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Theoretical investigations of solvent effects on nucleophilic substitution reactions of selected alkyl-substituted oxatriquinane derivatives with azide ion

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Abstract
A comprehensive density functional theory (DFT) study of solvent effects on the nucleophilic substitution reaction between azide ion and five oxatriquinane analogues, 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), have been carried out. This was to predict possible changes in reaction mechanism and spontaneity due to solvents. The effects of solventson the energy of conversion from the non-reactive G_3 to the reactive $^2G_1$ conformation of the oxatriquinanes were insignificant. Meanwhile, the activation energies for the S_N2 reactions of OTQ, TMO, and TEO were raised, while those ofS_N1 was lowered by the solvents. However, none of the solvents investigated could change the reaction mechanism to S_N1 because the reduction in S_N1 activation energies was insufficient to override the S_N2 pathway. Reaction feasibility generally decreased with increasing solvent polarity. Reactions of TIO and TTO appeared barrierless, and the products of the reactions were generally more stable than those of OTQ, TMO, and TEO in all the solvents on considered. It could be concluded that the preferred mechanism for the reactions of OTQ, TMO, and TEO is S_N2 while that of TIO and TTO is S_N1, and is suspected to be diffusion-controlled. The polar effect of the alkyl substituents appeared insignificant; hence, their effects on the reactions were concluded to be of steric origin.

Keywords: Oxatriquinanes, DFT, S_N2 mechanism, Solvent effect, Steric effect.

INTRODUCTION
Theoretical investigations of the mechanism of azide ion (N_3^-) attack on the tertiary electrophilic carbons (3^0) of a set of alkyl-substituted oxatriquinane derivatives in the gas phase, using density functional theory (DFT) calculations were reported recently by our

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group (Wahab *et al*., 2018). The studied derivatives include 1,4,7-trimethyloxatriquinane (TMO), 1,4,7-triethyloxatriquinane (TEO), 1,4,7-triisopropyloxatriquinane (TIO), 1,4,7-tri-tert-butyloxatriquinane (TTO) and their parent unsubstituted oxatriquinane (OTQ) (Figure 1A). In agreement with experimental evidence from Mascal and co-workers (Mascal *et al*., 2008, 2010), our theoretical kinetic data revealed that the attack of azide ion on TMO and TEO tertiary electrophilic carbon centers followed S_N2 mechanism (Wahab *et al*., 2018), contrary to basic principles of nucleophilic substitution reactions (NSR) which assert that substitution at such center must follow S_N1 mechanism (Mehta and Mehta, 2005; Volhardt and Score, 2007; Wade, 2010; Jones and Fleming, 2010). On the other hand, the attack on TIO and TTO favored the S_N1 pathway and appeared barrierless.

An interesting discovery made for the first time in the study (Wahab *et al*., 2018) was the existence of a second geometrical conformation code named $^2G_1$ in addition to the G_3 conformation proposed by the Mascal group (Mascal *et al*., 2008, 2010, 2012, and 2013) for OTQ derivatives. The difference between the two conformers (Figure 1B), their relative stability, and reactivity with azide ion (in the gas phase) had also been explained in the earlier paper (Wahab *et al*., 2018). The study led to an important conclusion that an alkyl-substituted oxatriquinane compound must first isomerize from the more stable G_3 conformation to the less stable $^2G_1$ conformation before undergoing a nucleophilic substitution reaction (NSR), and the energy of isomerization is equal to the energy difference between the two isomeric forms.

Since the previous study was conducted in the gas phase, and considering the sensitivity of NSR mechanism to reaction solvent (Hamlin *et al*., 2018; Zhao *et al*., 2019), investigating the effects of solvents on the behavior of OTQ derivatives in NSR becomes necessary. This will not only provide adequate insights on the likelihood of change in mechanism and reaction feasibility due to solvent but also provide adequate basis for efficiency modulation and selectivity control in this reaction. A good understanding of solvent effects is necessary for selecting a suitable solvent for a target nucleophilic substitution reaction and preventing unwanted side reactions, which is an essential focus of green chemistry (Zhao *et al*., 2019).
Numerous theoretical studies focusing on the impact of solvents on NSR have been reported (Jorgensen *et al*., 1984 and 1985; Jorgensen and Buckner, 1986; Kuechler and York, 2014; Hamlin *et al*., 2018). Jorgensen and co-workers (Jorgensen *et al*., 1985) in their study of symmetric S_N2 reaction between chloride ion and chloromethane using quantum and statistical mechanical methods observed an increase in activation free energy in aqueous solution.By using polarizable continuum models (PCM) and hybrid quantum mechanical/molecular mechanic (QM/MM) simulations, Brauman and co-workers studied the effects of solvent and substituent groups on the S_N2 reactions of chlorine with alkyl chlorides and chloronitriles (Brauman *et al*., 2004 and 2009).The hydrolysis of benzyl chlorides in protic solvent was reported to proceed via S_N1 mechanism when substituted with a strong electron donating group (Ruff and Farkas, 2007).

While considerable reports on NSR have focused on simple aliphatic substrates as evident from the above literature, studies on nucleophilic substitution reactions of unique substrates such as OTQ derivatives are still scanty in the literature. Since our first gas phase study was reported (Wahab *et al*., 2018), it appears there has been no further reports on this subject, particularly on solvent effects. Therefore, in furtherance to research exposition on the NSR of oxatriquinane compounds, the present study investigated the role of solvents in the reactions between OTQ, TMO, TEO, TIO, and TTO (Figure 1A), and azide ion. It examines the effects of solvents of different polarities on the isomerization energies (ΔE_{isom}), activation

energies ($\Delta E^{\neq}$), and Gibb's free energy changes (ΔG) of the reactions. To the best of our knowledge as at the time of writing this manuscript, this work has not been reported elsewhere.

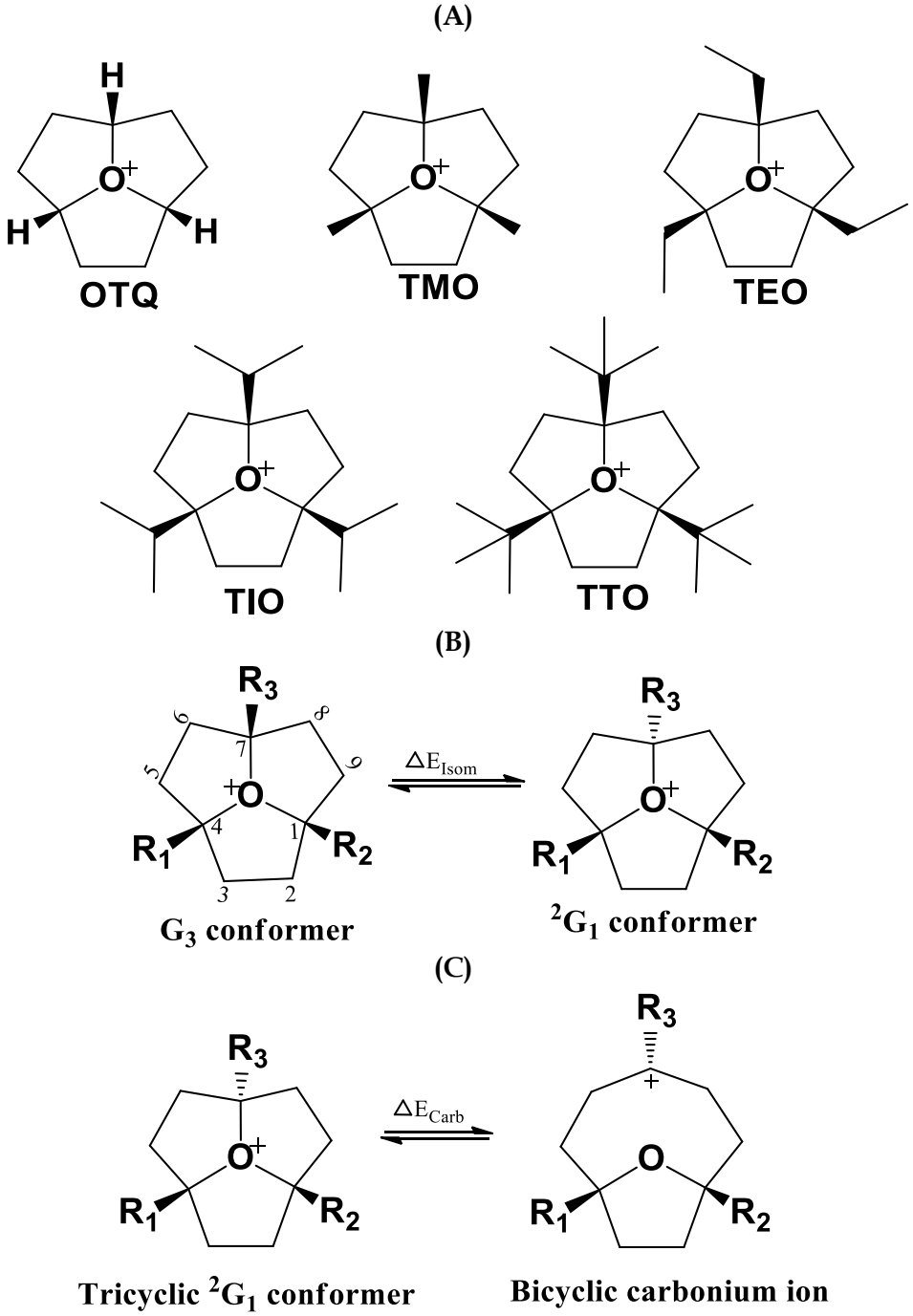


Figure 1: (A) Molecular structures of the studied oxatriquinane derivatives. (B) The geometrical transition of the G_3 conformation to the $^2G_1$ through a change in orientation of R_3. (C) Formation of carbocation by the $^2G_1$ conformer through cleavage of the C_7 – O bond.

Computational details and method of calculation

This study was carried out on a personal computer (PC) using the Spartan 10 computational package (Hehre and Ohlinger, 2011). All calculations were done without symmetry constraints using the B3LYP/6-31+G(d,p) model (Becke, 1993; Lee *et al*., 1988; Truhlar *et al*., 2003). This method has been reported to be efficient for a satisfactory prediction of nucleophilic substitution reaction mechanisms (Lee *et al*., 2003; Kim *et al*., 2009; Mascal *et al*.,

2010). The adopted model has successfully provided adequate theoretical evidence supporting the unusual occurrence of S_N2 reaction at tertiary (3^0) electrophilic carbons (Mascal *et al*., 2010; Wahab *et al*., 2018). It yielded bond lengths for the G_3 structures of some oxatriquinane derivatives in very good agreement with X-ray crystallographic data (Mascal *et al*., 2012 and 2013; Wahab *et al*., 2018). Solvent phase calculation was achieved with the aid of solvation model 8.0 (SM 8.0) implemented in the Spartan program where the solvents were selected in order of increasing dielectric constant (polarity) as: n-hexane (Ɛ = 1.89), chloroform (Ɛ = 4.81), dichloromethane (DCM: Ɛ = 9.08), 1-butanol (Ɛ = 17.80), ethanol (Ɛ = 24.60), acetonitrile (Ɛ = 37.50), dimethylsulfoxide (DMSO: Ɛ = 47.00) and water (Ɛ = 78.54). SM 8.0 model helps to compute solvation free energies for structures held fixed at their gas phase geometries and hence, calculate their total energy in the solvent (Hehre, 2003; Hehre and Ohlinger, 2011).

All stationary point geometries (i.e. reactant complex, transition state (TS) structures, and product complex) of each reaction were first determined in the gas phase through energy profile calculation before being subjected to full optimization in gas and solvent phases. The optimized TS structures were confirmed to have only one negative vibrational frequency while the reactant and product complexes were ascertained by the absence of such frequency. Zero-point energies (ZPEs) were not included in the calculations.
From the calculated free energy of solvation (FES) and the total energy in the gas phase, the energy of each stationary point geometry in each solvent ($E_{solvent}$) was calculated using Eq. 1. Isomerisation energy (ΔE_{isom}), activation energy ($\Delta E^{\neq}$), and free energy change (ΔG) in each medium were calculated using Eq. 2, 3, and 4, respectively (Hehre, 2003; Hehre and Ohlinger, 2011; Wahab et al., 2018),

$$E_{solvent} = E_{gas} + FES \quad (1)$$

$$\Delta E_{isom} = E_{2G1} - E_{G3} \quad (2)$$

$$\Delta E^{\neq} = E_{TS} - (E_{reactant1} + E_{reactant2}) \quad (3)$$

$$\Delta G = \sum G_{product} - \sum G_{reactant} \quad (4)$$

Where $E_{solvent}$ and E_{gas} are the total energies in solvent and gas, respectively. E_{2G1} and E_{G3} are the energies of the $^2G_1$ and G_3 isomeric structures. E_{TS} is the energy of the transition state. $E_{\text{reactant 1}}$ and $E_{\text{reactant 2}}$ are the energies of reactants 1 and 2, respectively. $G_{product}$ and $G_{reactant}$ are Gibb's free energies of the product and the reactant(s), respectively, and G = H – TS, where H and S are the corresponding enthalpies and entropies, and T is the temperature.
Although the SM8.0 model could also be employed for studying the effects of solvents on molecular geometries, the present work is however concerned with the effects on reaction rates and energetics as well as possible changes in the reaction mechanism. Therefore, changes in geometrical parameters such as bond length, bond angle, and dihedral angles due to solvents are not reported in this work.

Reactant 1 is the electrophile i.e. the $^2G_1$ configuration of each derivative while reactant 2 is the nucleophile i.e. the azide ion. Since the nucleophile does not take part in the rate-determining step of the S_N1 mechanism (Finar, 1964; Mehta and Mehta, 2005; Wade, 2010; Jones and Fleming, 2010), Eq. 3 was used without $E_{\text{reactant 2}}$ for estimating the $\Delta E^{\neq}$ of the S_N1 reactions, and the stability of the resulting carbocation was quantified using Eq. 5;

$$\Delta E_{carb} = E_{carbocation} - E_{2G1} \quad (5)$$

where ΔE_{carb} is the difference in the energy of the tricyclic $^2G_1$ conformation (E_{2G1}) and that of the bicyclic carbonium ion ($E_{carbocation}$) of respective derivatives.

RESULTS AND DISCUSSION

Effect of solvents on isomerization energy (ΔE_{isom})

Values of ΔE_{isom} for OTQ, TMO, TEO, and TIO in the solvent phase are compared with their respective gas phase values in Table 1, where the dielectric constant for the gas phase is assigned a value of 1 (i.e. ε_{gas} = 1.00). As evident from the table, changes in ΔE_{isom} due to solvation are generally insignificant, suggesting that both the G_3 and $^2G_1$ conformers of the compounds have comparable stabilities in the solvents. This implies that both conformers possess similar charge magnitude. In the case of TTO, its G_3 conformation isomerized very rapidly, forming directly a highly stable bicyclic carbonium ion (Figure 1C) without passing through the intermediate $^2G_1$ configuration (Wahab *et al.,* 2018). Hence, the absence of ΔE_{isom} data for TTO in Table 1.

The progressive decrease in ΔE_{isom} observed both in gas and solvent phases as substituent size increases from TMO to TIO is due to an increase in steric hindrance especially for the $^2G_1$ conformation. To reduce excess strain, the $^2G_1$ conformer undergoes steric relaxation through elongation of the C_7 – O bond, forming a more stable $^2G_1$ structure (Wahab *et al.*, 2018). The extent of relaxation or elongation in the C_7 – O bond depends on the size of the substituent. The fact that the tert-butyl group is the bulkiest of the substituents explains why the steric relaxation of TTO resulted directly in the formation of a bicyclic carbocation.

Table 1: Predicted isomerization energies for the studied derivatives.

Media	ε	ΔE_{isom} (kcal/mol)				
		OTQ	TMO	TEO	TIO	TTO*
Gas	1.00	11.66	26.17	24.79	17.21	-
Hexane	1.89	11.74	26.03	24.99	17.41	-
Chloroform	4.81	11.80	25.95	25.08	17.53	-
DCM	9.08	11.81	25.90	25.08	17.57	-
Butanol	17.80	11.92	25.85	25.09	17.65	-
Ethanol	24.60	11.92	25.84	25.10	18.05	-
Acetonitrile	37.50	11.87	25.82	25.08	17.65	-
DMSO	47.00	11.98	25.67	25.07	17.33	-
Water	78.54	11.18	25.66	24.85	17.52	-

*No stable $^2G_1$ conformer for TTO

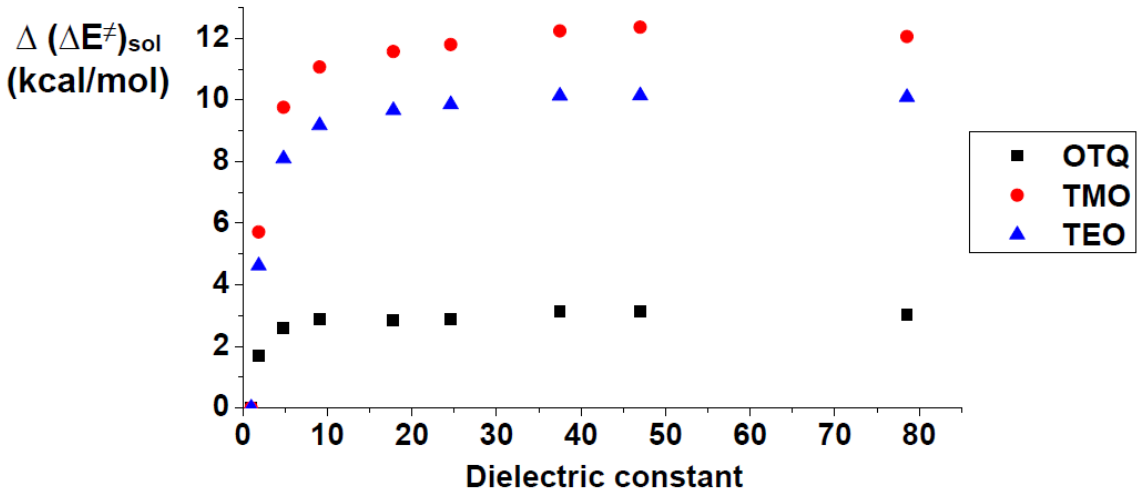
Solvent effect on the energies of activation ($\Delta E^{\neq}$) of the S_N2 and S_N1 pathways

The changes in activation energy for the S_N2 and S_N1 mechanisms as a function of solvent polarity are presented as $\Delta(\Delta E^{\neq})_{Sol}$ in Figure 2 where the $\Delta(\Delta E^{\neq})_{Sol}$ values were calculated by subtracting $\Delta E^{\neq}$ in the gas phase from those in the solvents (Table 2). Figure 2 reveals that the change in activation energy for the S_N2 mechanism increases with increasing solvent polarity while that of S_N1 decreases. Such opposite changes in activation energy can be traced to the relative stability of the reactants and the transition states (TS) of both mechanisms in the solvent phase. Generally, the stability of a molecule in a solvent depends on the degree of solvation experienced in the solvent which in turn depends on the charge magnitude of the molecule which in turn depends on the extent of charge dispersal in the molecule (Finar, 1964). In other words, a less dispersed or more localized charge promotes solvation, while a more dispersed or less localized charge inhibits solvation (Finar, 1964).

In the S_N2 mechanism, the charges of the reactants (i.e. the positive charge of the oxatriquinane derivatives and the negative charge of the azide ion) are more dispersed in the TS structure where the azide ion and the oxygen center are partially bonded to the electrophilic carbon center (Figure 3). Consequently, the reactants are more solvated than the TS and are as a result more stabilized by the solvent, leading to an increase in $\Delta E^{\neq}$. The extent of this increase depends on the dielectric constant of the solvent; the larger the dielectric constant, the more the solvation, the higher the activation energy, and the slower the reaction. This explains why the change in activation energy for the S_N2 mechanism increases with increasing solvent polarity as depicted in Figure 2A. Similar observation had been reported by a previous study (Cramer and Kormos, 2003).However, the effect of solvation on the activation energy appears to be insignificant at a dielectric constant above 40 where the change in activation energy approaches saturation.

The smallest $\Delta(\Delta E^{\neq})_{Sol}$ value obtained in hexane (Figure 2A) suggests that the reactions are faster in hexane than in any other solvent. Since the reactant molecules are ionic, they could separate into a distinct phase by crowding together away from the nonpolar solvent molecules. When this happens, the mean free path becomes smaller, the collision frequency increases producing more effective collisions between the reactant molecules. Consequently, the activation energy becomes lower. However, as the dielectric constant increases, reactant-solvent interaction becomes more appreciable. The mean free path becomes larger and the number of effective collisions decreases thereby raising the activation energy. The slight deviation observed in water for OTQ, TMO, and TEO could be attributed to the extra stability of their transition states in the solvent due to hydrogen bonding.

(A) S_N2 reaction



(B) S_N1 reaction

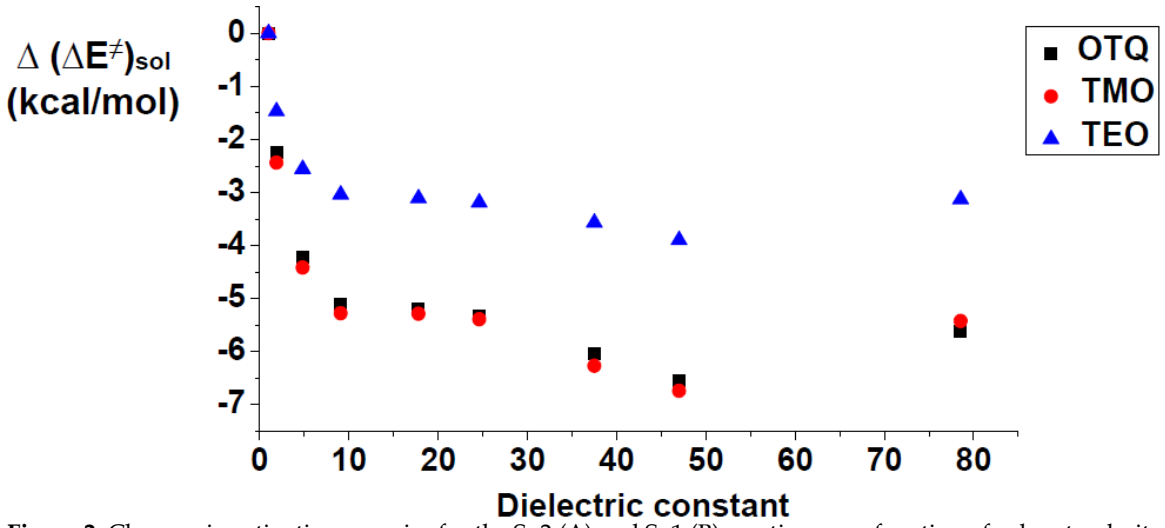


Figure 2: Changes in activation energies for the S_N2 (A) and S_N1 (B) reactions as a function of solvent polarity.

Table 2: Predicted activation energies for S_N2 and S_N1 reaction pathways.

Media	ε	ΔE≠ (kcal/mol)					
		S_N2 mechanism			S_N1 mechanism		
		OTQ	TMO	TEO	OTQ	TMO	TEO
Gas	1.00	6.23	11.36	12.38	54.18	56.29	53.00
Hexane	1.89	7.93	17.07	17.00	51.93	53.85	51.53
Chloroform	4.81	8.81	21.12	20.47	49.96	51.87	50.44
DCM	9.08	9.12	22.43	21.55	49.07	51.01	49.96
Butanol	17.80	9.08	22.93	22.04	48.99	51.00	49.89
Ethanol	24.60	9.13	23.16	22.23	48.85	50.90	49.81
Acetonitrile	37.50	9.35	23.60	22.51	48.13	50.02	49.43
DMSO	47.00	9.36	23.72	22.52	47.64	49.55	49.10
Water	78.54	9.26	23.42	22.47	48.56	50.87	49.87

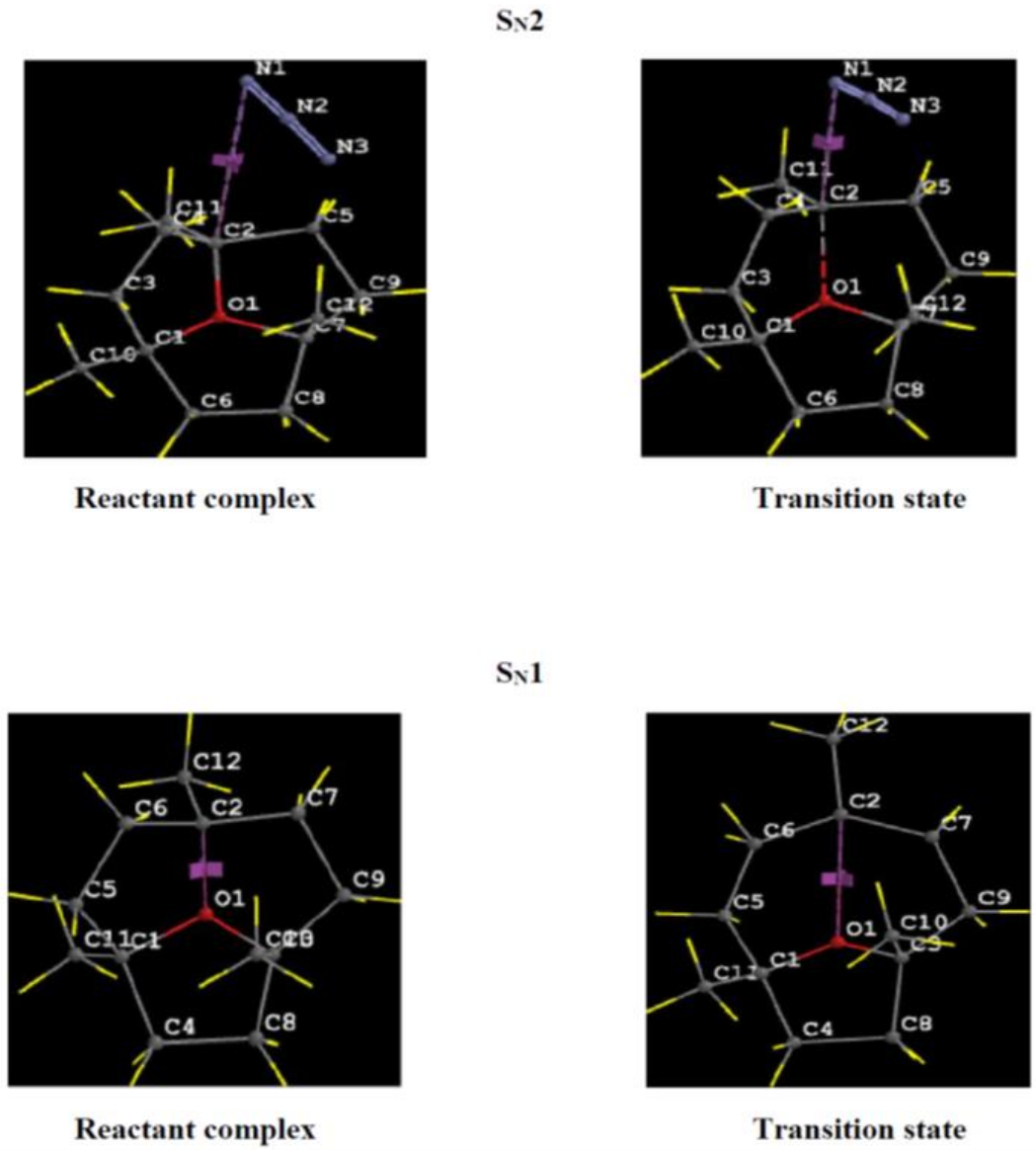


Figure 3: Optimized geometries of the reactant complex and transition state for S_N2 and S_N1 reactions of TMO.

For the S_N1 pathway, the decrease of $\Delta(\Delta E^{\neq})_{Sol}$ with increasing solvent polarity (Figure 2B) is as a result of the increase in stability of the transition state and the carbonium ion. Polar solvents promote the ionization of an S_N1 reactant better than nonpolar ones by stabilizing the transition state and the accompanying carbonium ion (Mehta and Mehta, 2005; Jones and Fleming, 2010). Thus, the transition states and carbonium ions formed from the intramolecular ionization of OTQ, TMO and TEO are stabilized by the solvents to an extent that depends on the solvents polarity. This stabilization seems to be higher than that of their respective $^2G_1$ geometries (Reactant 1) in which the positive charge on the oxygen atom is dispersed over three C–O bonds, unlike the carbonium ion in which the charge is localized on the electrophilic carbon (Figure 1C). The activation energy consequently decreased leading to increased favourability of the S_N1 mechanism. The term intra molecular ionization is used to describe the conversion from the tricyclic $^2G_1$ form to the bicyclic carbonium ion simply by the cleavage of the C_7 – O bond (Figure 1C). The slight deviation observed in water for the reactions of OTQ, TMO, and TEO suggests that their tricyclic $^2G_1$ form gained extra stabilization from water through a cooperative electrostatic and hydrogen bonding interaction between water molecules and the positively charged oxygen center of the

compounds. This increases the energy barrier between the reactants and the TS, hence the observed rise in activation energy in water.

Although, significant lowering in the S_N1 activation energy was obtained in the solvent phase for OTQ, TMO, and TEO (Table 2), this lowering is insufficient to override the more kinetically favored S_N2 pathway. Therefore, the reactions of OTQ, TMO, and TEO with azide ion will proceed via the S_N2 pathway, either in gas or in the presence of a solvent. To achieve a solvent-induced mechanistic change, the activation energy for the S_N1 pathway must be drastically lowered by the solvents than that of the S_N2.

Similar to the previous observations in the gas phase (Wahab *et al*., 2018), the reaction of TIO via the S_N1 pathway in the presence of solvent occurred without an energy barrier (i.e. no transition state was found between its tricyclic $^2G_1$ form and its bicyclic carbocation). This explains the absence of $\Delta E^{\neq}$ value in Table 2, indicating that the bicyclic carbocation of TIO is energetically more stable than its tricyclic $^2G_1$ conformation as confirmed by the ΔE_{Carb} values in Table 3. On the contrary, the positive ΔE_{Carb} values for TMO and TEO suggest that their bicyclic carbocations are energetically less stable than their tricyclic $^2G_1$ conformation, while the absence of ΔE_{Carb} data for OTQ is due to its lack of a stable carbocation structure (Wahab *et al*., 2018). Values of ΔE_{Carb} were obtained by subtracting the energy of the tricyclic $^2G_1$ conformation from that of the bicyclic carbonium ion.

Table 3: Values of ΔE_{carb} for predicting carbocation stability in the S_N1 mechanism.

Media	ε	ΔE_{carb}(kcal/mol)				
		S_N1 mechanism				
		OTQ	TMO	TEO	TIO[a]	TTO[b]
Gas	1.00	-	52.54	52.69	-6.76	-560057.78
Hexane	1.89	-	51.11	51.08	-9.07	-560061.20
Chloroform	4.81	-	49.95	49.87	-10.77	-560063.48
DCM	9.08	-	49.39	49.35	-11.46	-560064.34
Butanol	17.80	-	49.39	49.28	-11.43	-560064.02
Ethanol	24.60	-	49.32	49.20	-11.95	-560064.18
Acetonitrile	37.50	-	49.79	48.77	-12.07	-560064.80
DMSO	47.00	-	48.45	48.44	-11.83	-560064.64
Water	78.54	-	50.87	49.25	-11.08	-560063.04

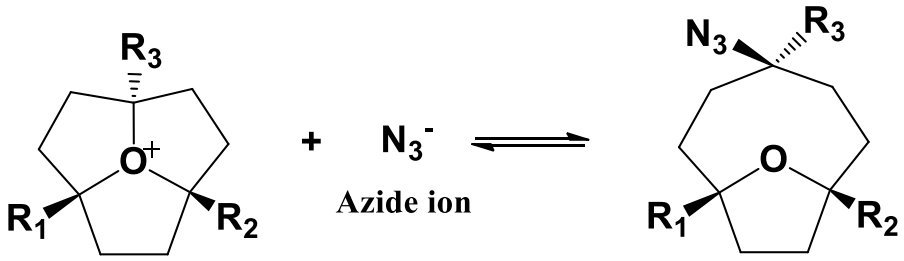
[a]A sufficiently stable $^2G_1$ conformation exists for TIO, but its conversion to the more stable bicyclic carbonium ion occurred without an energy barrier. Hence, the negative ΔE_{Carb} values.

[b]Conversion of TTO to its bicyclic carbonium ion is extremely fast, having no energy barrier and no stable $^2G_1$ conformation. Therefore, the $^2G_1$ is arbitrarily assigned an energy value of zero. Hence, the extremely large negative ΔE_{Carb} values.

Effect of solvents on the free energy change (ΔG)

The Gibb's free energy changes for the reactions of OTQ, TMO, TEO, TIO, and TTO with azide ion are presented as Table 4,and the changes in the free energy change $\Delta(\Delta G)_{Sol}$ as a function of solvent polarity are shown in Figure 4. Values of $\Delta(\Delta G)_{Sol}$ were obtained by subtracting ΔG in the gas phase from ΔG in the solvents. From the figure, the apparent increase in $\Delta(\Delta G)_{Sol}$ with dielectric constant suggests that the products of the reactions (Scheme 1) become increasingly less stable compared to their respective reactants as solvent polarity increases. The degree of solvation experienced by the products decreases with an increase in polarity, while that of the reactants increases in the same direction. This is not unexpected since the reactants are charged while the products are neutral (Scheme 1). The

reactants interacted more strongly with the polar solvents and areas a result more solvated and more stabilized than the products in the solvents. On the other hand, the products are more stable in the nonpolar solvents than the reactants due to the higher nonpolar character of the former (Bruice, 1998). This implies that the reactions are thermodynamically more feasible in nonpolar solvents.



Tricyclic $^2G_1$ conformer **Substituted Product**

Scheme 1: Reaction of the $^2G_1$ conformer of the studied derivatives with azide ion to form a bicyclic substituted product.

Table 4: Calculated free energy changes for the reactions of the derivatives with azide ion.

Media	ε	ΔG (kcal/mol)				
		OTQ	TMO	TEO	TIO	TTO
Gas	1.00	-124.09	-63.92	-53.95	-126.64	-127.65
Hexane	1.89	-66.36	-8.44	-0.14	-73.80	-75.80
Chloroform	4.81	-26.32	30.55	37.99	-35.93	-38.38
DCM	9.08	-13.77	42.64	54.42	-24.14	-26.78
Butanol	17.80	-8.33	48.60	55.83	-18.03	-20.60
Ethanol	24.60	-7.87	49.01	56.21	-17.68	-20.26
Acetonitrile	37.50	-2.73	53.39	60.25	-13.47	-16.23
DMSO	47.00	-2.84	53.30	60.16	-13.40	-16.19
Water	78.54	-4.95	54.85	59.54	-13.72	-16.17

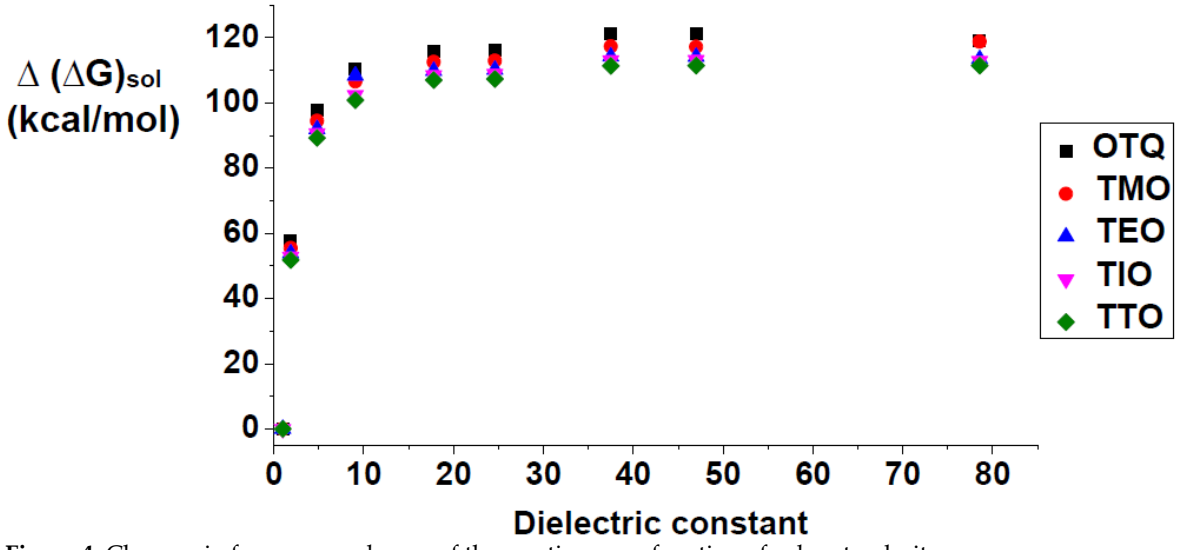


Figure 4: Changes in free energy change of the reactions as a function of solvent polarity.

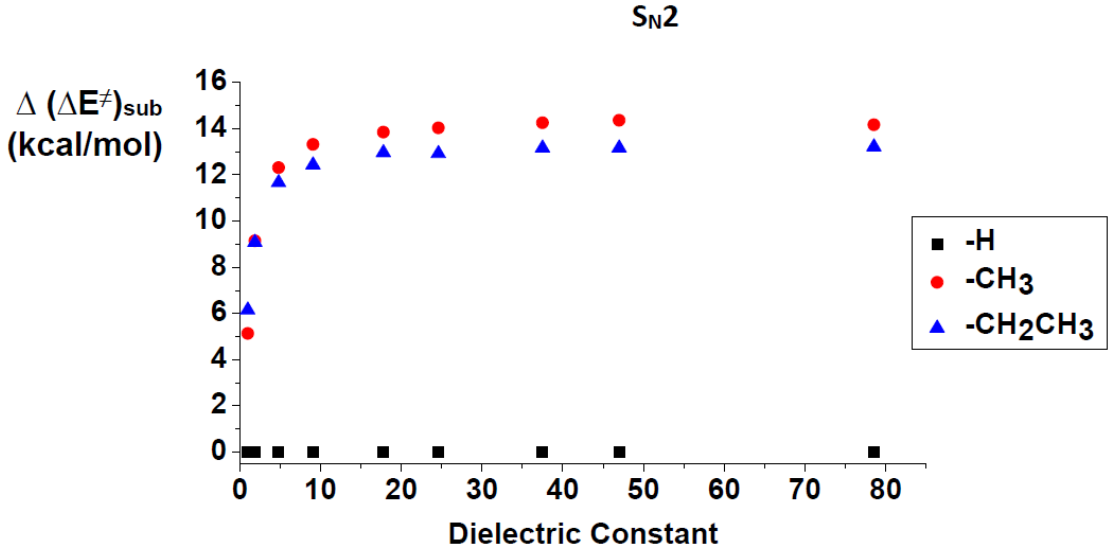
Effects of the alkyl substituents in the solvent phase

The substituent groups considered in this work are electron-donating alkyl groups which include methyl (in TMO), ethyl (in TEO), isopropyl (in TIO), and tert-butyl (in TTO). The effects of these substituents in the solvent phase are discussed relative to the unsubstituted

OTQ in terms of changes in activation energy,$\Delta(\Delta E^{\neq})_{Sub}$ and free energy change, $\Delta(\Delta G)_{Sub}$. Thus, values of $\Delta(\Delta E^{\neq})_{Sub}$ and $\Delta(\Delta G)_{Sub}$ were calculated by subtracting the activation energy ($\Delta E^{\neq}$) and free energy change (ΔG) for the reaction of unsubstituted OTQ from those of substituted OTQ.

Two competing effects of alkyl groups that affect activation energy include the steric effect due to the substituent size and the polar effect due to the electron-donating strength of the substituent. The steric effect increases the activation energy while the polar effect decreases it (Vayner, 2004; Kim et al, 2009). Also, there exists in the solvent phase a non-inductive, non-steric effect of alkyl groups called solute shielding in which a large alkyl group near a polar functional group in a solute prevents the close approach of solvent to the polar group (Kim et al., 2009).

Inspection of Figure 5 reveals that the activation energies for both the S_N2 and S_N1 pathways are raised by methyl and ethyl groups, with the effect of the ethyl group being smaller than that of the methyl group. This increase in activation energy may be ascribed to the steric effect of the substituent groups. However, the ethyl group (being bulkier than the methyl group) offers more hindrance to the approach of solvent molecules, thereby inhibits solvation of the compound leading to lower stability and lower activation energy compared to the methyl group (Table 2, Figure 5). The lowering of S_N1 activation energy obtained with the ethyl group in hexane suggests the prevalence of the electron-donating effect of the ethyl group in this solvent.



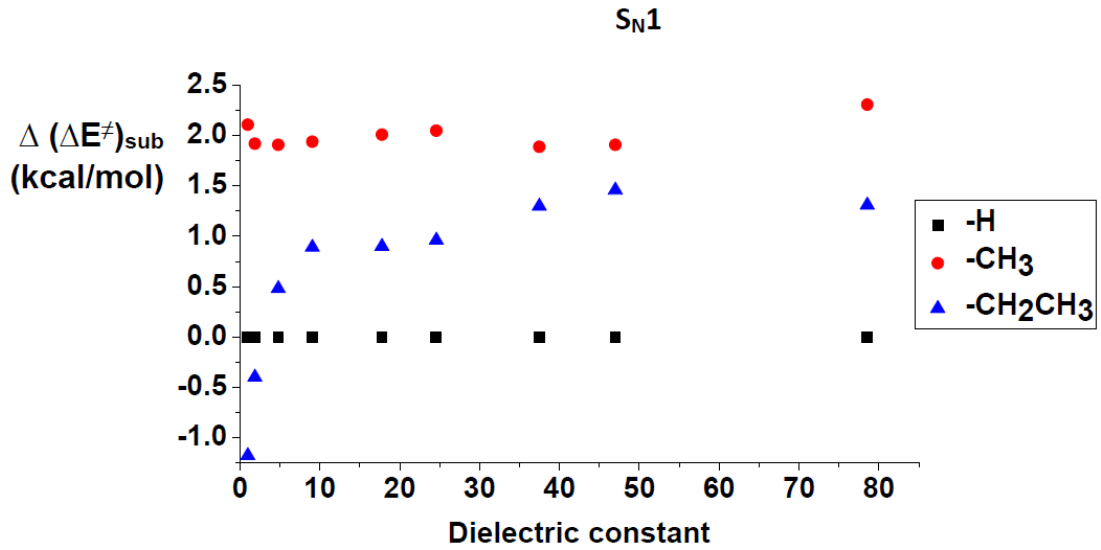


Figure 5: Changes in S_N2 and S_N1 activation energies due to substituent group as a function of solvent polarity.

It is evident from Figure 6 that both methyl and ethyl groups reduce reaction spontaneity because $\Delta(\Delta G)_{Sub} > 0$ with $\Delta(\Delta G)_{methyl}$ being less than $\Delta(\Delta G)_{ethyl}$. This is due to the lower steric effect of methyl and its relatively lower hindrance to solvation.
For the same charge magnitude and same dielectric constant, the ease of solvation depends only on the molecular size. Smaller molecules tend to experience greater solvation than larger ones. This explains why the reactions of the methyl and the ethyl derivatives are less spontaneous compared to the unsubstituted OTQ (Fig. 6, Table 4).

In the cases of isopropyl and tert-butyl groups as in TIO and TTO, respectively, the negative $\Delta(\Delta G)_{Sub}$ values (Figure 6) show that the reaction feasibility is enhanced by these substituent groups. Steric repulsion between these bulky substituents as well as the extreme strain imposed by the substituents causes TIO and TTO to undergo a spontaneous substitution reaction with azide ion (Table 4).

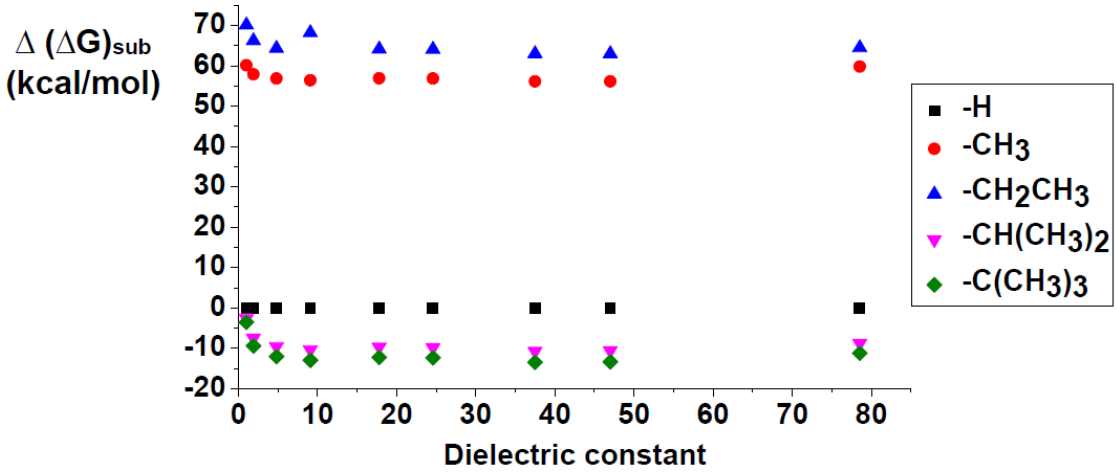


Figure 6: Changes in free energy change of the reactions due to substituent group as a function of solvent polarity.

CONCLUSION

The effects of solvent on the nucleophilic substitution reactions between oxatriquinane alkyl derivatives and azide ion have been investigated. The following conclusions were drawn from the study:

- The effect of solvent on the transition of the studied oxatriquinanes from the non-reactive G_3 to the reactive $^2G_1$ conformation was insignificant.
- Contrary to expectation, none of the studied solvents was able to change the mechanism of the reactions of OTQ, TMO, and TEO to S_N1. Hence, the preferred mechanism for these reactions was concluded to be S_N2, irrespective of the reaction medium.
- Reaction feasibility generally decreased with an increase in solvent polarity and the reactions of TMO and TEO became non-spontaneous at a dielectric constant value greater than 4.
- Contrary to the trend in the gas phase, increasing substituent size from methyl to ethyl group enhanced the substitution reaction in the solvent phase, due to reduction in the reactant stability as a result of lower reactant –solvent interaction.
- The electron-donating effect of the alkyl groups on the rate of S_N1 mechanism could not be ascertained with substantial evidence. Hence, the effects of the alkyl groups on the rate of S_N1 reaction were concluded to be of steric origin.
- The reactions of TIO and TTO with azide ion favored the S_N1 mechanism with high kinetic and thermodynamic feasibility. These reactions involve spontaneous steric relaxation and are close to being diffusion controlled.

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