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Graphical Abstract

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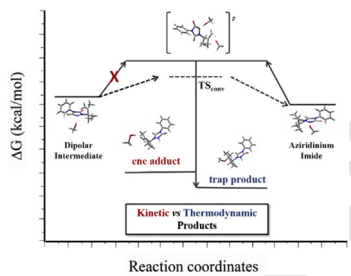

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Solvent-trap reaction of triazolinediones with simple alkenes: an experimental/theoretical study of thermodynamic and kinetic parameters

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This work is dedicated to the memory of Professor Yiannis Elemes

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ABSTRACT

The reaction of *N*-phenyltriazolinedione 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 ($\Delta\Delta H^{\neq}_{ene,trap}$ and $\Delta\Delta S^{\neq}_{ene,trap}$). 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 S_N2-'like' nucleophilic attack of the nucleophile-solvent to a closed aziridinium imide (AI) intermediate. Computational models were investigated in order to both 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 electrophiles[1,2] 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 hydrogens[15–17] continues to receive strong interest both from synthetic and mechanistic points of view,[18–22] and it has been recently reviewed.[23–25] 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.[26,27]

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 perepoxide 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.[32]

Recently, the existence of open biradical intermediates has been proposed.[33] This proposal was subsequently supported on the basis of stereochemical and stereoisotopic studies.[34,35] However, the exclusive formation of ene products on alkenes which bear a cyclopropyl moiety at the allylic position was considered as strong evidence against the intervention of open biradical intermediates.[36]

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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 AI intermediates.[37] 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 ($\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$) 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.[45] 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]

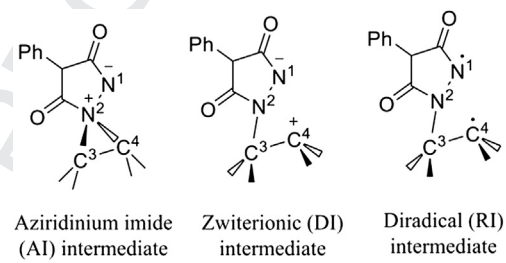
The progress on the new mechanistic features of the reaction of TADs with alkenes in polar protic solvents prompted us to expand our work and to include additional model alkenes in a series of alcohols as nucleophilic solvents. We report here on reactions of 2,3-dimethylbut-2-ene (TetraME), 2-methylbut-2-ene (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 –OD deuterated alcohols compared to their –OH analogues. Competition experiments between the nucleophilic solvents (reactions in equimolar binary solutions of alcohols, R^1OH and R^2OH) 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,[37] such a size effect would be expected to be minimal, if any, and irrespective of differences in nucleophilicity.[47–49]

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.



Scheme 1. Proposed structures for the intermediate species in the reaction between the model alkenes and PhTAD.

All the solvent trap products were chromatographically isolated in good yields (see SD) 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 $-OCH_2-$ 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 $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$ 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 $\Delta\Delta H^{\neq}_{ene,trap}$ and $\Delta\Delta S^{\neq}_{ene,trap}$ 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

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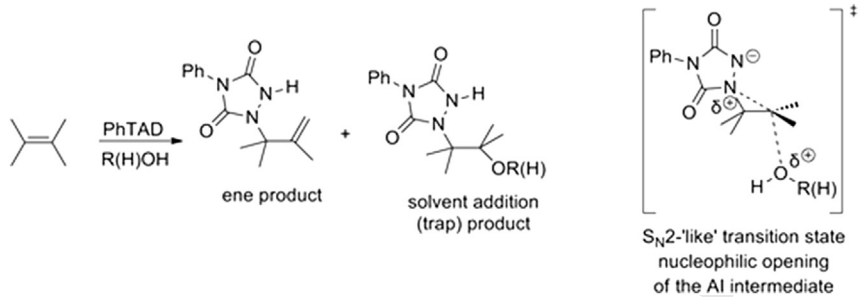
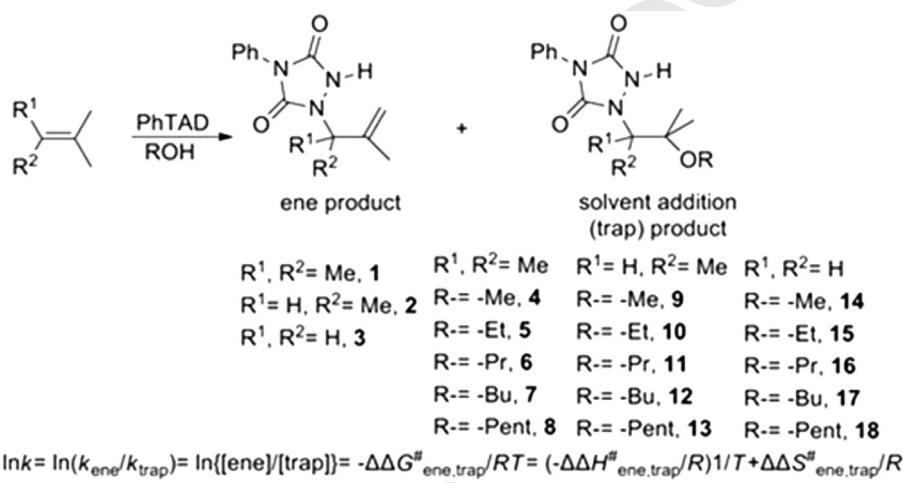


Scheme 2. General reaction scheme between the model alkenes and PhTAD in different alcohols as nucleophilic solvents.



Scheme 3. General scheme representing the different solvents and alkenes investigated, and the structures of the isolated products. The equation correlating the [ene]/[trap] ratio with measured thermodynamic parameters is herein reported.

the solvent (i.e., *i*-PrOH, *i*-BuOH) gave much higher [ene]/[trap] molar ratios (the accuracy of those results was lower; for this reason they have not been included in the present discussion).

The above-presented length correlation is considered as strong evidence for an S_N2-'like' 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-,[43] and tetra-substituted alkenes,[38] 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

Table 1
[ene]/[trap] ratios evaluated for the examined experimental conditions

	TetraME	TriME	Isobutylene
MeOH	1.28	0.46	0.45
EtOH	4.66	1.67	0.86
PrOH	4.55	1.65	1.07
BuOH	6.25	1.97	1.32
PentOH	7.51	1.82	1.25

Table 2
Differences in the activation parameters $\Delta\Delta H^{\neq}_{ene,trap}$ and $\Delta\Delta S^{\neq}_{ene,trap}$ calculated for the reaction of PhTAD with simple alkenes in alcohols as solvents

	Alcohol/Solvent[a]	(TetraMe)		(TriME)		(Isobutylene)	
		$\Delta\Delta H^{\neq}_{e,t}$[b] (kcal/mol)	$\Delta\Delta S^{\neq}_{e,t}$ (e.u.)	$\Delta\Delta H^{\neq}_{ene,trap}$[b] (kcal/mol)	$\Delta\Delta S^{\neq}_{e,t}$ (e.u.)	$\Delta\Delta H^{\neq}_{e,t}$[b] (kcal/mol)	$\Delta\Delta S^{\neq}_{e,t}$ (e.u.)
1	MeOH	5.5±0.1	19±1	6.8±0.1	21±1	6.0±0.1	20±1
2	EtOH	4.7±0.1	19±1	5.1±0.1	19±1	3.9±0.1	14±1
3	PrOH	4.0±0.1	17±1	4.6±0.1	17±1	3.3±0.1	12±1
4	BuOH	3.5±0.1	16±1	3.7±0.1	14±1	3.0±0.1	12±1
5	PentOH	3.3±0.1	15±1	3.2±0.1	12±1	2.4±0.1	9±1

[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 r2 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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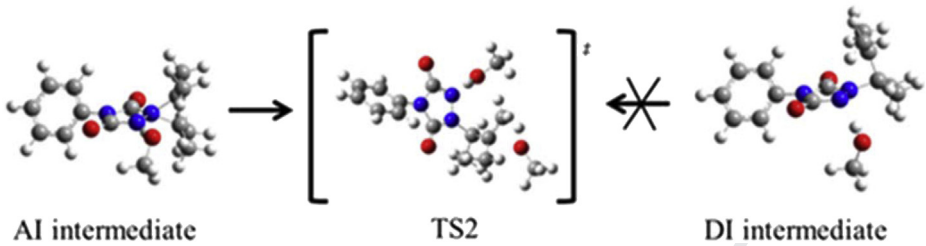
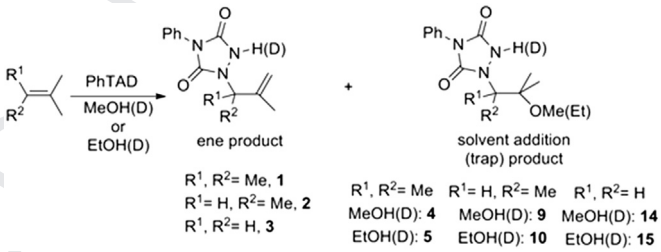


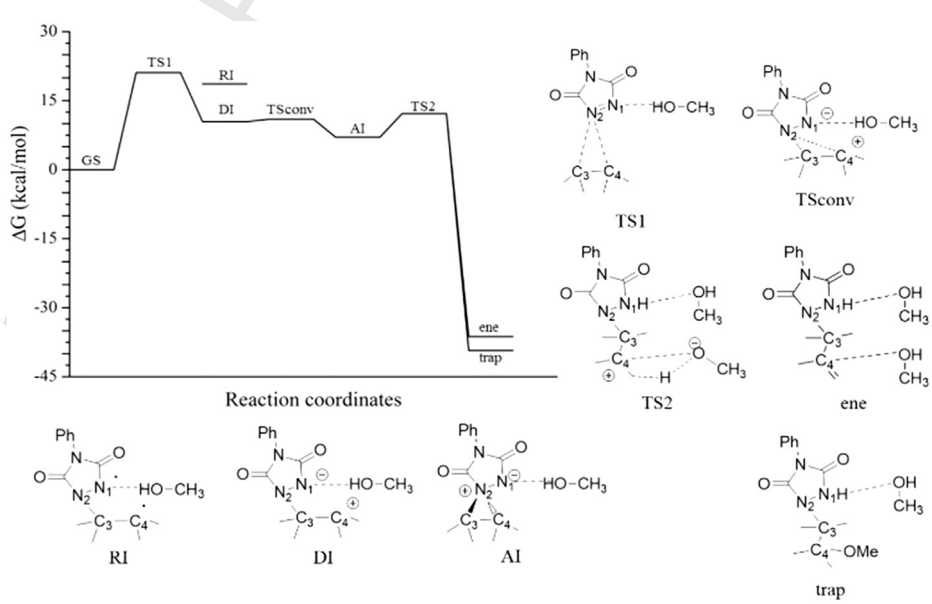
Fig. 1. Allowed nucleophilic addition of a solvent molecule from intermediate AI to TS2, and forbidden addition from intermediate DI to TS2.

the literature for such type of study.[37] Here we proceeded with fully quantum-chemical Density Functional Theory (DFT) calculations[50] for the characterization of the different intermediates and the three transition states (for the formation of the intermediates, TS1 and TS^{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, ΔG ~21 kcal/mol, Scheme 4), which appears to be the rate-determining step (rds.) of the reaction. Two different intermediates have been found as a result of the addition step: the open dipolar species (DI, ΔG ~10.5 kcal/mol) and the diradical intermediate (RI, ΔG ~18.7 kcal/mol). The diradical species is less stable with respect to the DI, with a ΔΔG of ~8 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_{conv}, ΔG ~11 kcal/mol), leading to the most stable intermediate AI (ΔG ~7.1 kcal/mol). This intermediate is more stable than DI by 3 kcal/mol and its formation is reversible, because the energy of TS_{conv} is lower than the energies of all other transition structures (ΔΔG ~0.5 kcal/mol from DI to AI, and ΔΔG ~4 kcal/mol from AI to DI). Both DI and AI intermediates are thermodynamically more stable with respect to RI, with ΔΔG of ~8 and ~11 kcal/mol, respectively, in agreement with previously reported ab initio results.[37] 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 S_N2-'like' transition state (TS2). The relatively small free energy barrier of TS2 (ΔG ~12 kcal/mol) with respect to the intermediate AI (ΔΔG ~5 kcal/mol) can either lead to the strongly stabilized ene-product (ΔG ~ −36 kcal/mol) or to the most stable trap-product (ΔG ~ −39 kcal/mol) (see Scheme 5).



Scheme 5. Reaction of PhTAD with the model alkenes, in deuterated alcohols.

From a thermodynamic point of view, the stability difference between the two products (ΔΔG ~3 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



Scheme 4. Reaction profile determined on the basis of the theoretical calculations for the test reaction of PhTAD and TetraME in MeOH as solvent/nucleophile. The structures labelled in the reaction profiles are also reported.

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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 ΔG ~10.5 kcal/mol in MeOH to ΔG ~20.3 kcal/mol in PrOH for DI, and ΔG ~7.1 kcal/mol in MeOH to ΔG ~8.0 kcal/mol in PrOH for AI, while it does not affect the RI intermediate that present similar barriers of ΔG ~18.6 kcal/mol in MeOH and ΔG ~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-PCM[51,52]). In all cases, methanol leads to the most stable AI intermediate, in accordance with its higher acidity; the formation of an efficient hydrogen bond prevents electron delocalization from N1 to N2, hence stabilizing the intermediates; this effect is even more pronounced when TS2 is considered. In particular, the increase of the alcohol length leads to a lower acidity, and to a destabilization of the transition structure, which is responsible for the increased energy barrier, from ~12 kcal/mol in MeOH to ~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 ΔG ~5.1 kcal/mol (in MeOH) to ΔG ~6.9 kcal/mol (in PrOH) for TriME and from ΔG ~5.8 kcal/mol (in MeOH) to ΔG ~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 S_N2-'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 sites simultaneously. As a consequence, it is possible to conclude that TS2 is concerted and it probably involves several solvent molecules, like in a Grotthuss-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 ΔΔG ~7.5 kcal/mol, going from TetraME to TriME and ΔΔG ~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 (~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 –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 $\Delta\Delta H^{\neq}$ and $\Delta\Delta S^{\neq}$, 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).

Table 3
C–O distance, free energy (kcal/mol) and charge analysis for the TS2 for the different alkenes in MeOH as solvent/nucleophile

	C_4–$O_{nucleophile}$ (Å)	ΔG	C_4 (ESP)
TetraME	2.32	12.2	0.52
TriME	2.21	4.7	0.69
Isobutylene	2.13	3.7	0.76

Table 4
Differences in the activation parameters $\Delta\Delta H^{\neq}_{ene,trap}$ and $\Delta\Delta S^{\neq}_{ene,trap}$ calculated for the reaction of PhTAD with the model alkenes in deuterated alcohols as solvents

Entry	Alcohol/Solvent[a]	(TetraMe)		(TriME)		(Isobutylene)	
		$\Delta\Delta H^{\neq}_{ene,trap}$[b] (kcal/mol)	$\Delta\Delta S^{\neq}_{ene,trap}$ (e.u.)	$\Delta\Delta H^{\neq}_{ene,trap}$[b] (kcal/mol)	$\Delta\Delta S^{\neq}_{ene,trap}$ (e.u.)	$\Delta\Delta H^{\neq}_{ene,trap}$[b] (kcal/mol)	$\Delta\Delta S^{\neq}_{ene,trap}$ (e.u.)
1	CH_3OH	5.5±0.1	19±1	6.8±0.1	21±1	6.0±0.1	20±1
2	CH_3OD	5.0±0.1	17±1	5.6±0.1	18±1	3.9±0.1	12±1
3	EtOH	4.7±0.1	19±1	5.1±0.1	19±1	3.9±0.1	14±1
4	EtOD	4.2±0.1	17±1	3.5±0.1	13±1	2.9±0.1	11±1

[a] All reactions were performed in 1 mL of solvent. Before the addition of the solid PhTAD, the solution of the alkene was equilibrated at the desired temperature (at least three different temperatures).
[b] Accepted standard deviations r2 were ≥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.

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Since H is more electropositive than D, it forms stronger hydrogen bonds with the nitrogen atom of the AI 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 $H(D)^{\delta+}$—$N^{\delta-}$ interaction appears to be of prime importance, and reflects on the lower differences in $\Delta\Delta H^{\neq}_{ene,trap}$ (stabilization through bond formation) calculated for R-OD. This would mean less D transfer compared to H at the transition state, or stronger $H^{\delta+}$—$N^{\delta-}$ interaction from a shorter distance, compared to D. Along the same line, the differences in $\Delta\Delta S^{\neq}_{ene,trap}$ (more symmetry demand, better organization or less freedom) also becomes smaller, because there is less organization with R-OD due to the weaker $D^{\delta+}$—$N^{\delta-}$ interaction, compared to R—OH, Fig. 2.

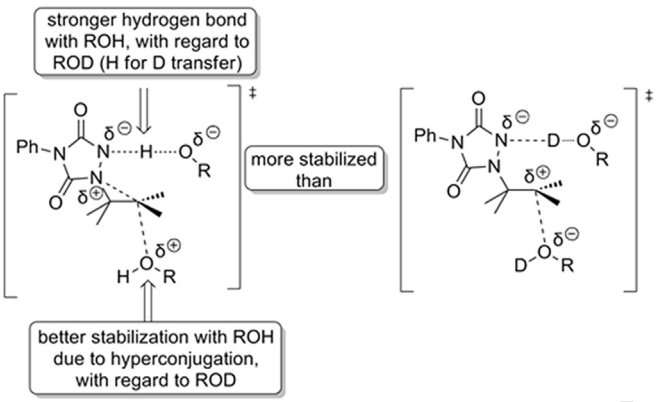


Fig. 2. Transition states for the nucleophilic addition of a solvent molecule to a closed AI intermediate, TS_{conv}, and to an open dipolar intermediate, TS_{convb}, shown for TetraME.

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 δ^+ 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 TS_{conv} (Fig. 2). Furthermore, the involvement of a solvent molecule in the transition state of the intermediate formation (closed AI or open dipolar) is expected to be efficient in lowering the energy demand through an $H^{\delta+}$—$N^{\delta-}$ interaction, even in the ene reaction mode.

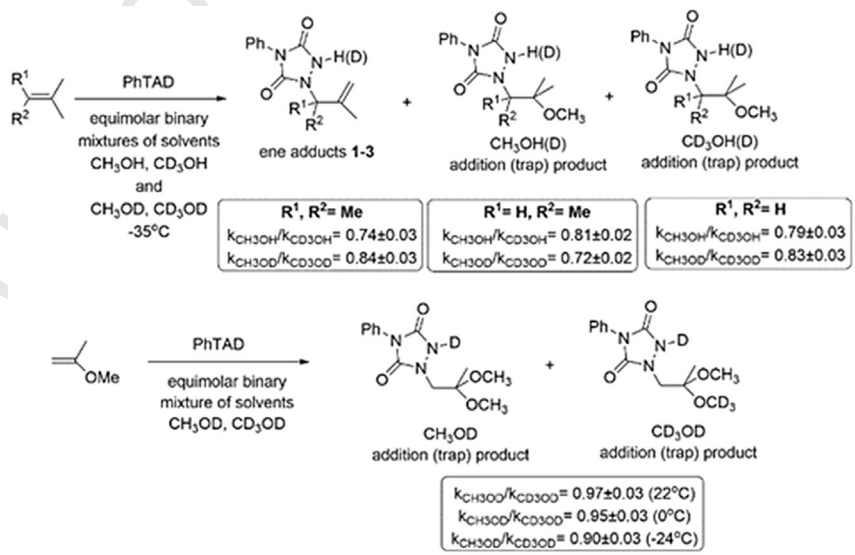
Such stabilization is in agreement with the theoretical models, and finds confirmation in the recently proposed mechanistic profile for the ene reaction of PhTAD in alcohols as solvents,[38] where there is an extended equilibration of the open (dipolar) and closed (AI) intermediates with the reagents prior to the rate-determining allylic hydrogen abstraction step.

Finally, we went a step further in the involvement of the above-mentioned S_N2-'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.[53,54]

Kinetic isotope effects (both with regard to deuterated substrates and incoming nucleophile) are known in nucleophilic substitution reactions.[55–59] Solvent isotope effects are decisive tools for the description of transition states for hydrogen transfer reactions[60,61] and have been thoroughly applied to biological systems.[62–69]

We have recently reported[44] competition experiments in equimolar binary solutions of isotopomeric methanols, i.e., CH_3OH versus CD_3OH, and CH_3OD versus CD_3OD. 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_N1-'like' nucleophilic addition to a planar electrophilic center. They differ in bulkiness, since C-D and O-D bonds are shorter 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 AI 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.

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dipolar 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 expected 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 propene. This is considered as strong experimental evidence 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 experiments to the different alcohols used in this study, in couples. In this analysis, no significant competition is expected for an open intermediate, except for some differentiation due to the (small) differences in nucleophilicity between the alcohols. In contrast, in the case of an S_N2-'like' interception of an AI intermediate by the solvent 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

R^1OH/R^2OH	$[trap^1_R]/[trap^2_R]$, (T°C)	$[trap^1_R]/[trap^2_R]$, (T°C)	$[trap^1_R]/[trap^2_R]$, (T°C)	$[trap^1_R]/[trap^2_R]$, (T°C)
MeOH/EtOH	2.03±0.03(19 °C)[a]	1.86±0.03(24 °C)	1.44±0.03(0 °C)	1.32±0.03 (23 °C)
	2.08±0.03(0 °C)	1.96±0.03(0 °C)	1.46±0.03(−17 °C)	1.36±0.03 (0 °C)
	2.12±0.03(−18 °C)	2.02±0.03(−18 °C)	1.47±0.03(−30 °C)	1.41±0.03(−30 °C)
	2.18±0.03(−26 °C)	2.15±0.03(−30 °C)		
MeOH/PrOH	2.12±0.03(21 °C)	1.67 (19 °C)	1.32±0.03(−27 °C)	1.43±0.03(22 °C)
MeOH/BuOH	2.09±0.03(21 °C)	1.50±0.03(21 °C)	1.62±0.03(−27 °C)	1.78±0.03(24 °C)
MeOH/PentOH	2.20±0.03(24 °C)	1.67±0.03(24 °C)	1.73±0.03(−27 °C)	1.72±0.03(24 °C)
EtOH/PrOH	0.98±0.03(22 °C)	0.98±0.03(25 °C)	1.00±0.03(0 °C)	0.99±0.03(24 °C)
	1.00±0.03(0 °C)	0.97±0.03(0 °C)	1.00±0.03(−17 °C)	
	0.97±0.03(−27 °C)	0.98±0.03(−31 °C)	1.01±0.03(−31 °C)	
EtOH/BuOH	1.00±0.03(23 °C)	0.97±0.03(23 °C)	0.99±0.03(−27 °C)	1.03±0.03(22 °C)
				1.06±0.03(0 °C)
				1.04±0.03(−27 °C)
EtOH/PentOH	1.00±0.03(23 °C)	1.00±0.03(24 °C)	1.00±0.03(−27 °C)	1.01±0.03(24 °C)
PrOH/PentOH	1.00±0.03(23 °C)	1.00±0.03(24 °C)	1.00±0.03(−32 °C)	0.99±0.03(24 °C)

What is striking from those results is the absence of any competition 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 intermediate 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, $[trapR^1OH]/[trapR^2OH]$. 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 alkene substitution, going from 1.36 to 1.44 at 0 °C for methoxypropene and isobutylene, respectively, to 1.96 for TriME and 2.08 for TetraME at the same temperature. We consider this size dependence (a smaller alcohol adds faster and gives higher concentrations of the corresponding trap adduct) and the size limitation (no competition with larger than MeOH alcohol couples) in favor of an S_N2-'like' transition state for the solvent molecule addition to closed AI intermediates. In the case of an open intermediate, the $[trapR^1OH]/[trapR^2OH]$ ratios would be very close to unity without being dependent so much on the size of the alcohol molecule.

The combination of the present experimental results and recent mechanistic studies[22,37] leads us to confirm that the reaction of PhTAD with alkenes in alcohols as solvents proceeds stepwise, with the formation of an intermediate that equilibrates with the reagents before the second. The transition state for the intermediates formation is stabilized by the interaction of the solvent-alcohol with the nucleophilic centre of the intermediates (negatively-charged nitrogen atom). This stabilization through a distant $N^{\delta-}$—$H^{\delta+}$ interaction in the intermediate becomes stronger (the alcohol molecule behaves as a proton donor), when going to the transition state, where the intermediate evolves to the trap product 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 competition experiments and the calculated differences in the activation 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 effects 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 evidence of S_N2-'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

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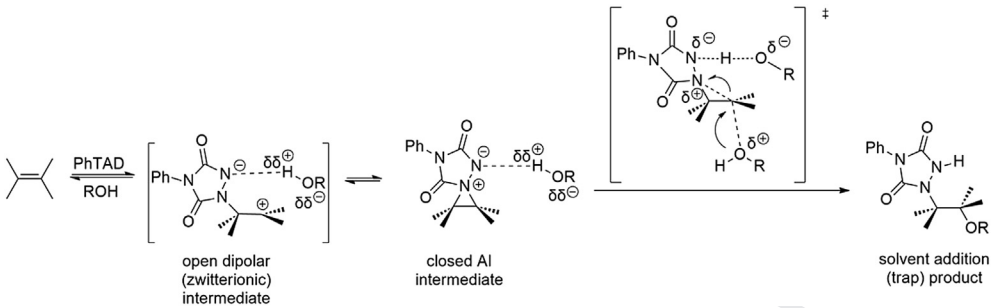

Fig. 3. Intermediates and transition state for the solvent nucleophilic addition to an AI intermediate.

−OD deuterated alcohols, c) inverse solvent isotope effects in the solvent-addition product formation calculated from reactions in equimolar isotopomeric methanol mixtures, where there is stronger interaction between the heavier and smaller nucleophile and 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 intermediated. Closed AI intermediates prevail even with alkoxy-substituted alkenes. Theoretical calculations confirm the experimental trend of stability of the intermediates, and support the S_N2-'like' nucleophilic addition, confirming the prominent role of solvent 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 important 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 $CDCl_3$ 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 Orbitrap instrument in ESI positive ion mode. The structure and the assignment of the isolated compounds was confirmed with ^{1}H and ^{13}C 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 GaussView v.5.0.8 for the graphic representation of the results.[70] Geometry optimization of the reagents, products, intermediates, and transition states has been performed with the screened exchange hybrid density functional HSE.[71] Solvent effects (MeOH, EtOH and PrOH) were introduced by the Polarizable Continuum Model (IEF-PCM).[51,52] 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).[72,73] 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. Therefore, to obtain a qualitatively correct electronic wavefunction and energy estimate relevant to a diradicaloid singlet, the spin-unrestricted DFT (UDFT) was used.[74] This was obtained by allowing 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.

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Supplementary data

Supplementary data (General methods followed for the synthesis of the compounds, characterization data, ^{1}H and ^{13}C NMR spectra of solvent and ene adducts, 2D NMR spectra for EtOH adducts 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/10.1016/j.tet.2015.10.047.

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