Transition States of Homologous S_N' Reactions of *All-(E)*-Polyenolate Derivatives

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$S_N 2'$ reaction of allylic substrates is one of the most fundamental reaction in organic chemistry, but the stereochemistry of reaction has remained a point of controversy since the inception of the $S_N 2'$ reaction. There are two possible pathways for the $S_N 2'$ reaction with an allylic substrate: an incoming nucleophile (Nu) approaches to the π-orbitals of the allylic carbon with either a syn or an anti relationship to a leaving group (LG). Since the first experimental documentation of predominant syn-$S_N 2'$ stereochemistry was reported by Stork *et al.*,[1] it inspired many theoretical chemists, including Fukui,[2] Liotta,[3] and others,[4-6] to search for reasonable justifications for this observation.

Although explanation of early theoretical studies were mainly based on the alignment of orbitals,[2-3] recent theoretical results were elucidated largely by steric nature.[4-6] We also believe that all the systems studied above are significantly affected by the interaction between Nu and LG as well as the other substituent effects. Since most of the previous works were focused on the S_N' reactions with 1,3-relationship between Nu and LG, a large steric and/or electrostatic interactions between these two groups should be unavoidable during the reaction. One of excellent methods to gauge these interactions probably is to investigate the transition states of homologous S_N' reactions[7] of conjugated *all-(E)*-polyene system, Nu-CH$_2$-(CH=CH)n-CH$_2$-LG. In a series of these model systems, as the length of carbon chain is increased, steric and/or electrostatic interactions of the TS between Nu and LG is probably diminished. On the other hand, the distance between Nu and LG in the transition state may not have a subtle effect on orbital interactions, which Liotta proposed for the alternating stereochemistry (syn/anti) of $S_N 2'$ reactions in conjugated diene system.[8]

Our studies have been initiated by calculating TSs of the S_N' reaction from (E)-4-halo-2-butenolate anions (O-CH$_2$-CH=CH-CH$_2$-X, X=Cl for **1**, X=Br for **2**) with HF/6-31+G(d) and B3PW91/6-31+G(d) methods.[9] The TSs for anti- and syn-stereochemistry of are illustrated by **TS-1-anti**, **TS-1-syn**, **TS-2-anti** and **TS-2-syn** in Figure. The geometric nature of the TSs seems to be a typical example of concerted S_N' mechanisms, and clearly shows that the X atom departs simultaneously by anti or syn manner as the O anion attacks. According to HF/6-31+G(d) calculations, anti attacks are more favored than a syn attacks by 3.16 kcal/mol for **1** and 2.92 kcal/mol for **2**. When we employ the calculation with B3PW91/6-31+G(d), all of anti attacks are computed to be more favorable than the corresponding syn attacks by 0.97

and 0.65 kcal/mol, respectively. These energy differences are substantially smaller than those from HF calculations, which appears to show that including electron correlation effect is important to understand the nature of the reactions. Although anti attacks show more favorable routes than syn modes according to the both calculation results, the anti/syn energy difference with X=Br shows by 0.65 kcal/mol, which is smaller than expected regarding an atomic size X (0.97 kcal/mol for X=Cl). According to the optimized TSs of anti and syn modes, it is noticed that the distances of O···Br are longer than those of O···Cl (6.062 and 5.169 in **TS-2-anti** and **TS-2-syn**, 5.909 and 5.071 in **TS-1-anti** and **TS-1-syn** see Figure). Thus, although Br is bigger than Cl, the size effect of the X atom appears to be attenuated as the distance becomes longer from the incoming O atom to the leaving X atom.

In order to understand our initial speculation, we also have investigated the TSs of homologous S_N' reactions of conjugated *all-(E)*-enolate anions (O-CH$_2$-(CH=CH)n-CH$_2$-Cl; n=2 for **3**, n=3 for **4**, n=4 for **5**). The calculational results in this series of compounds provide a clear view regarding the preference between different attacks (see Figure 1). HF/6-31+G(d) calculations shows that all the anti attacks are favorable than the corresponding syn attacks. As shown before, the preference of anti stereochemistry for reaction of **1** (X=Cl, n=1) is predicted by 3.16 kcal/mol. As 'n' is increased, the preferences of anti over syn mode are continuously decreased by 1.54, 0.71 and 0.40 kcal/mol for the reaction of **3**, **4** and **5**, respectively. This result along with the one by changing the X atom clearly shows that unfavorable electrostatic repulsions between Nu and LG appear to play a major role in deciding which mode of attack is favorable. Our analysis is simple, yet provides important knowledge regarding the origin of relative preferences in modes of attack. Based on our results, the predictive trend is not supporting the alternating syn/anti preference as 'n' is increased, which is predicted by orbital interactions.[3a] Our calculations were extended to B3PW91/6-31+G(d) to incorporate the electron correlation. The B3PW91/6-31+G(d) calculations predict that the preferences of the anti attack over the syn attack are calculated to be 1.03, 0.32 and 0.16 kcal/mol for **TS-3**, **TS-4** and **TS-5**, respectively. These results, although the values get smaller than those from HF calculation, concur with the HF results. According to our calculational results, we can conclude that preferential anti attacks are basically attributed to steric and/or electrostatic
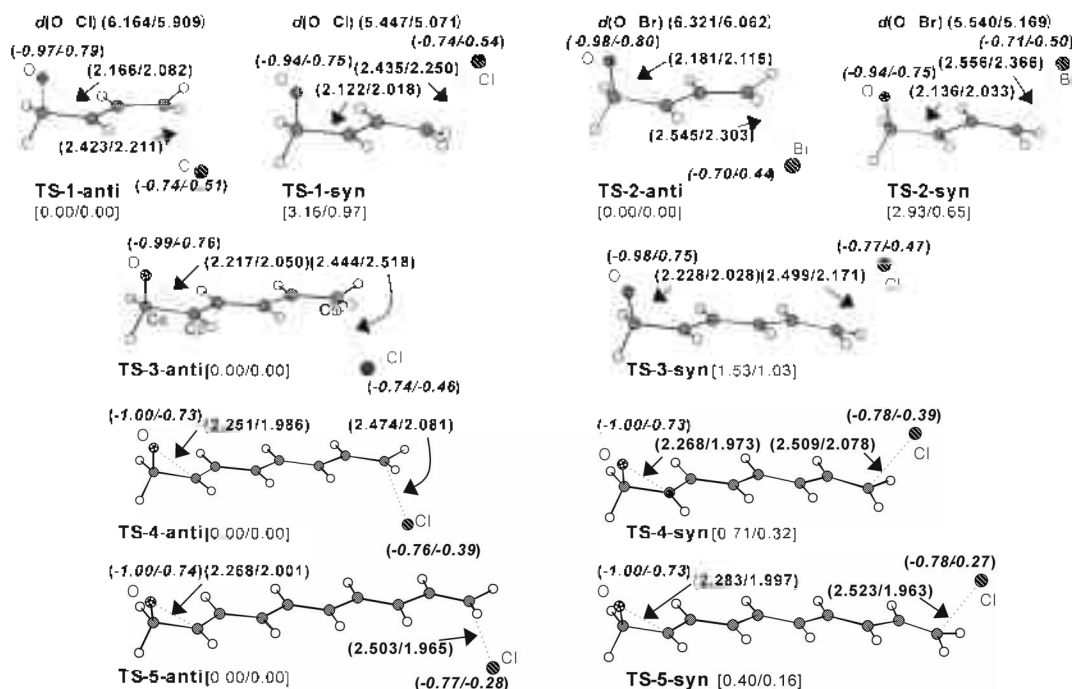
Figure 1. The optimized TS structures (**TS-1-anti, TS-1-syn, TS-2-anti, TS-2-syn, TS-3-anti, TS-3-syn, TS-4-anti, TS-4-syn, TS-5-anti** and **TS-5-syn**) on S_N' and homologous S_N' reactions of *all-(E)*-polyenolate anions at the B3PW91/6-31+G(d) level. The HF/6-31+G(d) optimized structures are almost identical. The values in parentheses are NPA atomic charges and distances (Å). The values in brackets are relative energy differences (kcal/mol) between syn and anti attacks. All values in both parentheses and brackets are at HF/B3PW91 levels. Absolute energies for **TS-1-anti, TS-2-anti, TS-3-anti, TS-4-anti,** and **TS-5-anti** are -689.2410392/-691.3004796, -2799.6731759/-2802.8681281, -766.1312099/-768.6842739, -843.0196422/-846.0667827 and -919.9074054/-923.4497562.

interactions. Unless these effects are present, these reactions in gas phase would not be shown for the relative preference in the mode of attack.

In summary, we have calculated the TSs for anti- and syn-S_N' by intramolecular nucleophiles (O⁻) attack on *all-(E)*-polyenolate anions (⁻O-CH₂-(CH=CH)n-CH₂-X; where X=Cl, Br in 'n'=1 and X=Cl in 'n'=2 to 4) at the HF/6-31+G(d) and B3PW91/6-31+G(d) levels. According to our results, an anti mode of attack is always more favorable than the corresponding syn mode mainly due to *steric and/or electrostatic interactions*. The trend of the relative preference in the modes of attack due to the change of the leaving X atom is explained by a compromise between the size of X and the distance from incoming Nu and X in the TS. The smooth decline in the relative of the anti attacks over the syn as the increase of 'n' clearly illustrates that the electrostatic repulsions present in syn attacks are relieved. We are not able to find supportive evidences in the prediction of alternating stereochemistry (syn/anti)[3a] as the preferential mode of attack when 'n' is increased.

References and Notes

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7. In system of Nu-CH₂-(CH=CH)n-CH₂-X (n=1, 2, 3, ···, n), 'homologous S_N' reaction' is defined by bond forming between Nu and C_β carbon as well as bond breaking of X from C_α carbon. It is a typical S_N' reaction for the number of vinyl chain ('n') is one.
8. It has been predicted that Nu's are to be attached in an alternation manner: syn-mode for C3 and anti-mode for C5 in C5-C4-C3-C2-C1-X system. See ref. 3a.
9. Frisch, M. J. *et al. Gaussian 98*, Revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.