Communications to the Editor

Open Shell Analogs of Closed Shell Reaction Paths: The $S_{RN}2'$ Case

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Two major pathways exist in substitution reactions of nucleophiles with allylic substrates (Scheme 1).[1-3] Attack of the nucleophile at the carbon atom bearing the allylic leaving group leads to direct displacement in a classic S_N2 mechanism. Alternatively, attack can also occur at the terminal carbon atom of the allylic double bond, displacing the leaving group in a concerted or consecutive manner. This process is usually referred to as the S_N2' mechanism. We have recently shown that barriers for S_N2 displacements are considerably lower in open shell systems compared to the closed shell analogs.[4] In analogy to the closed shell situation one might ask whether a second pathway exists, in which attack occurs at the radical center with concomitant displacement of the leaving group. This process, which appears not to have been considered before in the literature, might be termed the $S_{RN}2'$ mechanism. We now show on the basis of ab initio calculations that this additional pathway is even more favorable than the direct substitution mechanism. $S_{RN}2'$ reactions should therefore be considered an additional mechanistic possibility in reactions of open shell species. In a more general sense, this result also provides a first indication of the possibility that the vinylology principle of closed shell chemistry might be complemented by a "methylenology" principle in open shell compounds.

To facilitate comparison of the $S_{RN}2$ and $S_{RN}2'$ reaction pathways, we have again chosen the $Cl^- + \beta$-chloroethyl radical system.[4] Geometry optimizations have been performed at the ab initio UMP2/6-31G* level of theory for various structures along the reaction coordinate, which has been taken as the Cl−C bond distance. Single point energies have been calculated for the UMP2/6-31G* structures at the MP2, MP3, and QCISD level of theory with the 6-31+G** basis set.[5] Spin projected energies have been used for the calculation of relative energies.[6] The resulting reaction profiles are shown in Figure 1. The reaction path starts out from ion−dipole complex **1** at R(C−Cl) = 3.52 Å. In this complex, the chloride anion coordinates to two positively charged hydrogen atoms at the two carbon atoms of the chloroethyl radical. The transition from the side-on to the anti orientation causes a small kink in the potential energy curve at around 3.2 Å. Further shortening of the C−Cl distance then leads to an energy maximum in the PMP2/6-31+G** curve around 2.65 Å. This maximum is followed by a small decline to reach a minimum at the C_{2h} symmetric structure **2**, in which both C−Cl bonds have equal lengths of 2.34 Å. Frequency analysis shows that this structure is not the expected transition structure for chloride exchange, but a minimum on the UMP2/

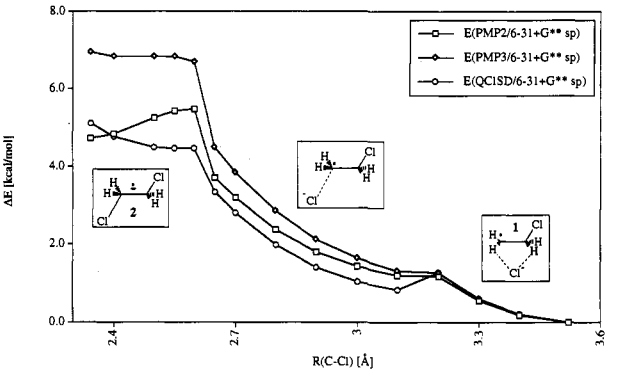
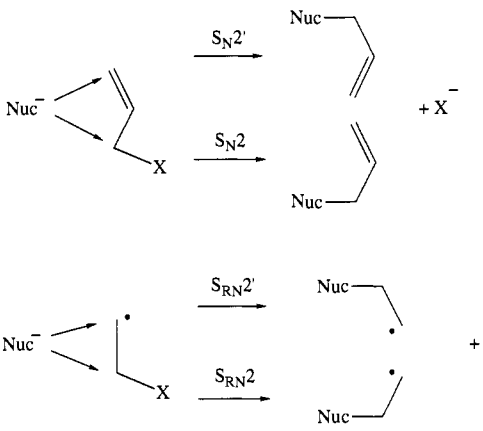


Figure 1. Chloride self-exchange in the $Cl^- + \bullet CH_2CH_2Cl$ system through the $S_{RN}2'$-reaction path.

Scheme 1



6-31G* PES. The smallest positive vibrational frequency (99 cm^{-1}) describes the geometrical distortion expected for the imaginary frequency of a C_{2h} symmetric transition structure. The shape of the potential energy curve as well as the spurious minimum for the expected transition structure clearly shows that UMP2 theory is not fully adequate to describe mixing of the electronic states, which are most dominant in the region between complex **1** and structure **2**. This is also true for UMP3 theory, which still predicts a very flat surface for R(C−Cl) < 2.65 Å. Finally, the QCISD/6-31+G** curve shows the C_{2h} structure to be the highest point on the reaction path, with a small shoulder still remaining around 2.65 Å. This artifact might well vanish if QCISD/6-31+G** optimized geometries were used. The situation is very similar to that described recently for the F• + H−F substitution reaction.[7] The most remarkable feature of Figure 1, however, is the narrow range of activation barriers calculated at various levels of theory. In Table 1 we compare these barriers with those for the $S_{RN}2$ process at theoretical levels up to PMP4 using various basis sets. Comparison of UMP2 vs PMP2 and UMP4 vs PMP4 barriers for both pathways shows that spin contamination has little influence on relative or even absolute barriers. The choice of basis set is more critical. The difference in PMP2/6-311+G(d,p) and PMP2/6-311++G(2d,p) barriers points to the fact that even the 6-311+G(d,p) basis set is by no means sufficient to accurately predict absolute barriers within 3 kcal/mol. The large effect of multiple polarization functions in ab initio calculations of chlorine-containing compounds is also known from closed shell species and thus is not

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Table 1. Energy Differences ΔE (kcal/mol) between Ion−Dipole Complex **1** and Transition Structures for $S_{RN}2'$ and $S_{RN}2$ reactions **2** and **3**, Respectively, at Various Levels of Theory

method[a]	$\Delta E(S_{RN}2')$	$\Delta E(S_{RN}2)$	$\Delta\Delta E(S_{RN}2' - S_{RN}2)$
UMP2(FC)/6-31G(d)	3.71	9.75	−6.04
PMP2(FC)/6-31G(d)	3.89	9.36	−5.47
PMP2(FC)/6-31+G(d,p)	4.70	10.25	−5.55
PMP2(FC)/6-311+G(d,p)	4.55	11.28	−6.73
PMP2(FC)/6-311++G(2d,p)	1.25	6.88	−5.63
PMP3(FC)/6-31G(d,p)	6.92	10.80	−3.88
PMP3(FC/6-311+G(d,p)	7.09	12.04	−4.95
UMP4(FC)/6-311+G(d,p)	3.26	9.42	−6.16
PMP4(FC)/6-311+G(d,p)	3.44	9.01	−5.57
QCISD(FC)/6-31+G**	5.09	7.84	−2.75

[a] UMP2(FC)/6-31G(d) optimized geometries have been used for all single-point calculations.

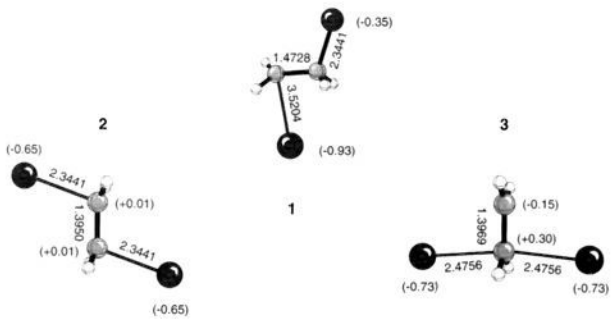

Figure 2. UMP2(FC)/6-31G* optimized geometries for minima and transition structures on the $S_{RN}2$ and $S_{RN}2'$ pathways. Bond lengths are given in angstroms. Values in parentheses are monopole charges fitted to the UMP2(FC)/6-31G* molecular electrostatic potential.

a characteristic aspect of the open shell systems studied here.[8] The differences between the $S_{RN}2'$ and $S_{RN}2$ activation barriers included in Table 1 show a significantly smaller variation compared to the absolute barriers. Assuringly, the $S_{RN}2'$ reaction pathway is the *preferred one* at all levels of theory considered here. Including the effects of multiple polarization functions into the PMP4 or QCISD values would predict a barrier below 2 kcal/mol for the $S_{RN}2'$ pathway. In a similar way, one would estimate the $S_{RN}2$ barrier to be 3−5 kcal/mol higher in energy.

This gas phase scenario can, of course, be altered significantly by solvent effects.[4,9] For closed shell S_N2 and open shell $S_{RN}2$ reactions we have recently shown that aqueous solvation dramatically alters the absolute barrier, but hardly affects the *relative* barrier height. This is due to the fact that changes in charge distribution are very similar for open and closed shell systems. Comparing charges obtained by fitting the UMP2/6-31G* electrostatic potential[10] in structures **2** and **3**, however, one finds significantly lower charges on chloride in **2** compared to **3** (Figure 2). This is counterbalanced by higher positive charges on carbon in **3** as compared to **2**. This charge shift is found to a similar extent with QCISD/6-31G*, UHF/6-31G*, and BP86/6-31G* electrostatic potentials or when charges based on the Mulliken population analysis are used. Since lower chloride charges in the transition state equate to higher desolvation energies along the reaction coordinate, the $S_{RN}2$ mechanism could well win out over the $S_{RN}2'$ one if the reaction were conducted in a polar medium. We have estimated the relative free energies of solvation in water using the Monte Carlo free energy perturbation technique as implemented in BOSS 3.4.[11] Simulations were performed using 396 TIP4P water molecules at 298 K and 1 atm. Coulomb parameters for the solute were obtained from UMP2/6-31G* monopole charges,[10] and Lennard-Jones parameters were obtained as described before.[4]

Structure **2** was perturbed to structure **3** in 10 steps requiring five separate simulations with double wide sampling.[12] Equilibration for 1M MC steps was followed by averaging over 4−8M configurations, such that the root mean square deviation was less than 10% of the free energy difference calculated for the corresponding window. The overall free energy of solvation of structure **2** is 4.17 ± 0.11 kcal/mol less favorable compared to structure **3**. This difference is similar in size to the gas phase potential energy difference for structures **2** and **3 but** opposite in sign. The $S_{RN}2$ and $S_{RN}2'$ reaction paths should therefore face almost identical barriers in aqueous solution.

For $S_{RN}2$ and $S_{RN}2'$ reactions to be observed, they have to compete against typical homolytic processes such as radical−radical recombination reactions, disproportionation reactions, hydrogen atom abstraction from solvent, etc. The high rates and low barriers achieved in the latter processes are possible, because reaction of the uncharged species involved does not require significant amounts of desolvation energy. In contrast, this is a major factor in $S_{RN}2$ and $S_{RN}2'$ reactions in polar media.[4] Conversely, if the reactions were performed in nonpolar solvents typically used for synthetic purposes, formation of free ions necessary for $S_{RN}2$ reactions is unfeasible altogether. It thus appears unlikely that bimolecular $S_{RN}2$-type processes will be observed in competition to radical chain reactions. It follows that the interplay between radical and ionic chemistry could potentially best be observed in biochemical studies, in which radicals are formed in a nonchain process in a highly polar medium. The presence of internal nucleophiles for intramolecular $S_{RN}2$ reactions will certainly improve the situation even further. Results on model studies for radical-induced DNA strand cleavage, for example, appear to support this conclusion.[13,14]

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