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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 ($\Delta\Delta H^{\ddagger}_{\text{ene,trap}}$ and $\Delta\Delta S^{\ddagger}_{\text{ene,trap}}$). 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 peroxide analogue,²⁸ intervenes in the reaction. AI intermediates have been observed spectroscopically in the reactions of biadamantylidene,²⁹ *trans*-cycloheptene³⁰ 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 ¹H 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 ($\Delta\Delta H^\ddagger$ and $\Delta\Delta S^\ddagger$) 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, R¹OH and R²OH) 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.

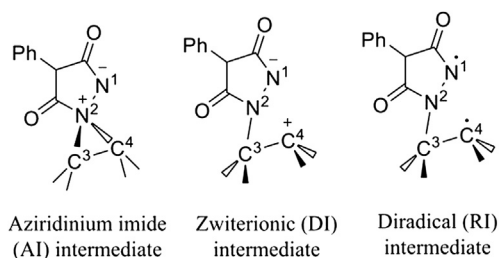
2. Results and discussion

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 ¹H 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 –OCH₂– bearing alcohols) are diastereotopic due to the asymmetric carbon center connected to the nitrogen atom. Due to this asymmetric carbon, the two geminal CH₃– groups show a diastereotopic relation and differ in their chemical shifts both in the ¹H and ¹³C NMR spectra.

From the ¹H 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 $\Delta\Delta H^\ddagger$ and $\Delta\Delta S^\ddagger$ 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 $\Delta\Delta H^\ddagger_{\text{ene,trap}}$ and $\Delta\Delta S^\ddagger_{\text{ene,trap}}$ 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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