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The C- and D-ring problems of sterol biosynthesis: hydride shift versus carbon–carbon bond migration due to conformational changes controlled by counteranion

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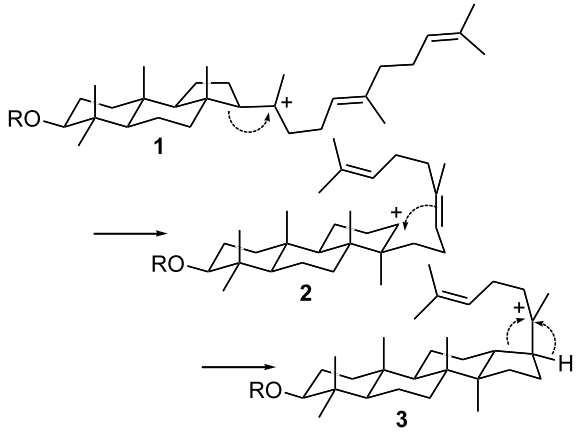
Abstract—The first calculations of a C-ring model cation of sterol biosynthesis in the presence of selected counteranions have been performed. $[TiCl_4OH]^-$ ion significantly stabilizes the perpendicular cation conformer that leads to carbon–carbon bond migration and formation of a six-membered ring secondary cation. The $[TiF_4OH]^-$ ion, however, stabilizes the parallel cation conformer that leads to hydride shift as observed indeed.

The cyclization of oxidosqualene to lanosterol or plant sterol is one of the most exciting transformations of organic chemistry and biochemistry.[1] After introduction of the idea of a stepwise mechanism of biomimetic olefin cyclization[2] as well as enzymatic cyclization[3] via conformationally flexible cationic intermediates, significant attention has focused on each step of the cyclization. Particularly, the problem regarding C-ring formation has evoked considerable discussion since this step includes rearrangement from a more stable *tert*-cation **1** to a less stable six-membered ring secondary cation **2**.[4] Although the hydride shift from the D-ring cation **3** competes with C–C bond migration to give a six-membered ring secondary cation in plant sterol biosynthesis,[5,6] this step did not receive much attention of theoretical chemists. Furthermore, most of the theoretical studies on C-ring formation generating cation **2** have concluded that this rearrangement required too much energy to be feasible.[4]



We have recently accomplished a model study using diol **4** and investigated the fate of the corresponding *tert*-cation **5** generated from reactions with a variety of Lewis acids.[7] The cation generated with $BF_3{\cdot}Et_2O$, $SnCl_4$, $Sc(OTf)_3$, $FeCl_3$, TiF_4 and CF_3SO_3H underwent hydride shift to provide cation **6** that corresponds to the initiation of the backbone rearrangement on the D-ring of **3**. On the other hand, $TiCl_4$ selectively induced rearrangement to the secondary cation **7** by ring expansion that corresponds to C-ring formation in sterol biosynthesis and D-ring formation in plant sterol biosynthesis. MM2 calculation[7] of cation **5** using CONFLEX[8] and further refinement by MOPAC[9] indicated the existence of two conformers, **5a** and **5b**. The conformer **5a**, that takes parallel alignment of the five-membered ring and the cation plane, is geometrically suited for hydride shift to generate cation **6**. The conformer **5b**, that takes a perpendicular relationship of the cation plane and the five-membered ring, should instead result in a marked carbon–carbon bond migration and afford the anti-Markovnikov cation **7**. Not only our MM2 calculations, but also almost all other publications dealing with the calculation of carbocations[3b,4] have been carried out without any counteranion; only the stabilities of the naked cations were discussed. However, the major stabilization of a

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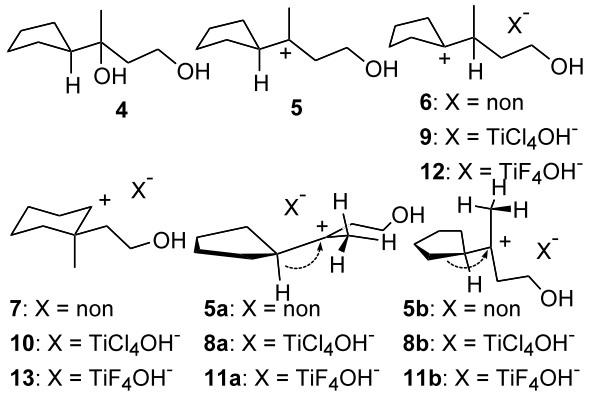
cation is very likely to be derived from a counteranion through electrostatic effects. The location of the counteranion in respect of the cation should therefore constitute the most important factor in controlling the conformation of the latter. Thus, we undertook the first calculations of the conformers **5a** and **5b** in the presence of counteranions $[TiCl_4OH]^-$ and $[TiF_4OH]^-$. As expected, the counteranion indeed contributed significantly to the stabilization of carbocation, leading us to conclude that the rearrangement from cation **1** to cation **2** is a reasonable pathway.



We have performed ab initio Hartree Fock molecular orbital calculations with 6-31G* basis set.[10] Cations **5a**, **5b**, **6**, **7** and anions $[TiCl_4OH]^-$ and $[TiF_4OH]^-$ were completely optimized separately using the Berny optimization algorithm[11] of the Gaussian 98 package.[12] The anions were slowly brought in from a distance to the cation and, at each point, the interaction energy of the two was calculated using supermolecule calculations. These interaction energies are without the incorporation of basis set superposition error (BSSE). In this manner, the optimal cation–anion distance was determined at which the attractive interaction energy was the maximum. The counteranion was then placed at this optimal distance and the cation was completely optimized in its presence to locate the stationary point for the supermolecule. Although the anion was kept frozen in a particular orientation and the stationary point was found using only partial optimization, all gradients were found to be within the convergence criterion.[13] The anion was then rotated to a different orientation and the resultant supermolecule was optimized for yet another stationary point. Stationary points corresponding to several possible orientations of the counteranion were calculated.

The fully optimized conformations and relative energies for the naked cations **5a**, **5b**, **6** and **7** are given in Figure 1. The perpendicular cation **5b**, that is suitable for carbon–carbon bond migration, is energetically more favored than the parallel cation **5a** that is suitable for hydride transfer. As expected, the conversion of **5b** into the anti-Markovnikov cation **7** is an unfavorable process with an energy requirement of 9.8 kcal/mol that is

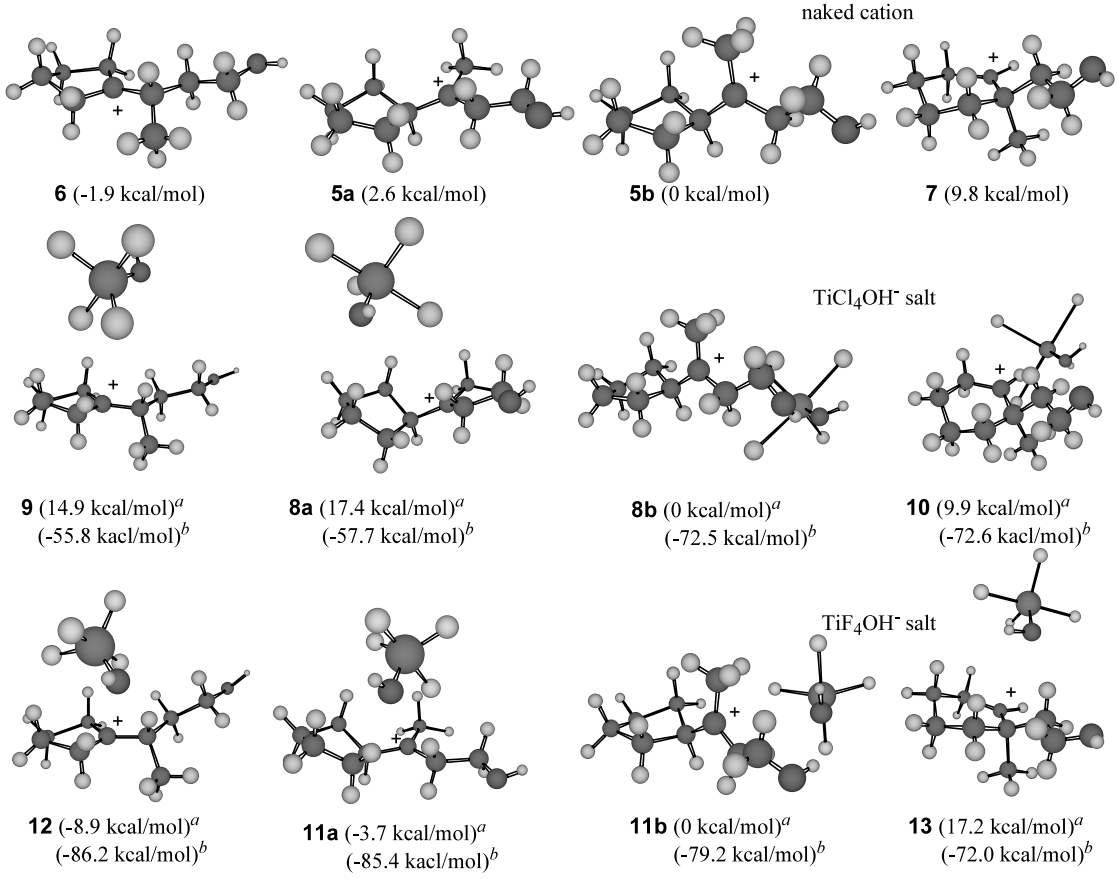


Figure 1. Conformation of cation. [a] Relative energy, [b] interaction energy.

comparable to 12 kcal/mol reported by Jorgensen.[4a] In contrast, the transition of cation **5a** to **6** is favored by 4.4 kcal/mol. The cations **5a** and **5b** being in equilibrium due to a small energy difference (2.6 kcal/mol) are therefore expected to rearrange to **6** in preference to **7**. This, however, contrasts our experimental findings.[7]

In this study we demonstrate the stabilization of a cation by a counteranion and its effect on the energetics of the reaction and thus the fate of the cation. The relative stabilities of the energetically most favored conformations of cations in the presence of $[TiCl_4OH]^-$ indicate that it stabilizes preferentially the cation **5b** that is suitable for C–C migration. A close examination reveals that the counteranion approached closer ($C^+\cdots Ti = 4.82$ Å) to cation **5b** (Fig. 1, **8b**) than to cation **5a** ($C^+\cdots Ti = 5.5$ Å) (Fig. 1, **8a**). This allows better electrostatic interactions in **8b** than in **8a**. An estimate of interaction energy of cation with counteranion helps us understand the contribution from electrostatic interactions in preferential stabilization of one cation over the other. We note that 14.8 kcal/mol out of a total difference of 17.4 kcal/mol is due solely to the difference in electrostatic interactions; the remaining difference is of conformational origin. However, minor anion-induced conformational changes in cation do take place to allow any possible H-bonds or to maximize interactions with counteranion.

The relative energies of the optimized product cations in the presence of a counteranion (**9** and **10**) indicate that **8a**, once formed, will quickly rotate to **8b** and initiate carbon–carbon bond migration to form **10**, even though it is an endothermic reaction. The conversion of **8b** back to **8a** and then to **9** is unlikely as it was indeed observed from our model study.[7]

From the above discussion, the shape and size of the counteranion appears to be important in determining its electrostatically most favored disposition with respect to the cation that, in turn, may determine the fate of the cation. To evaluate this, we considered calculations with $[TiF_4OH]^-$ that carries the same Ti metal but has a smaller ligand (F versus Cl). It can be seen clearly that the counteranion can now penetrate much closer to the cation to benefit from greater electrostatic stabilization. The relative energies indicate that the energetics are now controlled largely by the electrostatic interactions and that the conformational effects are reduced to marginal, if not negligible, due to the smaller size of the counteranion. From rotationally isomeric **11a** and **11b**, **11a** is transformed to **12** via hydride shift in a process that is predicted to be exothermic by 5.2 kcal/mol (8.9 kcal/mol from **11b**). On the contrary, the transformation of **11b** to **13** via C–C migration is predicted to be endothermic with as high an energy requirement as 17.2 kcal/mol. This is supported from our experimental results as we observed only the product of hydride migration.

We conclude from the foregoing discussions that the energetics of the reaction of a carbocation should be determined by taking the counteranion into account and not just the naked cation as the counteranion may preferentially stabilize one cation over the other through electrostatic interactions and, thus, selectively determine its fate for either hydride transfer or carbon–carbon bond migration. The shape and size of the counteranion is very important in determining its stabilization effect as the electrostatic interaction is the major control factor. Although calculations with several other Lewis acids are in progress, our preliminary results with $[BF_3OH]^-$ are similar to those obtained with $[TiF_4OH]^-$. This is also in accordance with our experimental findings.[7]

We surmise that the control of cation conformation (parallel or perpendicular) by the carboxylates of glutamic and aspartic acids (to act as counteranions) in enzymatic cavity is a distinct possibility. This concept is currently being explored.

Acknowledgements

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13. The largest gradients for the frozen internal coordinates of anion were of the order 10^{-2}.