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Solvent-trap reaction of triazolinediones with simple alkenes: an experimental/theoretical study of thermodynamic and kinetic parameters

Fotios Koutsianopoulos, Aurelio Bonasera, Silvio Osella, Roberto Lazzaroni, Zois Syrgiannis*, Yiannis Elemes

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Solvent-trap reaction of triazolinediones with simple alkenes: an experimental/theoretical study of thermodynamic and kinetic parameters

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A R T I C L E   I N F O

Article history:
Received 23 July 2015
Received in revised form 5 October 2015
Accepted 16 October 2015
Available online xxx

This work is dedicated to the memory of Professor Yiannis Elemes

Keywords:
Ene reaction
Triazoline dione
Solvent isotope effect
Alkenes
Solvent addition
Activation parameters

A B S T R A C T

The reaction of N-phenyltriiazolinedione with simple alkyl-substituted alkenes in a series of simple alcohols as nucleophilic solvents affords two products: a solvent-addition product (trap) and the ene adduct. Herein we present different experimental data which allow the estimation of different kinetic parameters (ΔΔH°,ΔΔS°,ΔH°,ΔS°). The values of those parameters are found to be lower with a longer nucleophile-solvent molecule. Solvent isotope effects are also estimated and found in favour of the heavier (and smaller) deuterated compounds. Results from competition experiments in equimolar binary mixtures of different alcohols as solvents also point to the prevalence of the smaller alcohol. A length limitation is observed in the competition of EtOH versus PrOH couple, the absence of any competition for the formation of the two solvent-addition (trap) products. All the results are consistent with an Sn2-like nucleophilic attack of the nucleophile-solvent to a closed aziridinium imide (AI) intermediate. Computational models were investigated in order to confirm the stability of the different possible intermediates and to confirm the experimentally observed trends and kinetic profiles. Furthermore, the results show the existence of a single transition state from which both products are formed.

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1. Introduction

Triazolinediones are very reactive electrophiles1,2 with rich reactivity patterns, ranging from cycloadditions,3–6 aromatization reactions,7 and polymer modification,8,9 to initiation of radical addition reactions,10 and have been extensively used in the synthesis of poly-ureas.11–14 The ene reaction of triazolinediones (TADs) with alkenes bearing allylic hydrogens15–17 continues to receive strong interest both from synthetic and mechanistic points of view,18–22 and it has been recently reviewed.23 The heterocyclic ring of TADs in the ene adducts can be transformed to an amino functionality by strong basic treatment, and the procedure can be used for the synthesis of the corresponding allylic amines.24,27

Mechanistically, the reaction appears to be stepwise and much of the discussion has been devoted to describe the structure of possible intermediates. Isotope effect studies led to the conclusion that an intermediate with the structural characteristics of an aziridinium imide (AI),18–22 i.e., a peroxide analogue,28 intervenes in the reaction. AI intermediates have been observed spectroscopically in the reactions of biadamantylidene,29 trans-cycloheptene,30 and trans-cyclooctene.31 Theoretical calculations support the presence of an AI intermediate, in which the conversion to the reactants is less probable than the allylic hydrogen abstraction in the second product-forming step.22

Recently, the existence of open biradical intermediates has been proposed.32 This proposal was subsequently supported on the basis of stereochemical and stereoisotopic studies.33 However, the exclusive formation of the products on alkenes which bear a cyclopropyl moiety at the allylic position was considered as strong evidence against the intervention of open biradical intermediates.34

Please cite this article in press as: Koutsianopoulos, F.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.10.047

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Open zwitterionic intermediates were also proposed for the reaction of TADS with alkenes in polar protic solvents, which lead to ene adducts without the intervention of Al intermediates.\(^{25}\) The work triggered further studies that showed large changes in the intermolecular isotope effect for the ene reaction of TADS with deuterated alkenes in MeOH as solvent. This result confirmed the extended reversal of a closed AI to an open dipolar intermediate and to the reactants, prior to hydrogen withdrawal, and rate-determining step.\(^{38}\)

Previously, we have been involved in studies of the chemistry of PhTAD,\(^{39-41}\) reporting that the reaction of TADS with alkenes in methanol affords the solvent-addition product together with the ene adduct.\(^{42-46}\) The molar ratio of the two products, calculated by integration of the \(^1\)H NMR spectra of the crude reaction mixture, was found to strongly depend on the reaction temperature, with the solvent-addition (trap) product predominating at lower temperatures. The differences in activation parameters (\(\Delta H^e\) and \(\Delta S^e\)) were calculated and they suggested the nucleophilic substitution opening of a closed AI intermediate by a methanol molecule. The reaction was found to be under entropic control. The enthalpic term favors the solvent-addition product (nucleophilic solvent interaction with the AI intermediate) whereas the entropic term favors the ene adduct formation (bimolecular vs unimolecular path). We have also reported on the reactions of 2-methylbut-2-ene with \(N\)-phenyltriazolinedione in a variety of alcohols as solvents, for which the calculated differences in the activation parameters are correlated with the size of the nucleophile-solvent molecule. Larger differences in activation parameters were calculated for smaller nucleophile-solvent molecules, such as MeOH.\(^{46}\) Along the same lines, inverse solvent isotope effects were measured, from their addition (trap) adducts, when reactions were performed in equimolar binary mixtures of isotopomeric methanols as solvents.\(^{44}\) Water was also employed as the nucleophilic solvent and found to give an alcohol as the solvent (water) addition product and the ene adduct.\(^{46}\)

The progress on the new mechanistic features of the reaction of TADS with alkenes in polar protic solvents prompted us to expand our work and to include additional model alkenes in a series of alcohols as nucleophilic solvents. We report here on reactions of 2,3-dimethylbut-2-ene (TetraME), 2-methylbut-2-ene (TriME), and methylpropene (Isobutylene), with \(N\)-phenyltriazolinedione in five simple alcohols as solvents: methanol (MeOH), ethanol (EtOH), n-propanol (PrOH), n-butanol (BuOH), and n-pentanol (PentOH). The differences in the activation parameters were calculated from the Arrhenius equation. The importance of the \(N\)–H bond formation during the transition state that leads to the products was revealed by the fact that smaller thermodynamic parameters are observed in reactions of the above alkenes in \(\mathrm{OD}\) deuterated alcohols compared to their \(\mathrm{OH}\) analogues. Competition experiments between the nucleophilic solvents (reactions in equimolar binary solutions of alcohols, \(\mathrm{ROH}\) and \(\mathrm{ROH}^2\)) showed higher reactivity of the smaller nucleophile, in line with the calculated inverse solvent isotope effects. The above findings are regarded as qualitative evidence for an \(S_n2\)-like transition state for the nucleophilic interception of a closed AI, rather than an open dipolar, intermediate from the solvents. In all cases, the solvent-addition products were isolated and spectroscopically characterized. The experimental results were corroborated by quantum-chemical calculations, which also provide insights into the reaction paths followed during the reaction.

### 2. Results and discussion

This study is based on the hypothesis that in a nucleophilic, \(S_n2\)-like, interception of a closed AI intermediate from the solvent, the detection of a bulkiness effect of the incoming nucleophile-solvent molecule would be possible. In the case of an open dipolar intermediate,\(^{27}\) such a size effect would be expected to be minimal, if any, and irrespective of differences in nucleophilicity.\(^{29-31}\)

Here we chose the three simplest alkyl-substituted alkenes, i.e., TetraME, TriME and Isobutylene. These alkenes have a high degree of structural similarity, with gradual differences in substitution with a potential to impose an increased steric hindrance to the attacking nucleophile in the solvent-addition transition state. In this context, the reactions of those alkenes with \(N\)-phenyltriazolinedione were performed in five simple alcohols (from MeOH to PentOH) at different temperatures (at least three for every alcohol).

From the \(^1\)H NMR spectra of the crude reaction mixture, the concentration ratio of the ene to the solvent-addition (trap) products, Scheme 1, was calculated by integration of the appropriate signals for each run.

All the solvent trap products were chromatographically isolated in good yields (see SI) and spectroscopically characterized, confirming their structures. It is worth mentioning at this point that in the case of TriME solvent adducts, the two methylenic hydrogen atoms (in the \(-\mathrm{OCH}_2\)–bearing alcohols) are diastereotopic due to the asymmetric carbon center connected to the nitrogen atom. Due to this asymmetric carbon, the two geminal CH\(_3\) groups show a diastereotopic relation and differ in their chemical shifts both in the \(^1\)H and \(^13\)C NMR spectra.

From the \(^1\)H NMR spectra (SI) of the crude reaction mixtures, it is clear that the calculated [ene]/[trap] ratios are strongly dependent on the size of the alcohol used as solvent. As a general trend, for the same reaction temperature the [ene]/[trap] ratio is found to be higher with longer alcohols, for all three alkenes. Furthermore it is characteristic that gradually larger ratios are found when passing from Isobutylene to TriME and to TetraME. This observation reveals a steric effect due to the higher substitution in the alkene and implies an increase in difficulty for the solvent addition, which implies a more crowded transition state (see Table 1).

The best fit straight line from the plot of ln[ene]/[trap] as a function of \(1/T\) led to the estimation of the \(\Delta H^e\) and \(\Delta S^e\) parameters from the Arrhenius equation, for the three alkenes in five different solvent-alcohols (Arrhenius plots are presented in the SI).

The calculated parameters are listed in Table 2.

The analysis of those data reveals a close correlation between the calculated differences in activation parameters and the size (bulkiness) of the nucleophile-alcohol molecule; the smaller the length of the alcohol, the higher the difference in the activation parameters. This clear correlation with the length of the solvent molecule is nicely demonstrated when going from MeOH to PentOH (entries 1–5, Table 2), for all three alkenes. As the alcohol molecule becomes longer, both \(\Delta H^e\) and \(\Delta S^e\) are calculated to decrease (i.e., from 6.8 kcal/mol and 21 e.u. for MeOH to 3.2 kcal/mol and 12 e.u. for PentOH in the case of TriME). We would like to mention at this point that alkyl-group branching in...
Table 1

<table>
<thead>
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<th>Alcohol/Solvent</th>
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<th>TriME</th>
<th>Isobutylene</th>
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Table 2

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<th>(\Delta S^{e,t}_{\text{ene,trap}}) (e.u.)</th>
<th>(\Delta H^{e,t}_{\text{ene,trap}}) (kcal/mol)</th>
<th>(\Delta S^{e,t}_{\text{ene,trap}}) (e.u.)</th>
<th>(\Delta H^{e,t}_{\text{ene,trap}}) (kcal/mol)</th>
<th>(\Delta S^{e,t}_{\text{ene,trap}}) (e.u.)</th>
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<tr>
<td>EtOH</td>
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<td>19±1</td>
<td>5.1±0.1</td>
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<td>PrOH</td>
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<td>BuOH</td>
<td>3.5±0.1</td>
<td>16±1</td>
<td>3.7±0.1</td>
<td>14±1</td>
<td>3.0±0.1</td>
<td>12±1</td>
</tr>
<tr>
<td>PentOH</td>
<td>3.5±0.1</td>
<td>15±1</td>
<td>3.2±0.1</td>
<td>14±1</td>
<td>2.4±0.1</td>
<td>9±1</td>
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</table>

a All reactions were performed in 1 mL of solvent. The solution of the alkene was equilibrated before the addition of the solid PhTAD at the desired temperature (at least three different temperatures).

b Accepted coefficients of determination \(r^2\) were ≥0.96. The values in the Table are average values of two independent runs and errors are the highest deviations from the mean value. All values were calculated from integral ratios in the 1H NMR spectra of the crude reaction mixtures; e.u.—entropic units; e, t—ene, trap.

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The above-presented length correlation is considered as strong evidence for an \(S_n2^-\) interception of a closed AI intermediate from a nucleophile-solvent molecule rather than an \(S_n1\)-like nucleophilic addition to an open dipolar intermediate. In the latter case, much less (if any) size correlation of the parameters is expected during the addition of a nucleophilic solvent molecule to a planar, positively charged, carbon atom (see Fig. 1). Additionally, an open dipolar intermediate would give the opportunity for syn-addition of the nucleophile-solvent to the planar carbocationic center, together with the anti-addition. The exclusive anti-addition pathway was proved by the stereospecific formation of Markovnikov MeOH adducts in the reaction of PhTAD with di-, tri-,\(^3\) and tetra-substituted alkenes,\(^3\) in MeOH.

In order to gain insight into the properties of the AI intermediate and support the experimental data, we performed an in silico investigation of the reaction profile for the three different alkenes in different solvents. A mixed quantum and molecular mechanics (QM/MM) simulations approach has been previously proposed in...
the literature for such type of study. Here we proceeded with fully quantum-chemical Density Functional Theory (DFT) calculations for the characterization of the different intermediates and the three transition states (for the formation of the intermediates, TS1 and TS\textsubscript{conv}, and the products, TS2) along the reactions path studied. The full reaction path for TetraME and PhTAD in MeOH is studied (details on the full reaction path considering ethanol and 1-propanol as solvents are reported in the SI). The first step of the reaction is the ene-reaction between TetraME and PhTAD in methanol, through an addition process (TS1, \( \Delta G \sim 11 \text{ kcal/mol} \)) and the diradical intermediate (RI, \( \Delta G \sim 18.7 \text{ kcal/mol} \)). The diradical species is less stable with respect to the DI, with a \( \Delta \Delta G \) of \( \sim 8 \text{ kcal/mol} \). Interestingly, we did not find the direct formation of the aziridinium imide intermediate (AI) from TS1. Instead, it forms from the ring closure of the DI intermediate through an interconversion process (TS\textsubscript{conv}, \( \Delta G \sim 11 \text{ kcal/mol} \)), leading to the most stable intermediate AI (\( \Delta G \sim 7.1 \text{ kcal/mol} \)). This intermediate is more stable than DI by 3 kcal/mol and its formation is reversible, because the energy of TS\textsubscript{conv} is lower than the energies of all other transition structures (\( \Delta \Delta G \sim 0.5 \text{ kcal/mol} \)) from DI to AI, and \( \Delta \Delta G \sim 4 \text{ kcal/mol} \) from AI to DI). Both DI and AI intermediates are thermodynamically more stable with respect to RI, with \( \Delta \Delta G \) of \( \sim 8 \) and \( \sim 11 \text{ kcal/mol} \), respectively, in agreement with previously reported ab initio results. In the next step, the addition of a second solvent molecule on the AI intermediate leads to the formation of both the trap- and ene-products through a Sn2-like’ transition state (TS2). The relatively small free energy barrier of TS2 (\( \Delta G \sim 12 \text{ kcal/mol} \)) with respect to the intermediate AI (\( \Delta \Delta G \sim 5 \text{ kcal/mol} \)) can either lead to the strongly stabilized ene-product (\( \Delta G \sim -36 \text{ kcal/mol} \)) or to the most stable trap-product (\( \Delta G \sim -39 \text{ kcal/mol} \)) (see Scheme 5).

![Scheme 5. Reaction of PhTAD with the model alkenes, in deuterated alcohols.](image)

From a thermodynamic point of view, the stability difference between the two products (\( \Delta \Delta G \sim 3 \text{ kcal/mol} \)) leads to the formation of the trap product as the major product of the reaction. Although this scheme is in agreement with the experiment, the free energy difference is too high to reproduce the [ene]/[trap] ratio found experimentally. This could be due to an overestimation of the solvent effects in stabilizing the structures, and we believe that this deviation is the same along the whole potential energy profile. Therefore, we expect that the differences between the species are

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properly estimated. The higher stabilization of the trap product is mainly due to the presence of the alkoxy group, which provides further stabilization to the molecule in the polarized medium.

Similarly to what was done in the experimental part, we studied the influence of different alkenes (TriME and Isobutylene) and alcohols (MeOH, EtOH and PrOH) as solvent/reagent on the stability of the intermediates. For TetraME, the increase in the length of the alcohols leads to a destabilization of the DI and AI intermediates, going from $\Delta G \sim 10.5$ kcal/mol in MeOH to $\Delta G \sim 20.3$ kcal/mol in PrOH for DI, and $\Delta G \sim 7.1$ kcal/mol in MeOH to $\Delta G \sim 8.0$ kcal/mol in PrOH for AI, while it does not affect the RI intermediate that present similar barriers of $\Delta G \sim 18.6$ kcal/mol in MeOH and $\Delta G \sim 18.8$ kcal/mol in PrOH for RI (Table S8 in Supplementary data). In all different solvents, AI is the most stable of the three possible intermediates.

To establish the relationship between the relative energy of the intermediate species and the nature of the alcohol, one explicit solvent molecule interacting with the negatively-charged nitrogen atom was considered, while the molecules of the bulk were described with the integral equation formalism version of the PCM model (IEF-PCM51,52). In all cases, methanol leads to the most stable description of the system, while alcoholic solvents give rise to similar energies, the stabilization of the transition structure, which is responsible for the increased energy barrier, from $\sim 12$ kcal/mol in MeOH to $\sim 14$ kcal/mol in PrOH (see Tables S2–S7 in SD). Similarly to what was found for the TetraME molecule, the relative stability of the AI intermediate also decreases with the increase in the alcohol chain length for the other two alkenes studied (TriME and Isobutylene), going from $\Delta G \sim 5.1$ kcal/mol (in MeOH) to $\Delta G \sim 6.9$ kcal/mol (in PrOH) for TriME and from $\Delta G \sim 5.8$ kcal/mol (in MeOH) to $\Delta G \sim 7.4$ kcal/mol (in PrOH) for Isobutylene, confirming that the acidity of the alcohol used as solvent plays an important role in the stability of the intermediates.

Next, the influence of the different alkenes on the stability of the AI intermediate and on the energy barrier leading to the formation of the products (TS2) is examined with methanol as the solvent (see Table 3 and Table S9 for the study with other solvents). For all alkenes, we found an SN2-like transition state (TS2), in which the proton provided by the alcohol molecule and the alkoxy nucleophile generated in the dissociation are approaching the reaction site simultaneously. As a consequence, it is possible to conclude that TS2 is concerted and it probably involves several solvent molecules, like in a Grothuss-like mechanism (proving the occurrence of that mechanism is beyond the purpose of this study). We find that the energy trend for TS2 is the following: TS2iso-TS2TriME<TS2TetraME with a total energy difference $\Delta \Delta G \sim 7.5$ kcal/mol, going from TetraME to TriME and $\Delta \Delta G \sim 1$ kcal/mol going from TriME to Isobutylene (see Table 3).

These results can be rationalized considering the steric hindrance in the transition state, and the charge distribution over the alkenes. The highest energy barrier can be expected for TS2TetraME since it is the most bulky molecule, so that the solvent molecule is located farther from the reaction site (distance $\sim 2.32$ Å). In TS2TriME and TS2iso the TriME and Isobutylene fragments are less bulky, decreasing the steric hindrance and favoring the proximity of the solvent molecule to the reaction site (distance of 2.21 and 2.13 Å for TriME and Isobutylene) when decreasing the degree of substitution on the alkenes can also be understood considering the charge distribution. The presence of four methyl units in the TetraME fragment delocalizes the partial charge over the two carbon atoms, making the reaction site less active. The substitution of methyl groups with hydrogen atoms in TriME and Isobutylene leads to a stronger localization of the charge over the reaction site, making it more active for the addition of a solvent molecule (see Table S10).

Another important aspect is the possible interaction of the negatively-charged nitrogen atom of the intermediates, originated from the PhTAD moiety, with the $\sim$OH hydrogen of a solvent molecule. If such interaction takes place in the solvent addition transition state, then we would expect changes in the differences of activation parameters with the use of OD instead of OH alcohols, related to the acidity difference between O–D and O–H. To support this hypothesis, we performed the reactions of the three model alkenes in deuterated isotopomers of MeOH and EtOH, applying the experimental conditions previously described. The results are listed in Table 4; those for MeOH and EtOH (entries 1 and 3) are included for comparison.

Interestingly, the [ene]/[trap] ratios were found to decrease slower when going to lower reaction temperatures with the –OD deuterated alcohols compared to their –OH isotopomers (see Table S1).

Consequently, from the Arrhenius plots it is clear that the differences in the activation parameters, both $\Delta \Delta H^{\ddagger}$ and $\Delta \Delta S^{\ddagger}$, are smaller in all deuterated alcohols used as the nucleophilic solvent with respect to their hydrogenated isotopomers, as can be seen from Table 4.

It appears that the –OD functionality stabilizes the transition state of the solvent addition to a lesser extent in comparison with the –OH functionality, due to the lower acidity of the deuterated moiety. This is nicely demonstrated with the gradual decrease of the experimental values going from MeOH to MeOD (entries 1, 2, Table 4), and from EtOH to EtoD (entries 3,4, Table 4), for the three alkenes of this study. We consider this result to be evidence for a transition state TS2 (Scheme 2).

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<th>Entry</th>
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<th>$\Delta ^{\ddagger}H_{\text{ene,trap}}$( kcal/mol)</th>
<th>$\Delta ^{\ddagger}S_{\text{ene,trap}}$( e.u.)</th>
<th>$\Delta ^{\ddagger}H_{\text{ene,trap}}$( kcal/mol)</th>
<th>$\Delta ^{\ddagger}S_{\text{ene,trap}}$( e.u.)</th>
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<th>$\Delta ^{\ddagger}S_{\text{ene,trap}}$( e.u.)</th>
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<tr>
<td>2 CH3OD</td>
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<td>5.6±0.1</td>
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<tr>
<td>3 ETOH</td>
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a All reactions were performed in 1 mL of solvent. Before the addition of the solid PhTAD, the solution of the alkenes was equilibrated at the desired temperature (at least three different temperatures).

b Accepted standard deviations $r^2$ were $\pm 0.96$. Values in the Table are average values of two independent runs and error bars are the highest deviations from the mean value. All values were calculated from integral ratios in the 1H NMR spectra of the crude reaction mixtures.
Since H is more electropositive than D, it forms stronger hydrogen bonds with the nitrogen atom of the Al moiety, and so with MeOH (or EtOH) the stabilization of the solvent-addition transition state is higher, compared to that with MeOD (or EtOD). Such a H(D)-N+ interaction appears to be of prime importance, and reflects the lower differences in $\Delta \Delta H^\text{ene,trap}$ (stabilization through bond formation) calculated for R-OD. This would mean less D transfer compared to H at the transition state, or stronger H(D)-N+ interaction from a shorter distance, compared to D. Along the same line, the differences in $\Delta \Delta S^\text{ene,trap}$ (more symmetry demand, better organization or less freedom) also becomes smaller, because there is less organization with R-OD due to the weaker D(D)-N+ interaction, compared to R-OH, Fig. 2.

**Fig. 2.** Transition states for the nucleophilic addition of a solvent molecule to a closed Al intermediate, $T_{S_{\text{conv}}}$, and to an open dipolar intermediate, $T_{S_{\text{comp}}}$, shown for TetraME.

An additional factor that could contribute to the lower differences in the activation parameters with deuterated alcohols as solvents could be the lower stabilization of the solvent-addition transition state through hyperconjugation at the $\delta^+$ bearing oxygen atom of the alcohol, with regard to their hydrogenated isotopomers. Both of the above factors can justify the involvement of a second alcohol molecule during the trap product-forming transition state $T_{S_{\text{conv}}}$ (Fig. 2). Furthermore, the involvement of a solvent molecule in the transition state of the intermediate formation (closed Al or open dipolar) is expected to be efficient in lowering the energy demand through an $H^+\cdots N^-$ interaction, even in the ene reaction mode.

Such stabilization is in agreement with the theoretical models, and finds confirmation in the recently proposed mechanistic profile for the ene reaction of PhTAD in alcohols as solvents, where there is an extended equilibration of the open (dipolar) and closed (Al) intermediates with the reagents prior to the rate-determining allylic hydrogen abstraction step.

Finally, we went a step further in the involvement of the above-mentioned $S_{\text{2,2-like}}$ nucleophilic solvent-addition transition state, by investigating solvent isotope effects. The isotope effect is a powerful tool for the clarification of organic reaction mechanisms and it has been widely used over the years.

Kinetic isotope effects (both with regard to deuterated substrates and incoming nucleophile) are known in nucleophilic substitution reactions, and have been thoroughly applied to biological systems.

We have recently reported competition experiments in equimolar binary solutions of isotopomeric methanols, i.e., CH$_3$OH versus CD$_3$OH, and CH$_3$OD versus CD$_3$OD. In the case of an open dipolar intermediate, the above two couples of alcohols would be expected to be roughly equal in reactivity towards an $S_{\text{2,2-like}}$ nucleophilic addition to a planar electrophilic center. They differ in bulkiness, since C-D and O-D bonds are longer than their C-H and O-H counterparts, but such a size difference would have no effect on the solvent molecule additions to an open dipolar intermediate. The measured solvent isotope effects are depicted in Scheme 6.

From the calculated ratios shown in Scheme 6, it is clear that for all three alkyl-substituted alkenes considered in this study, the heavier isotopomeric methanol is added more efficiently to the tertiary carbon atom of the former double bond. In all these cases, an inverse solvent isotope effect has been measured, in support of a nucleophilic addition to a closed Al intermediate. Furthermore, we have included an alkoxy-substituted alkene (methoxy propene) in this study, which is an ideal substrate to test the intervention of an open dipolar intermediate in the context of the above solvent competition experiments. With methoxypropene, in an open

**Scheme 6.** Solvent isotope effects in the reaction of PhTAD with TetraME, TrIME, Isobutylene and methoxypropene.
diol intermediate the positive charge on the carbon at the more
substituted end of the former double bond would have been
delocalized by the resonance effect of the oxygen atom of the
alkoxy-substituent. In such a case, the solvent isotope effect is ex-
pected to be very close to unity, revealing almost no competition
between the isotopomeric solvents. From the experiments at three
different temperatures, it is obvious that this is not the case since
the solvent isotope effects are found to be below unity, even for
methoxy propane. This is considered as strong experimental evi-
dence for the intervention of a closed intermediate with structural
similarity to AI. Interestingly, the AI intermediate is preserved going
from TetraME, to TriME and isobutylene and still exists in the case
of alkoxy-substituted alkenes.

Based on these results, we extended the competition experi-
ments to the different alcohols used in this study, in couples. In this
analysis, no significant competition is expected for an open in-
termediate, except for some differentiation due to the (small) dif-
ficulties in nucleophilicity between the alcohols. In contrast, in the
case of an Sn2-like interception of an AI intermediate by the sol-
vent molecule, the size of the alcohol molecule is expected to play
a major role (the results are listed in Table 5).

Table 5: Competition experiments with equimolar binary alcohol mixtures.

<table>
<thead>
<tr>
<th>R1OH/R2OH</th>
<th>[trapR1OH]/[trapR2OH] (T°C)</th>
<th>[trapR2OH]/[trapR1OH] (T°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeOH/EtOH</td>
<td>2.03±0.03 (19 °C)</td>
<td>1.86±0.03 (24 °C)</td>
</tr>
<tr>
<td>MeOH/PrOH</td>
<td>2.12±0.03 (21 °C)</td>
<td>2.02±0.03 (18 °C)</td>
</tr>
<tr>
<td>MeOH/BuOH</td>
<td>2.09±0.03 (21 °C)</td>
<td>1.50±0.03 (27 °C)</td>
</tr>
<tr>
<td>MeOH/PentOH</td>
<td>2.20±0.03 (24 °C)</td>
<td>1.67±0.03 (24 °C)</td>
</tr>
<tr>
<td>EtOH/PrOH</td>
<td>0.98±0.03 (22 °C)</td>
<td>0.98±0.03 (25 °C)</td>
</tr>
<tr>
<td>EtOH/BuOH</td>
<td>1.00±0.03 (20 °C)</td>
<td>0.97±0.03 (20 °C)</td>
</tr>
<tr>
<td>EtOH/PentOH</td>
<td>1.00±0.03 (23 °C)</td>
<td>0.97±0.03 (23 °C)</td>
</tr>
<tr>
<td>PrOH/PentOH</td>
<td>1.00±0.03 (23 °C)</td>
<td>1.00±0.03 (24 °C)</td>
</tr>
</tbody>
</table>

What is striking from those results is the absence of any com-
petition for the four alkenes (from EtOH vs PrOH, EtOH vs BuOH and
EtOH vs PentOH), revealing a steric hindrance factor that operates
during the AI interception from the alcohol molecule; the biggest
effect is revealed between methanol and ethanol. For the other
longer but ‘linear’ alcohols very small variations could be expected
because, since the main contribution is offered from the portion of
chain close to the nucleophilic oxygen, their behaviour is almost
similar and no relevant differences were revealed experimentally.

In contrast, competition of MeOH with the other four alcohols (i.e.,
couples MeOH vs EtOH, MeOH vs PrOH, MeOH vs BuOH, MeOH vs
PentOH) shows a clear preference for the interception of an in-
termediate by the smaller alcohol molecule (MeOH), as it was found
also from the calculated inverse solvent isotope effects, shown in
Scheme 3. In addition, there is a relationship between the alcohol
size and the concentration ratio, [trapR2OH]/[trapR1OH]. This is
clear for all the four studied alkenes, where the solvent-addition
product ratio gradually increases, in favor of MeOH, going from
MeOH versus EtOH to MeOH versus PentOH. In the case of MeOH
versus EtOH competition, a slightly larger preference for the MeOH
trap product was found at lower reaction temperatures for all four
alkenes. Such an increase was not observed in the case of EtOH
versus PrOH and EtOH versus BuOH competitions. We also observe
a dependence of the [trapMeOH]/[trapEtOH] from the alkenes
after the nucleophilic addition of a second solvent molecule. The
intermediate has to possess the structural characteristics of an
aziridinium imide according to the above-discussed solvent com-
petition experiments and the calculated differences in the activa-
tion parameters. If such an open dipolar intermediate exists, then it
has to transform very fast to the AI intermediate, in view of the
observed differences in activation parameters, inverse isotope ef-
fects and the favorable interception of the intermediate from the
smaller solvent molecule, Fig. 3.

3. Conclusion

This study provides a deep insight into the reaction of PhTAD
with simple alkyl-substituted alkenes in alcohols as solvents, and
a robust combination of experimental results and new theoretical
models support the proposed mechanism. The experimental evi-
dence of Sn2-like nucleophilic solvent addition to a closed AI
intermediate was generated from: a) calculated differences in the
activation parameters which showed strong dependence on the
size of the incoming solvent molecule, smaller alcohol molecules
interacting more strongly with the intermediate, b) stabilization of
the transition state of the solvent addition by a second solvent
molecule through hydrogen bond formation, as it was inferred from
the reduction of the differences in the activation parameters with

Please cite this article in press as: Koutsianopoulos, F.; et al., Tetrahedron (2015), http://dx.doi.org/10.1016/j.tet.2015.10.047
the relevance for the de
vent molecules in the stabilization of the intermediate species and
with the screened exchange hybrid density functional HSE. Sol-
products, intermediates, and transition states has been performed
were optimized and characterized with the 6-311
alcohol solutions, (MeOH, EtOH and PrOH) were introduced by the Po-
assignment of the isolated compounds was con-
trap instrument in ESI positive ion mode. The structure and the
13C NMR spectroscopy (DEPT, COSY, NOESY, HMBC and HSQC
substituted alkenes. Theoretical calculations con-
the electrophilic centre of the intermediate, and d) competition
experiments between the nucleophilic solvents, which were found
in favour of the smaller alcohol addition to the closed AI inter-
mediate. Closed AI intermediates prevail even with alkoxysubstituted alkenes. Theoretical calculations confirm the experi-
mental trend of stability of the intermediates, and support the S(O2-
like) nucleophilic addition, confirming the prominent role of sol-
vent molecules in the stabilization of the intermediate species and
the relevance for the definition of the kinetic profile. In addition,
these combinatorial data reveal the complete reaction pathway in
which three Transition States and one Intermediate are involved.
This mechanism is common for both products and the most im-
portant outcome is the appearance of the first intermediate, which
is the rate determining step. This work is thus providing a strong
background for resolving mechanisms and elucidating different
nucleophilic addition reactions in protic solvents. In addition, these
results can work as an initiative point for further structural and
synthetic studies with the use of different environments (acidic or
basic), different type of alcohols and even more other protic media.

4. Experimental and theoretical methods

4.1. General

All reagents and solvents were purchased from commercial
suppliers and were used without further purification. Dry quality
solvents were obtained according to literature procedures, and
stored over MS 4 Å under Ar atmosphere. All NMR spectra were
taken in CDCl₃ 98% D. ESI MS spectra were recorded on an LC/MSD
trap SL instrument. In FABMS measurements 3-nitrobenzylalcohol
was used as the matrix. HRMS spectra were recorded on an Orbi-
trap instrument in ESI positive ion mode. The structure and
the assignment of the isolated compounds was confirmed with ¹H and
¹³C NMR spectroscopy (DEPT, COSY, NOESY, HMBC and HSQC
spectra), and with FTIR, and ESI MS HRMS spectrometry.

4.2. Computational methodology

The calculations have been performed with the Gaussian 09
suite of programs and used GaussianView v.5.0.8 for the graphic rep-
resentation of the results. Geometry optimization of the reagents,
products, intermediates, and transition states has been performed
with the screened exchange hybrid density functional HSE. Sol-
vent effects (MeOH, EtOH and PrOH) were introduced by the Pol-
larizable Continuum Model (IEF-PCM). All stationary points
were optimized and characterized with the 6-311+G(d,p) Pople
basis set, and the nature of the critical points was checked by
vibrational analysis (all data are reported in the Supplementary
data, Tables S2–S9). The reaction path from the TS obtained
and the minima was confirmed by intrinsic reaction coordinate
(IRC) calculations. The DFT method for singlet species provides
closed-shell molecules. However, for some of them, the open-shell
solution (typical of diradicaloid structures) is more stable. There-
fore, to obtain a qualitatively correct electronic wavefunction and
energy estimate relevant to a diradicaloid singlet, the spin-
unrestricted DFT (UDFT) was used. This was obtained by allow-
ing contamination of the restricted singlet electronic function by
the triplet (spin contamination). The electronic-energy values were
then corrected including the zero point energy, ΔE (0 K), and the
thermal and entropy contributions to the free energy, ΔG (298 K).
The charge analysis was performed considering the electrostatic
potential (ESP) method.

Acknowledgements

Financial support from the Research Committee, University of
Ioannina (programme no. 1216 and 723), is gratefully acknowledge-
ed. We thank the NMR and the MS centers of University of
Ioannina, for the spectra. We thank Dr. C. Dolka for the help with
some HRMS spectra, at University of Geneva. Research in Mons
is supported by the European Commission (FP7-PEOPLE-ITN-2008-
238177 "SUPERIOR"), FNRS-FRFC, the Interuniversity Attraction Pole
program of the Belgian Federation Science Policy Office (PAI 7/05) and
the Programme d’Excellence de la Région Wallonne (OPT2MAT
project). Finally we thank Professor Michael Orfanopoulos for his
valuable comments.

Supplementary data

Supplementary data (General methods followed for the syn-
thesis of the compounds, characterization data, ¹H and ¹³C NMR
spectra of solvent and ene adducts, 2D NMR spectra for EtOH ad-
ducts 5, 10, and 15, [ene]/trap ratios, Arrhenius plots and calculated
geometrical parameters, calculated geometries and energies of the
reaction intermediates and transition states.) associated with this
article can be found in the online version, at http://dx.doi.org/
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References and notes

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