

Nucleophile-solvent isotope effects between methanol isotopomers during the interception of aziridinium imide-‘like’ closed intermediates

Zois Syrgiannis and Yiannis Elemes*

Department of Chemistry, University of Ioannina, 45110 Ioannina, Greece

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Abstract—Deuterated methanol isotopomers were found to compete efficiently with normal methanol during the interception of an intermediate with structural characteristics of the aziridinium imide, formed in the reaction of *N*-phenyltriazolinedione with simple alkenes such as 2-methylpropene, 2-methyl-2-butene, and 2,3-dimethyl-2-butene. In general, a (trideuterio)methyl-group bearing methanol was found to add at the tertiary carbon atom of the intermediate more efficiently with regard to hydrogen isotopomeric methanol, and this result is explained in terms of the nucleophile-solvent isotope effect in an S_N2 -‘like’ transition state of solvent addition to the intermediate.

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The ene¹ reactions of triazolinediones (TADs),² singlet oxygen (¹O₂),³ and nitrosoarenes (ArNO)⁴ with alkenes bearing allylic hydrogens have attracted much attention over the years from both synthetic⁵ and mechanistic⁶ points of view. Furthermore, they have recently been reviewed.⁷ The reactions proceed via stepwise processes through a three-membered-ring intermediate, namely a perepoxide, a diaziridinium imide and an aziridine-*N*-oxide, as evidenced by isotope effect studies.⁸ Recently, on the basis of computational results, a biradical intermediate was proposed in the ene reactions of TADs,⁹ which was consequently challenged by experimental evidence from stereochemical¹⁰ and stereoisotopic studies.¹¹ Further work is still needed with regard to this issue.

It has been reported that the reaction of *N*-phenyltriazolinedione (PTAD) in nucleophilic protic solvents affords, in addition to the ene adduct, a second alkoxy-substituted product, proposed to be the result of nucleophilic addition of the solvent to the diaziridinium imide intermediate, through an S_N2 -‘like’ transition state.¹² In the above study, it was suggested

that both of these final products originated from a common intermediate and that formation of the solvent adduct was under entropic control. Recently, we reported¹³ on the dependence of thermodynamic (enthalpy and entropy) parameters resulting from the size and bulkiness of the added nucleophilic protic solvent as studied in the reaction of PTAD with trimethyl-ethylene, and which were consistent with the proposed S_N2 -‘like’ transition state.

We decided to further test the involvement of the above mentioned S_N2 -‘like’ transition state in the nucleophilic addition of solvent to the aziridinium imide intermediate, with the use of solvent isotope effects. Isotope effects are a powerful tool for clarification of organic reaction mechanisms and have been widely used over the years.¹⁴ Kinetic isotope effects (both with regard to deuterated substrates and incoming nucleophile) are known in nucleophilic substitution reactions and have inspired the present work.¹⁵ On the other hand, solvent isotope effects are decisive tools for the description of transition states for hydrogen transfer reactions¹⁶ and have been thoroughly applied to biological systems.¹⁷ We were especially interested in the measurement of possible isotope effects that could arise from the incoming nucleophile, which in our case was the solvent used for the reaction, that is, methanol and deuterated isotopomers. We report here for the first time inverse solvent kinetic isotope effects measured during the nucleophilic

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* Corresponding author. Tel.: +30 26510 98432; fax: +30 26510 98799; e-mail: yelemes@cc.uoi.gr

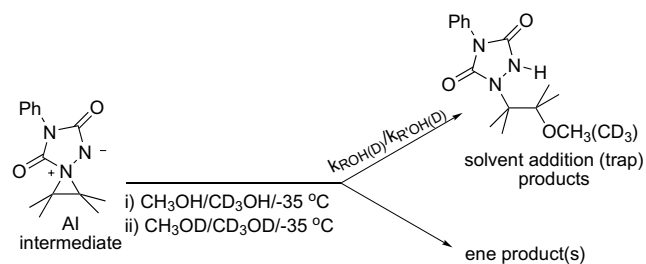
interception of an intermediate (with structural characteristics of the proposed diaziridinium imide) formed in the ene reaction of PTAD with simple alkenes, which provide strong experimental support for an S_N2 -‘like’ transition state.

We studied the reaction of *N*-phenyltriazolinedione with simple alkenes in equimolar mixtures of isotopomeric methanols, that is, CH_3OD/CD_3OD and CH_3OH/CD_3OH . The chosen alkenes were 2-methylpropene (isobutylene), 2-methyl-2-propene (trimethyl-ethylene, TriME) and 2,3-dimethyl-2-butene (tetramethyl-ethylene, TetraME). The basic idea was to measure any possible differentiation in concentrations of the solvent addition products, which could be devoted to the isotopic discrimination of the incoming nucleophilic-solvent molecule. In this way, solvent isotope effects would offer another basic criterion in the elucidation of the solvent addition transition state.

In this context, to a 10^{-1} M solution of the alkene in an equimolar mixture (1 ml of total volume) of isotopomeric methanols (i.e., CH_3OH/CD_3OH , and CH_3OD/CD_3OD), equilibrated to the desired temperature, solid PTAD (90% of the stoichiometric molar ratio with regard to the alkene) was added in one portion, and after decolorization of the red solution, volatile compounds were removed with the aid of a rotary evaporator and then with a high vacuum pump. After precipitation-purification of the mixture of ene and methanol adducts from CH_2Cl_2/n -hexanes, the 1H NMR spectra of the mixture were recorded, Scheme 1.

The molar ratios of the two solvent addition products were calculated from the 1H NMR integral ratio of the appropriate resonances.¹⁸ The ratios found are listed in Table 1.

The observed solvent isotope effect values listed in Table 1 reveal a consistent preference for the heavier deuterated over the lighter methanol-solvent, for interception of the aziridinium imide-‘like’ intermediate, for all the three model alkenes tested. This fact reveals that they all react in the same manner, with the intervention of similarly structured intermediates. At the same time, this coherence is valid for both pairs of isotopomeric methanols. It is interesting to note at this point that the calculated nucleophile-solvent isotope effects are of the same magnitude



Scheme 1. Solvent addition and ene products formed from the reaction of simple alkenes with *N*-phenyltriazolinedione in alcohol mixtures.

Table 1. Solvent isotope effects for the interception of aziridinium imide intermediates from the competition between methanol isotopomers^{a,b}

Alkene	Solvent mixture CH_3OD/CD_3OD Solvent isotope effect k_{CH_3OD}/k_{CD_3OD}	Solvent mixture CH_3OH/CD_3OH Solvent isotope effect k_{CH_3OH}/k_{CD_3OH}
Isobutylene	0.83 ± 0.03	0.79 ± 0.03
TriME	0.72 ± 0.02	0.81 ± 0.02
TetraME	0.84 ± 0.03	0.74 ± 0.03

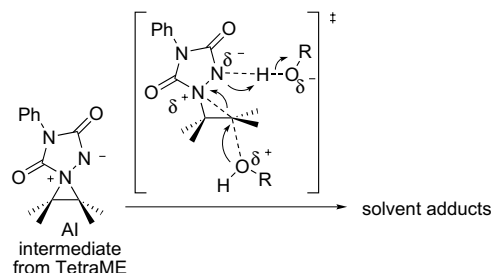
^a All reactions were conducted at -35 °C, unless otherwise indicated.

^b Numbers given are mean values of two independent runs. Errors are higher deviations from the mean value.

irrespective of the $-OH(D)$ bond bearing methanol pairs. We have restricted this study to the present isotopomer pairs, in order to avoid additional isotope effect contributions from mixed solvents (i.e., CH_3OH/CD_3OD , and CH_3OD/CD_3OH).¹⁹

The general $\sim 20\%$ preference for the CD_3 -bearing alcohols testifies to the competition of the solvent molecules towards a ‘closed’ intermediate rather than to an ‘opened’ one, because in the latter case a molar ratio very close to unity would be expected. Stereochemical studies for the reaction of various alkenes with *N*-phenyltriazolinedione have shown that nucleophilic-solvent addition to aziridinium imide intermediates is stereospecific with simple alkenes such as *cis*- and *trans*-2-butenes, specifically deuterated trimethyl-ethylenes and unsubstituted indene, and that it continues to be stereoselective with substituted indenenes.²⁰ An S_N2 -‘like’ transition state for solvent addition is considered as a plausible explanation for the above stereochemical results.

With regard to the inverse solvent isotope effects measured in the present study, our discussion is focused on the transition state for the solvent adduct formation. Initially, TetraME was used as the alkene. After electrophilic addition of triazolinedione to the alkene, the AI intermediate is symmetrical and in order to achieve the transition state for nucleophilic-solvent addition, one methanol molecule (acting as the nucleophile) has to interact with a tertiary carbon atom leading to C–N bond breaking (i.e., the leaving group), Scheme 2.



Scheme 2. Proposed transition state for solvent addition to the AI intermediate formed from PTAD and TetraME.

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