

Oxatriquinane Derivatives: A Theoretical Investigation of S_N1 - S_N2 Reactions Borderline

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Abstract

This study investigated the nucleophilic substitution reaction mechanisms of 5 oxatriquinane derivatives, namely: oxatriquinane (OTQ), 1,4,7-trimethyloxatriquinane (TMO), 1,4,7-triethyloxatriquinane (TEO), 1,4,7-tri-iso-propyloxatriquinane (TIO) and 1,4,7-tri-tert-butyloxatriquinane (TTO). In addition to the G_3 conformation (one with the substituent groups at 1,4 and 7 positions pointing into the plane of the paper) originally proposed by the previous workers, Mascial *et al.* in 2008 and Gunbas *et al.* in 2013, one more geometrical isomer was considered again for each of the derivatives, the 2G_1 isomer (one in which only 2 of the 3 substituent groups at 1,4 and 7 positions are into the paper plane). Geometry optimization and determination of transition state properties of the conformers corresponding to each molecule (in the presence of azide ion, N_3^-) provided theoretical evidences on the possible reaction mechanisms. The 2G_1 conformer for TTO was found to be unstable. The reactions of OTQ, TMO and TEO with azide ion (N_3^-) followed S_N2 pathway, with S_N1 mechanism completely lacking. This finding is in agreement with the first set of reports published on this subject in 2008 and 2010 by Mascial's group. For TIO (in the presence of azide ion), only the presence of S_N1 mechanism could be proved without any observation of transition state (TS), even though, it possesses a 2G_1 conformer. TTO surprisingly, showed marked evidence of S_N1 mechanism also without any evidence of TS. The results obtained showed that OTQ derivatives up to TEO undergo nucleophilic substitution predominantly via S_N2 , and above which (i.e. for TIO and TTO) the mechanisms predominantly become S_N1 .

Keywords: Oxatriquinane, kinetics, thermodynamics, geometry, free-energy

Introduction

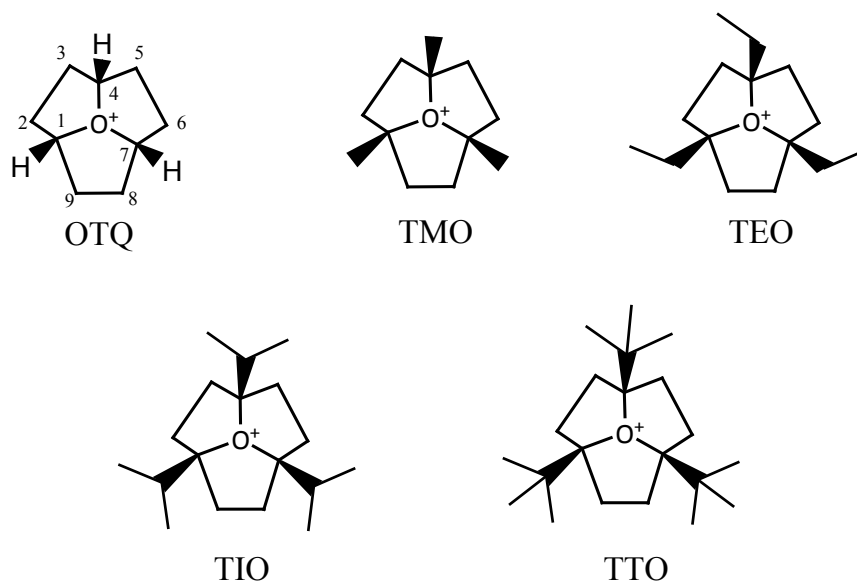
Nucleophilic substitution reaction (NSR) constitutes a class of elementary chemical reactions that play an important role in organic chemistry. It is a class of reactions in organic chemistry that has been and continues to be intensely investigated [1-5]. The fundamental principle of NSR taught in organic chemistry classes is that molecules containing tertiary (3°) electrophilic carbon preferably undergo substitution reactions via S_N1 mechanism, while those containing primary (1°) or secondary (2°) electrophilic carbon centers undergo substitution reactions via S_N2 mechanism. The first and the only known work which revealed the possibility of S_N2 reaction at a tertiary carbon center is that of Mascial and co-workers [6,7]. However, the details of the mechanisms in relation to the nature of the substituents at the 1,4 and 7 positions, **Figures 1(a)**, were not provided.

The molecules selected in the present study to demonstrate the occurrence of S_N1 or the 'expected' S_N2 reactions (based on the conclusions of Mascial and co-workers) at a 3° electrophilic carbon center are similar to those studied by Mascial *et al.* [6,7], and they are- oxatriquinane (OTQ), 1,4,7-trimethyloxatriquinane (TMO), 1,4,7-triethyloxatriquinane (TEO), 1,4,7-tri-iso-propyloxatriquinane

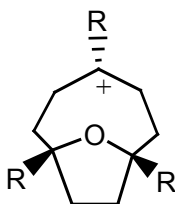
(TIO) and 1,4,7-tri-tert-butyloxatriquinane (TTO), the structures of which are shown in **Figure 1(a)**. As at the time of conducting this study, no single theoretical work on NSR of oxatriquinane derivatives has been reported. The only experimental investigation conducted on NSR of TMO, an example of OTQ derivatives was by the same group, Mascal *et al.* [6,7]. And since the reaction was reportedly carried out in chloroform and methanol, the effect of solvent media from this experimental report leaves room for an ambiguous or erroneous mechanistic interpretation due to the possible prevailing effect of transport phenomena (diffusion) and solvation. In many respect, the gas phase where single collision events are more probable provides an ideal environment for studying elementary chemical reactions. It is hence of mechanistic interest to investigate the possibility of the 2 pathways (S_N1 and S_N2) in gaseous medium without the interference from surrounding solvent molecules. In this way, the intrinsic behavior of the reaction may be studied and the role of solvent may be comparatively better deduced, considering the experimental results of Mascal and co-workers indicated above.

The carbon atoms at 1,4, and 7 positions are all tertiary carbons **Figures 1(a)**, and nucleophilic attack on these carbon atoms should be preceded by heterolytic fission of one of the 3 C-O bonds to produce a sufficiently stable S_N1 bicyclic carbocation **Figures 1(b)**. The oxatriquinane derivatives will undergo NSR through S_N1 mechanism if the carbocations **Figures 1(b)** exist with sufficient stability. On the other hand, the heterolytic fission of the C-O bond **Figures 1(a)** could be accompanied by the formation of a new bond between the incoming nucleophile and the carbon simultaneously as the C-O bond is breaking. This is S_N2 mechanism. But if the 2 structures are in equilibrium, as shown in **Figure 1(c)**, such that their energy difference is small, both S_N1 and S_N2 mechanisms are possible. This paper therefore reports on the theoretical evidences for these possibilities and the borderline conditions between the 2 reaction pathways (S_N1 and S_N2).

(a)



(b)



(c)

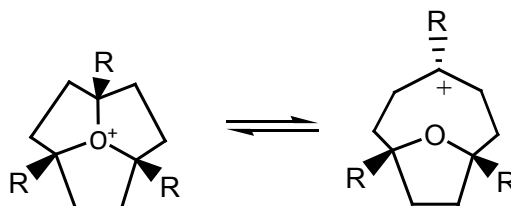


Figure 1 (a) Chemical structures of the studied molecules: oxatriquinane (OTQ), 1,4,7-trimethyloxatriquinane (TMO), 1,4,7-triethyloxatriquinane (TEO), 1,4,7-tri-iso-propyloxatriquinane (TIO) and 1,4,7-tri-tert-butyloxatriquinane (TTO). (b) bicyclic carbocation. (c) oxatriquinane derivative in equilibrium with its bicyclic carbocation (BC).

Computational details and methods of calculation

OTQ is the smallest member of the oxatriquinane series in which the 1,4,7-positions are substituted with hydrogen atoms. Therefore, the effect of the alkyl substituent groups was determined relative to OTQ. Azide ion (N₃⁻) was selected for this study because the theoretical studies on their reactions with OTQ and the other alkyl derivatives have not been done, while there is availability of experimental data of some azide-ion-OTQ dyads [6,7]. All calculations were performed with Spartan 10 package [8]. The oxatriquinane models (with and without alkyl substituents) were optimized using the B3LYP correlation functional [9,10] with 6-31+G* basis set, and without imposing any symmetry constraints [2,7]. The adopted method has been successfully employed by other investigators to study nucleophilic substitution reactions [11,13]. This model had produced results that support experimental findings in the S_N2 reaction of styrene oxide and amines [11]. It has also been used to compute energetics of transition state structures produced in the S_N2 reactions between alkylammonium ions and anionic nucleophile [12]. Even though the 6-31+G* basis set is small, it has been found to produce geometrical and thermochemical data comparable to those from experimental findings [13,14]. The model satisfies a common objective of most computational studies, which is to predict acceptable geometry and energetic parameters at moderate computational cost [15]. The transition state (TS) structure was determined by performing energy profile calculations [8,15]. The stationary points corresponding to the local maxima of an energy profile calculation were selected as the initial guesses of the TS structures, which were then subjected to full transition state optimization [8,15]. The optimized TS structure was confirmed by vibrational frequency calculation [8,15]. All calculations including the single-point (SP) energy calculation to determine the kinetics and the thermodynamics of the systems, were done at the same level of theory (B3LYP/6-31+G*). Zero-point energies (ZPE) were not included in the determination of the thermochemical data.

The activation energies (ΔE^\ddagger) of the reactions were calculated using Eq. (1) [7];

$$\Delta E^\ddagger = E_{\text{TS}} - E_{\text{reactant 1}} - E_{\text{reactant 2}} \quad (1)$$

where E_{TS} is the total energy of the transition state. $E_{\text{reactant 1}}$ and $E_{\text{reactant 2}}$ are the total energies of reactants 1 and 2 respectively.

It should be noted that reactant 1 is the ²G₁ conformer (electrophile) of the respective derivative, while reactant 2 is the azide ion (nucleophile).

The reaction rate constants (k_{rxn}) are related to Gibbs energies of activation by Eq. (2) [7,16];

$$k_{\text{rxn}} = (k_B T/h) \exp(-\Delta G^\ddagger/RT) \quad (2)$$

where k_B and h are the Boltzmann and Planck constants respectively, T is the temperature in Kelvin, ΔG^\ddagger is the Gibbs energy of activation and R is the molar gas constant.

In Eq. (2), concentration, temperature and pressure are assumed to be 1 M, 298.15 K and 1 atm respectively.

The free energy of activation can be expressed as Eq. (3);

$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger \quad (3)$$

where ΔH^\ddagger and ΔS^\ddagger are the enthalpy and entropy of activation respectively. It is worthy of note that the enthalpy of activation (ΔH^\ddagger) can be related to the activation energy (ΔE^\ddagger) by Eq. (4) [16];

$$\Delta H^\ddagger = \Delta E^\ddagger - (1 - \Delta n)RT \quad (4)$$

Putting Eq. (4) into (3), and the resulting equation into Eq. (2), gives Eq. (5);

$$k_{\text{rxn}} = (k_B T/h) \exp(-\Delta E^\ddagger/RT) \exp(1 - \Delta n) \exp(\Delta S^\ddagger/R) \quad (5)$$

For the reactions under study, it was assumed that the entropy contribution to the Gibbs energy of activation is small, and as such, ΔS^\ddagger can be neglected, thus reducing Eqs. (5) and (6);

$$k_{\text{rxn}} = (k_B T/h) \exp(1 - \Delta n) \exp(-\Delta E^\ddagger/RT) \quad (6)$$

where Δn is the change in molecularity on going from reactant(s) to transition state (TS). For unimolecular reactions such as S_N1, $\Delta n = 0$, and Eqs. (6) and (7);

$$k_{\text{rxn}} = e(k_B T/h) \exp(-\Delta E^\ddagger/RT) \quad (7)$$

Similarly, for the bimolecular reactions such as S_N2, $\Delta n = -1$, and Eq. (6) again becomes Eq. (8);

$$k_{\text{rxn}} = e^2(k_B T/h) \exp(-\Delta E^\ddagger/RT) \quad (8)$$

Eqs. (7) and (8) were used to compute the rate constants for the S_N1 and S_N2 mechanisms respectively.

For the S_N1 mechanism, formation of the bicyclic carbocation (BC) is the rate-determining step. Thus, the stability of the carbonium ion was quantified using Eq. (9);

$$\Delta E_{\text{carb}} = E_{\text{carbonium}} - E_{2G_1} \quad (9)$$

where ΔE_{carb} is the difference in energy of the ²G₁ conformation (E_{2G_1}) and energy of the BC ($E_{\text{carbonium}}$) of a particular derivative. ΔE_{carb} has been employed in Eq. (7) to replace ΔE^\ddagger , because the formation of the carbonium ion is the rate-determining step.

Results and discussion

On the basis of the previous experimental results and proposed mechanisms (S_N1 and S_N2) [6], we carried out DFT calculations to provide insight into the details of the reactions between the nucleophilic azide ion and the electrophilic oxatriquinane derivatives. The calculations were carried out using 2 models (as the starting geometry), G₃ and ²G₁ conformations **Figures 2**, for each of the derivatives (except for TTO as would be seen later in this paper). The G₃ conformation is one with all substituent groups at 1,4,7-positions pointing into the plane of the paper. It was originally proposed by Mascal *et al.* [6,7] and Gunbas *et al.* [17,18]. The ²G₁ is one in which only 2 of the 3 substituent groups at 1,4,7-positions are pointing into the plane of the paper, while the remaining one points outward (in the opposite direction). Our calculated results show that G₃ is more stable than ²G₁ **Table 1**. It was observed that the ease of conversion decreases generally from OTQ to TTO as shown by the values of isomerisation energy (ΔE_{isom}) in **Table 1**. However, the effect of the type of substituents is not indicated by the fuzzy nature of these values. Geometry optimization using the G₃ conformations however, gave reactants, product and proposed transition-state molecule that were distorted, and the vibrational frequency calculation on the activated molecule yielded no imaginary frequency. Thus, it became clear that G₃ was not going to give genuine transition states [15], unlike the ²G₁, whose reaction with azide ion appeared more feasible. Hence, the ²G₁ conformation was used as a better alternative to the known G₃ conformation.

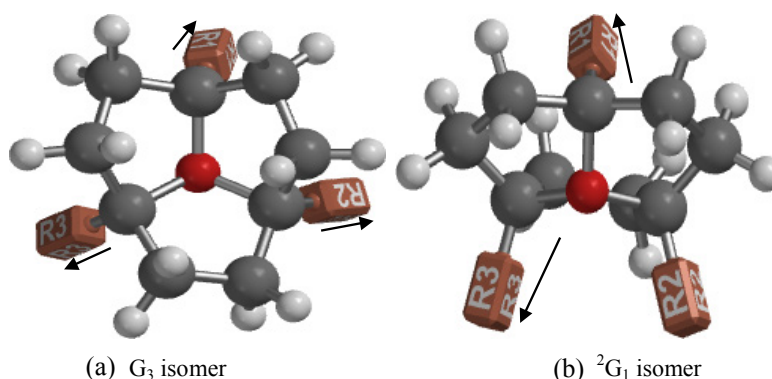


Figure 2 Geometrical isomers of oxatriquinanes, R1, R2 and R3 are alkyl substituent groups. R1, R2 and R3 are into the paper in the G₃, while only R1 and R3 are pointing into the plane of the paper in ²G₁, R2 is pointing out of the paper.

Table 1 Comparison between some reactivity parameters of G₃ and ²G₁ configurations.

Reactant	($E_{\text{HOMO(azide ion)}} - E_{\text{LUMO(reactant)}}$) (eV)	E (k.cal.mol ⁻¹)	ΔE_{isom} (k.cal.mol ⁻¹) from G ₃ to ² G ₁
OTQ: G ₃	3.81	-266180	
² G ₁	1.44	-266168	+12.0
TMO: G ₃	1.17	-339675	
² G ₁	0.65	-339649	+26.0
TEO: G ₃	1.02	-413152	
² G ₁	-1.83	-413127	+25.0
TIO: G ₃	1.12	-486608	
² G ₁	0.94	-486590	+18.0
TTO: G ₃	1.03	-560070	+12.0*
*BC	2.86	-560058	

*TTO transformed from G₃ directly to the bicyclic cationic structure. It has no ²G₁ (BC =bicyclic carbocation). E = the total energy of molecule (corresponding to either E_{G_3} or E_{2G_1} as the case may be) and $\Delta E_{\text{isom}} = E_{2G_1} - E_{G_3}$ (isomerisation energy from G₃ to ²G₁).

The reactivities of both conformations were compared based on the energy gap (**Figures 3**) between the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of the nucleophilic ion (azide ion) and the electrophiles (OTQ and derivatives) respectively. The measured HOMO-LUMO gaps, with the exception of TTO, show that the G₃ conformation is less reactive than the corresponding ²G₁. The exceptional case of the TTO can be attributed to the direct transformation from the G₃ conformation to the bicyclic carbocation without passing through the intermediate ²G₁ phase, hence, there is no ²G₁ conformer for TTO.

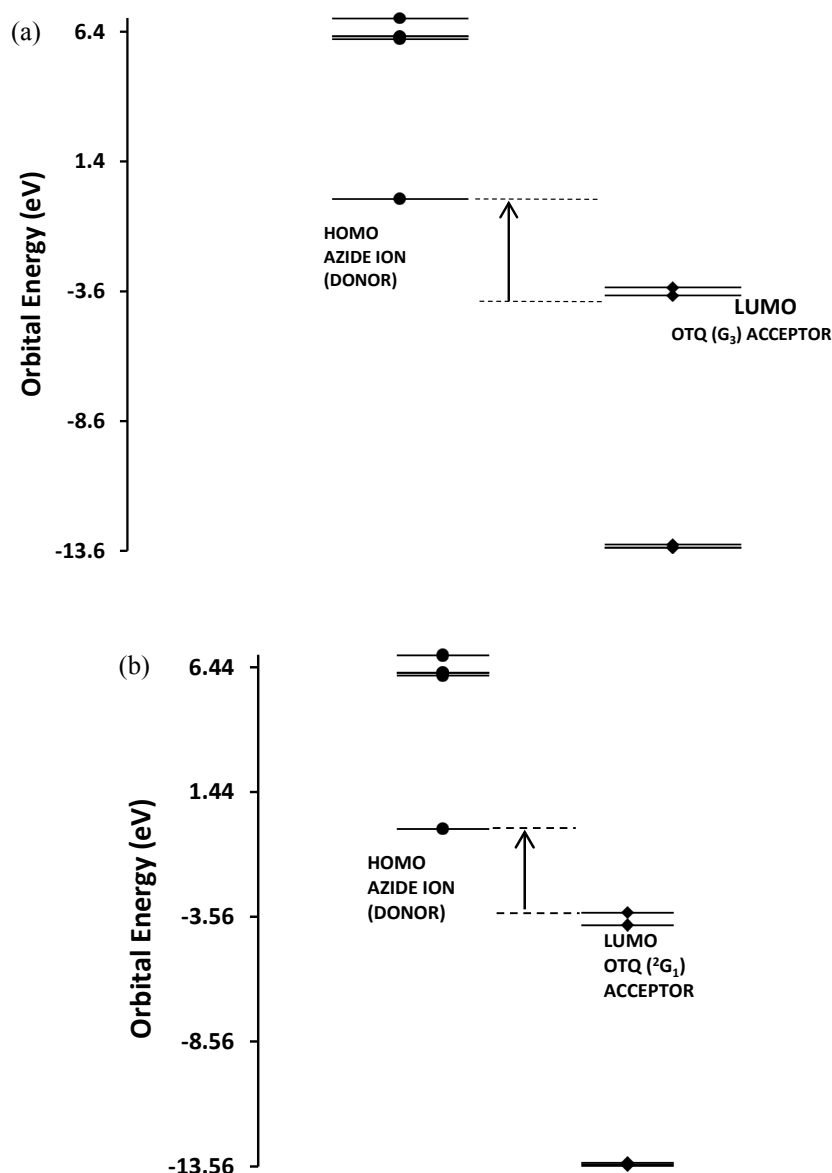


Figure 3 (a) Energy gap between the HOMO of azide ion and the LUMO of G_3 isomer of OTQ. (b) Energy gap between the HOMO of azide ion and the LUMO of 2G_1 isomer of OTQ.

The calculated bond lengths for G_3 OTQ and G_3 TMO are in good agreement with literature values as determined by X-ray studies [17,18], confirming that our method of calculation is suitable and the results therefrom are reliable. The bond lengths after optimization of the G_3 conformation are approximately equal in all the studied derivatives **Table 2**. These are shown by the difference between C_7 -O and the average of C_1 -O and C_4 -O bond lengths which are generally not following any particular trend and are equally negligible (since the values of the difference are less than the Bohr radius, which is 0.529 Å). However, upon optimizing the 2G_1 conformation, only 2 of the bonds for each derivative have approximately equal lengths, **Table 2**. The carbon-oxygen bond at position 7 (C_7 -O) was shown to have significantly longer values compared to C_1 -O and C_4 -O in 2G_1 of OTQ, TMO, TEO and TIO's

C₇-O bond being about the longest in these groups. This is expected for ²G₁ because of its lower symmetry properties relative to G₃, and the degree of bulkiness of the substituent groups. It is important to note that the estimated difference between C₇-O and the average of C₁-O and C₄-O bond lengths increases from OTQ to TTO (**Table 2**), suggesting increasing preference of the derivatives to react by S_N1 mechanism as the size of substituents increase.

Table 2 The lengths of the 3 C-O Bonds in the G₃ and ²G₁ isomers.

Reactant	G ₃ / Å	² G ₁ / Å	G ₃ / Å	² G ₁ / Å
			{C ₇ -O - [(C ₁ -O) + (C ₄ -O)]/2}	{C ₇ -O - [(C ₁ -O) + (C ₄ -O)]/2}
OTQ	C ₁ -O: 1.524	C ₁ -O: 1.497	0.029	0.018
	C ₄ -O: 1.515	C ₄ -O: 1.499		
	C ₇ -O: 1.548	C ₇ -O: 1.516		
TMO	C ₁ -O: 1.551	C ₁ -O: 1.500	0.002	0.067
	C ₄ -O: 1.551	C ₄ -O: 1.500		
	C ₇ -O: 1.553	C ₇ -O: 1.567		
TEO	C ₁ -O: 1.553	C ₁ -O: 1.503	0.003	0.073
	C ₄ -O: 1.552	C ₄ -O: 1.504		
	C ₇ -O: 1.555	C ₇ -O: 1.576		
TIO	C ₁ -O: 1.575	C ₁ -O: 1.490	0.014	0.164
	C ₄ -O: 1.589	C ₄ -O: 1.497		
	C ₇ -O: 1.596	C ₇ -O: 1.657		
*TTO	C ₁ -O: 1.615	C ₁ -O: 1.448	0.006	1.765
	C ₄ -O: 1.620	C ₄ -O: 1.443		
		*C ₇ -O: 3.210		
	C ₇ -O: 1.623			

*value is more than twice that of C₁-O or C₄-O bond length showing the absence of the C₇-O bond in TTO.

Attempt to optimize (with and without imposing any symmetry constraints) the bicyclic cationic structures of OTQ yielded no minimum energy species or stationary points of any description, as the oxygen and α-carbon in each case simply re-unite to give back the starting geometry. However, a minimum energy structure for TMO was obtained, which differ from the result reported previously by Mascal *et al.*, where they found no stationary point for the BC of TMO [6]. This contradiction has been attributed to the non-inclusion of the symmetry constraints in our calculation, since similar result to that obtained in this reference [6] was observed for TMO, when symmetry constraints were imposed. It may therefore be presumed that Mascal *et al.* might have carried out their calculations under the constraints of symmetry. However in this work, all geometry optimizations were done without imposing symmetry constraints. It is believed that the optimization process predicts a geometry that is closest to the true structure when it is done without imposing symmetry constraints [2,7].

Absence of minimum energy geometry for the BC structure of OTQ, with and without symmetry constraints, is due to the low stability of the resulting BC, since the surrounding methylene groups and the one hydrogen atom around the α-carbon cannot provide the required stabilization energy, **Figure 1(a)**. But like the TMO, bicyclic carbocations were obtained for TEO, TIO and TTO without applying any symmetry constraints. While TMO, TEO and TIO gave minimum energy structures for both ²G₁ and BC conformations, TTO gave only the BC directly as shown in **Figure 4(a)**, i.e. without passing through the

intermediate phase 2G_1 . This behavior was observed only for the TTO, and with the calculated value of C₇-O bond length being more than twice the value of each of C₁-O and C₄-O. Thus, one may conclude that the C₇-O bond is absent in TTO (**Table 2**).

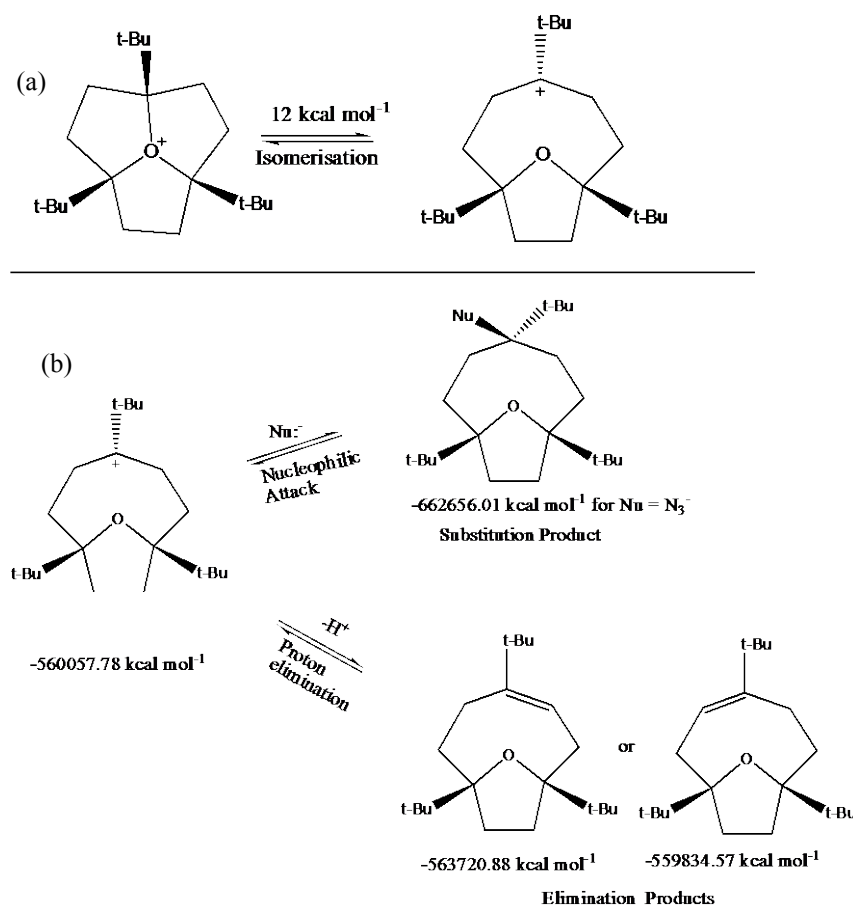


Figure 4 (a) Geometrical isomerisation between G_3 and the bicyclic carbocation of TTO, (b) Formation of substitution and elimination products from the 2G_1 isomer of TTO.

It could thus be argued based on the above that the stability of the bicyclic species increases with increasing size of the substituent group on the α -carbon, with the tert-butyl-substituted derivative having the most remarkably stable BC structure. This argument can be further proven with the ΔE_{carb} values (shown in **Table 3**) which were obtained using Eq. (9). The values are high for the bicyclic carbocations of TMO and TEO, hence, the reason for their extremely low BC stability. In contrast, they are low in TIO and TTO with values of -7.0 and $-56.0 \times 10^4 \text{ k.cal.mol}^{-1}$ (if E_{2G_1} is arbitrarily assigned 0 k.cal.mol^{-1} for TTO), respectively.

Table 3 Thermodynamic and kinetic data for the gas phase reactions of OTQ, TMO, TEO, TIO and TTO with azide ion.

Reactant	ΔE_{isom} (k.cal.mol ⁻¹)	S _N 1			S _N 2	
		ΔE^\ddagger (k.cal.mol ⁻¹)	ΔE_{carb} (k.cal.mol ⁻¹)	k_1 (s ⁻¹)	ΔE^\ddagger (k.cal.mol ⁻¹)	k_2 (dm ³ .mol ⁻¹ .s ⁻¹)
*OTQ	+12.0	+54.2	+26.6 × 10 ⁴	0	+6.23	1.31 × 10 ⁹
TMO	+26.0	+56.0	+53.0	2.37 × 10 ⁻²⁶	+11.0	3.96 × 10 ⁵
TEO	+25.0	+53.0	+53.0	2.37 × 10 ⁻²⁶	+12.4	3.73 × 10 ⁴
*TIO	+18.0	+48.7 × 10 ⁴	-7.0	2.29 × 10 ¹⁸	+48.7 × 10 ⁴	0
*TTO	-	-	-56.0 × 10 ⁴	Very large	-	-

*In these reactants $E_{\text{carbonium}}$ (i.e. for OTQ), E_{TS} (i.e. for TIO) and E_{2G_1} (i.e. for TTO) have been arbitrarily assigned the value of 0 k.cal.mol⁻¹ accordingly. E_{TS} is the energy of the transition complex.

As expected, the remarkably low ΔE_{carb} value for TTO is responsible for its high stability, and consequently its ability to undergo substitution reaction via S_N1 mechanism. In the same vein, the considerably low stability observed for the BC of TIO also makes it possible for it to undergo substitution reactions via S_N1 mechanism. The unsubstituted OTQ has no BC structure, and with the assumption of a 0 k.cal.mol⁻¹ $E_{\text{carbonium}}$ value, an extremely high ΔE_{carb} value (+26.6 × 10⁴ k.cal.mol⁻¹) was obtained, thus, justifying why OTQ does not undergo substitution reaction via S_N1 mechanism, therefore the reason for its 0 s⁻¹ k_1 value, **Table 3**. The energy profiles for S_N1 and S_N2 reactions of TMO and TIO as representatives are presented in **Figures 4** and **5**, where the relative positions of the equilibrium-energy states can be clearly seen. From the results in **Table 3**, the formation of the bicyclic carbocation is the rate-determining step for the S_N1 mechanism. This leading to a conclusion that the rate of formation of the nucleophilic-substituted complexes via S_N1 mechanism depends strongly on the stability of the intermediate bicyclic carbocation produced.

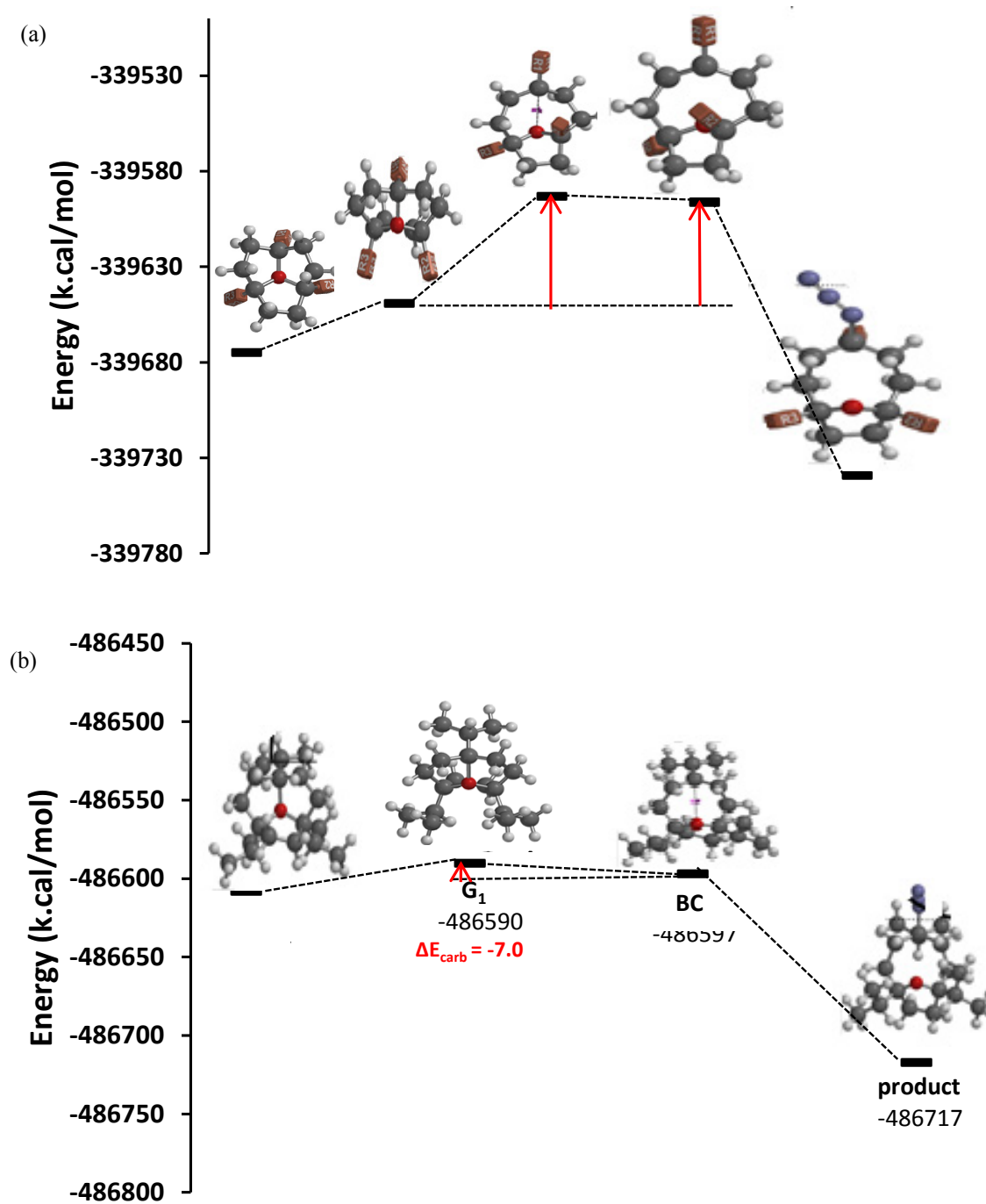


Figure 4 Energy profile calculated for the S_N1 pathway of the reaction of (a) TMO (b) TIO with azide ion as representatives. Note that TS and BC stand for transition state and bicyclic carbocation respectively, and that the TIO profile B, shows no transition state.

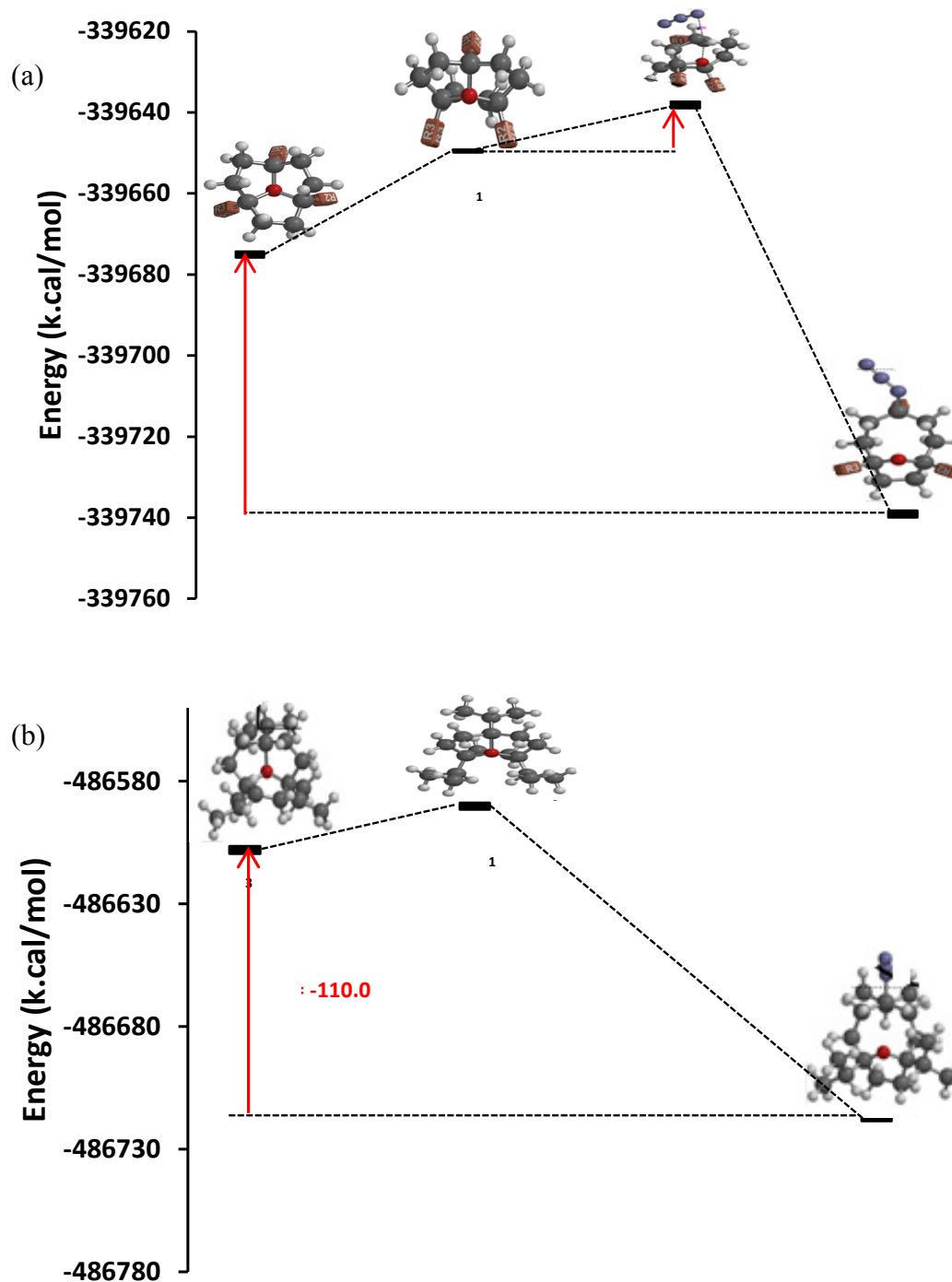


Figure 5 Energy profile calculated for the S_N2 pathway of the reaction of (a) TMO (b) TIO with azide ion as representatives. Note that the TIO profile B, shows no transition state.

The calculated k_2 presented in **Table 3** revealed that the nucleophilic substitutions of OTQ, TMO and TEO, with azide ion, followed S_N2 mechanism with k_2 (OTQ) > k_2 (TMO) > k_2 (TEO), which is in accord with the previous findings [6,15]. Nucleophilic substitution via S_N2 mechanism is not favored in TIO and TTO as no transition complexes consisting of the reactant and the nucleophile could be formed (**Table 3**). The absence of TS structures in TIO and TTO may be reasonably attributed to steric hindrance. The steric effect prevents the nucleophile from reaching the target position on the reactant.

An important measurable parameter to predict the reaction centers is the electrostatic charges (ECs) shown in **Table 4**. The carbon atom with the highest electrostatic charge (EC) is likely to be attacked among the 3 substituted carbon atoms. Our calculation predicts C₇ for all the reactants except TMO which has C₁ or C₄ (**Table 4**). The ²G₁ conformer (except for TTO where BC was employed) of each derivative was employed in the ECs determination.

Table 4 Electrostatic charges on the reactive carbon sites of the ²G₁ isomers reactants.

Reactant	C ₁	C ₄	C ₇
OTQ	0.137	0.184	0.203
TMO	0.493	0.493	0.435
TEO	0.462	0.527	0.529
TIO	0.233	0.268	0.434
*TTO	0.438	0.513	0.518

*The conformation employed is BC

The changes in the geometrical parameters of the participating species before the reaction (reactant) and at the transition states can be used as another source of evidence to decipher the prevailing reaction mechanism. **Tables 5** and **6** present the geometrical parameters such as the bond lengths and bond angles around the reactive centers. For the proposed S_N1 mechanism, there is an elongation of the carbon-oxygen (C-O) bond of the reactive carbon atom in all the derivatives at the transition states (except for TIO and TTO because they are without TS structures). This result is expected since this bond has to break to pave way for the formation of the carbocation. Similarly, the bond angles around the reactive carbon atoms (for examples C₆-C₇-C₈ for OTQ and TEO, and C₂-C₁-C₉ or C₃-C₄-C₅ for TMO) increase at the transition state in OTQ, TMO and TEO, while a decrease in the C₆-C₇-O (C₁ or C₄ in place of C₇ for TMO) bond angles was observed comparing the reactant to the transition state, in all the 3 derivatives, **Table 5**. For the S_N2 mechanism (**Table 6**), the nitrogen-carbon bond length (N-C) of the TS structure is shorter than that of the reactants, while the carbon-oxygen (C-O) bond length is longer at the TS than that of the reactant and with a simultaneous increase in the N-C-O bond angles as expected, **Table 6**.

Table 5 Geometrical parameters for the S_N1 reactions of OTQ, TMO and TEO.

Geometrical parameter	OTQ		TMO		TEO	
	Reactant complex	Transition state	Reactant complex	Transition state	Reactant complex	Transition state
C ₇ -O	1.499 Å	2.741 Å	^a 1.500 Å	^a 2.820 Å	1.509 Å	2.665 Å
C ₆ -C ₇ -C ₈	107°	128°	^b 108°	^b 132°	109°	130°
C ₆ -C ₇ -O	103°	69°	101°	74°	100°	67°

^aThe carbon atom involved here is C₁ or C₄ and not C₇. ^bThe Carbon atoms involved here are C₂-C₁-C₉ or C₃-C₄-C₅.

Table 6 Geometrical parameters for the S_N2 Reactions of OTQ, TMO and TEO with azide ion.

Geometrical parameter	OTQ		^a TMO		TEO	
	Reactant	Transition state	Reactant	Transition state	Reactant	Transition state
N ₁ -C ₇	4.152 Å	2.511 Å	3.384 Å	2.436 Å	3.760 Å	2.507 Å
C ₇ -O	1.534 Å	1.800 Å	1.526 Å	1.866 Å	1.523 Å	1.830 Å
N ₁ -C ₇ -O	98°	164°	159°	172°	151°	172°

^aThe carbon atom involved here is C₁ or C₄ and not C₇.

All the above put together indicate that the prevailing mechanism for the NSR of azide ion with OTQ, TMO and TEO is S_N2, while TIO and TTO undergo the same reaction but was predominantly via the S_N1 mechanism, therefore, the elimination products provided in **Figure 4(b)** can only possibly be produced with TIO or TTO derivative.

Conclusions

Geometry optimization and determination of transition state properties of the conformers corresponding to each molecule (in the presence of N₃⁻) provided theoretical evidences on the possible reaction mechanisms. Only the G₃ conformer existed for TTO as ²G₁ was found to be unstable. The reactions of OTQ, TMO and TEO with azide ion followed S_N2 pathway, with S_N1 mechanism found to be completely lacking. For TIO (in the presence of azide ion), only the presence of S_N1 mechanism could be proved without any evidence of transition state (TS), however, a ²G₁ conformation was obtained for this derivative. TTO surprisingly, showed marked evidence of S_N1 mechanism with no TS and ²G₁ conformer.

The calculated k_2 for OTQ, TMO and TEO, with azide ion, revealed that k_2 (OTQ) > k_2 (TMO) > k_2 (TEO), and are in agreement with the experimental results of Mascal and co-workers. In conclusion, our calculation revealed that nucleophilic substitution via S_N2 mechanism is not favored in TIO and TTO as no transition complexes consisting of the reactant and the nucleophile could be formed, thus suggesting that not all OTQ derivatives can undergo NSR via S_N2 mechanism. OTQ derivatives with substituents of more than 2 carbon atoms (heavily substituted), like TIO and TTO were shown to undergo NSR by S_N1, and this was attributed to stabilization of their bicyclic carbocations by the bulky substituent groups on the α -carbon atoms.

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