.6	−29.8	−7.9	−10.3

and Hessian calculations, the price worth being paid since both energetics and geometries obtained from M06−2X calculations are closer to values obtained experimentally and at the theoretical reference level. Mulliken partial atomic charges[21] are very close for both these functionals. Harmonic frequencies, on the other hand, show some differences. Most importantly, the imaginary vibrations differ quite significantly, especially in the case of the transition state for the E2 pathway. The high value of this frequency in M06−2X calculations indicates the dominating contribution of the proton movement in the reaction coordinate and implies that nonclassical effects, in particular tunneling, should be considered in the case of this mechanism.

Our focus in this contribution is on the consequences of using B3LYP in calculations of isotope effects because this functional has been used widely for many years in their calculations. It is thus encouraging to note that in general values of KIEs obtained for both mechanisms with B3LYP and M06−2X are not too far apart, and qualitative conclusions drawn on the basis of calculations at both considered theory levels should be quite similar. Among heavy-atom KIEs two values deserve closer inspection. ^{13}C-KIE on the central carbon atom (C_5) in the S_N2 mechanism is underestimated by about 1% in B3LYP calculations. The absolute values of these KIEs correctly indicate a primary isotope effect, but the position of the transition state

on the reaction coordinate may be assigned differently on the basis of the value obtained with the B3LYP functional. The other isotope effect is ^{18}O-KIE in the E2 mechanism. It is inverse KIE, i.e., it is smaller than unity. Inverse KIEs are obtained for the incoming group nucleophiles since the number of bonds increases on transition from reactants to the transition state. B3LYP underestimates this isotope effect which may lead to a conclusion that the reaction is stepwise and the intrinsic KIE is partially masked by a commitment, i.e., that an isotope-insensitive step is partly rate-determining.[22] Furthermore, if the observed value was close to 0.99, a different mechanism would be suggested on the basis of the B3LYP calculations. It is worth noticing that this ^{18}O-KIE is a good indicator of the mechanism since in E2 its value is closer to unity by 1% than when the S_N2 mechanism operates.

We are particularly interested in values of chlorine KIEs as they can potentially be used for analysis of dehalogenation pathways in environmental processes.[8,23] The role of the hypochlorite anion and its isotopic fractionation in enzymatic halogenation/dehalogenation processes remains unclear.[7] Disappointingly, present results indicate that chlorine KIEs do not provide any appreciable insight into the mechanism of the studied reactions. The incoming group chlorine KIE is slightly inverse for both mechanisms. The leaving group chlorine KIE is slightly larger for the S_N2 mechanism than for the E2 mechanism, but the difference is too small to be a diagnostic of the mechanisms.

Supporting Information Available: Structures, imaginary frequencies, and Gibbs free energies of the transition state structures optimized using continuum solvent model. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Gronert, S. *Acc. Chem. Res.* **2003**, *36*, 848. (b) Bickelhaupt, F. M.; Baerends, E. J.; Nibbering, N. M. M. *Chem. Eur. J.* **1996**, *2*, 196.

36 *J. Chem. Theory Comput., Vol. 5, No. 1, 2009*

Letter

(2) Hu, W.-P.; Truhlar, D. G. *J. Am. Chem. Soc.* **1996**, *118*, 860.

(3) Villano, S. M.; Kato, S.; Bierbaum, V. M. *J. Am. Chem. Soc.* **2006**, *128*, 736.

(4) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215.

(5) Goffin, V.; Piérard, G. E.; Henry, F.; Legawe, C.; Maibach, H. I. *Ecotoxicol. Environ. Saf.* **1997**, *37*, 199.

(6) Weinberg, H. S.; Delcomyn, C. A.; Unnam, V. *Environ. Sci. Technol.* **2003**, *37*, 3104.

(7) Yeh, E.; Blasiak, L. C.; Koglin, A.; Drennan, C. L.; Walsh, C. T. *Biochemistry* **2007**, *46*, 1284.

(8) Paneth, P. Chlorine Isotope Effects in Biological Systems. In *Isotope Effects in Chemistry and Biology*, 1st ed.; Kohen, A., Limbach, H. H., Eds.; CRC Press, Inc.: Baton Rouge, LA, 2006; pp 875−891.

(9) (a) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098. (b) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (c) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(10) Miertus, S.; Scrocco, E.; Tomasi, J. *J. Chem. Phys.* **1981**, *55*, 117.

(11) Rappe, A. K.; Casewit, C.; Colwell, K.; Goddard, W. A., III; Skiff, W. M. *J. Am. Chem. Soc.* **1992**, *114*, 10024.

(12) (a) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213. (b) Francl, M. M.; Pietro, W. J.; Hehre, W. J.; Binkley, J. S.; Gordon, M. S.; DeFrees, D. J.; Pople, J. A. *J. Chem. Phys.* **1982**, *77*, 3654.

(13) Zhao, Y.; Schultz, N. E.; Truhlar, D. G. *J. Chem. Phys.* **2005**, *123*, 161103.

(14) (a) Zhao, Y.; Schultz, N. E.; Truhlar, D. G. *J. Chem. Theory Comput* **2006**, *2*, 364. (b) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215. Erratum: *Theor. Chem. Acc.* **2008**, *119*, 525.

(15) Müller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618.

(16) Woon, D. E.; Dunning, T. H., Jr. *J. Chem. Phys.* **1993**, *98*, 1358.

(17) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03; Revision E.01 ed.*; Gaussian, Inc.: Wallingford, CT, 2008.

(18) (a) Xidos, J. D.; Li, J.; Hawkins, G. D.; Winget, P.; Zhu, T.; Rinaldi, D.; Liotard, D. A.; Cramer, C. J.; Truhlar, D. G.; Frisch, M. J. *MN-GSM-version 99.8*; University of Minnesota: Minneapolis, 2001. (b) Olson, R. M.; Marenich, A. V.; Chamberlin, A. C.; Kelly, C. P.; Thompson, J. D.; Xidos, J. D.; Li, J.; Hawkins, G. D.; Winget, P.; Zhu, T.; Rinaldi, D.; Liotard, D. A.; Cramer, C. J.; Truhlar, D. G.; Frisch, M. J. *MN-GSM-2008*; University of Minnesota: Minneapolis, 2008.

(19) Anisimov, V.; Paneth, P. *J. Math. Chem.* **1999**, *26*, 75.

(20) (a) Lingwood, M.; Hammond, J. R.; Hrovat, D. A.; Mayer, J. M.; Thatcher Borden, W. *J. Chem. Theory Comput.* **2006**, *2*, 740. (b) Lynch, B.; Truhlar, D. G. *J. Phys. Chem. A* **2001**, *105*, 2936. (c) Ignatyev, I. S.; Sundius, T. *Chem. Phys. Lett.* **2006**, *326*, 101. (d) Baptisto, L.; Bauerfeldt, G. F.; ArbillaG.; Silva, E. C. *J. Mol. Struct. THEOCHEM* **2006**, *761*, 73. (e) Bento, A. P.; Sola, M.; Bickelhaupt, F. M. *J. Chem. Theory Comput.* **2008**, *4*, 929.

(21) Mulliken, R. S. *J. Chem. Phys.* **1955**, *23*, 1833.

(22) Dybala-Defratyka, A.; Szatkowski, L.; Kaminski, R.; Wujec, M.; Siwek, A.; Paneth, P. *Environ. Sci. Technol.* **2008**, *42*, 7744.

(23) Paneth, P. *Acc. Chem. Res.* **2003**, *36*, 120.