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

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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.

The ene[1] reactions of triazolinediones (TADs),[2] singlet oxygen ($^1O_2$),[3] and nitrosoarenes (ArNO)[4] with alkenes bearing allylic hydrogens have attracted much attention over the years from both synthetic[5] and mechanistic[6] 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 stereochemical[10] 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 reported[13] 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 reactions[16] 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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Keywords: Ene reactions; Triazolinediones; Solvent addition; Solvent isotope effects.

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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 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]

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

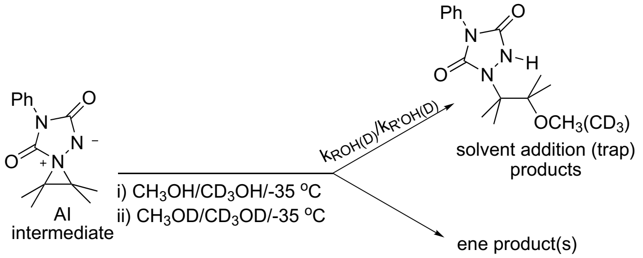
Alkene	Solvent mixture CH_3OD/CD_3OD Solvent isotope effect k_{CH_3OD}/k_{CD_3OD}	Solvent mixture CH_3OH/CD_3OH Solvent isotope effect k_{CH_3OH}/k_{CD_3OH}
Isobutylene	0.83 ± 0.03	0.79 ± 0.03
TriME	0.72 ± 0.02	0.81 ± 0.02
TetraME	0.84 ± 0.03	0.74 ± 0.03

[a] All reactions were conducted at −35 °C, unless otherwise indicated.

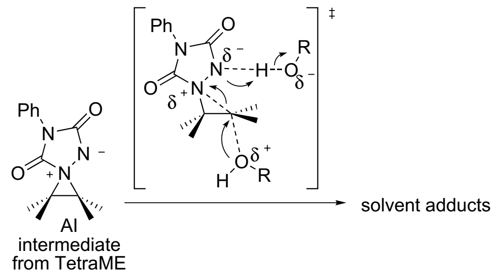
[b] Numbers given are mean values of two independent runs. Errors are higher deviations from the mean value.

The general ~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 indenes.[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 1. Solvent addition and ene products formed from the reaction of simple alkenes with *N*-phenyltriazolinedione in alcohol mixtures.



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

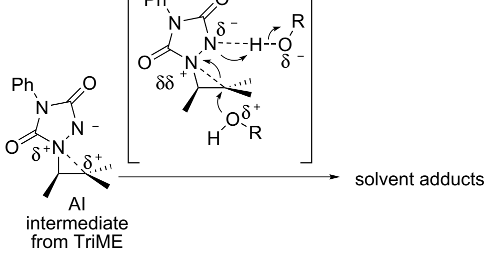
The fact that a substantial inverse solvent isotope effect of ~0.80 was measured in the case of TetraME testifies to a large extent of bond making between the O atom (of the incoming methanol molecule) and the tertiary C atom (of the AI intermediate) in the transition state. Alternatively, such an inverse isotope effect from the side of the incoming nucleophile could be taken as evidence for a 'tight' transition state, that is, interaction from a short distance. It is well documented in the literature that inverse isotope effects measured in S_N2 nucleophilic substitutions for deuterated incoming nucleophiles owe their existence to differences in the bulkiness of a 'tight' transition state and for this reason are also called steric isotope effects.[15] We propose that this is the case for the present reaction.

It is known that a C–D bond is shorter than a C–H bond by 10^{-3} Å.[14] Thus, CD_3OD is a smaller nucleophile and in competition with CH_3OD interacts from a shorter distance with the tertiary carbon atom in the AI intermediate, and leads to a thermodynamically more stable transition state. Therefore, CH_3OD approach faces repulsive steric interactions due to greater hindrance in a 'tight' transition state, the CH_3 group being more 'crowded'. The same holds for the CD_3OH/CH_3OH pair of nucleophilic solvents and the isotope effects measured for these were of the same magnitude.

The inverse solvent isotope effect still persists with TriME, albeit in this case there is some charge separation at the tertiary carbon atom in the non-symmetrical intermediate as has been postulated by Greene et al.,[8c] due to the geminal selectivity found in the ene reactions of triazolinediones with tri-substituted alkenes. The existence of the C–N bond between the tertiary carbon atom and the bridged nitrogen in the AI intermediate was evidenced from the stereospecificity of methanol adduct formation from (trideuterio)methyl-trimethylethylenes.[20]

We again consider the transition state resulting from solvent addition to a non-symmetrical AI intermediate, Scheme 3.

In this context, the tertiary carbon atom in the AI intermediate from TriME is more 'loose' bearing a partial $\delta+$ charge. For this reason, the transition state for solvent addition is expected to also be more 'loose' with regard to that derived from TetraME. So, we could expect steric hindrance (although present) to be less pronounced, thus leading to less competition between the two isotopomeric methanols, and consequently to higher (less inverse) solvent isotope effects. The results obtained show that steric hindrance is decisive even in this case and that the smaller nucleophilic-solvent can insert closer to the, still sp^3 hybridized, tertiary carbon of the closed intermediate.



Scheme 3. Proposed transition state for the solvent addition to the AI intermediate formed from PTAD and TriME.

The same arguments as above would also apply in the case of isobutylene, where the solvent isotope effects measured were very close to those of the first two cases.

It is important to note here the fact that the magnitude of the nucleophile-solvent isotope effects measured in this study, $k_H/k_D = \sim 0.92$ per (H/D) atom, are very close to those reported in the literature for solvolysis reactions of various methyl derivatives in water where the inverse substrate α-deuterium secondary isotope effects were taken as evidence for an S_N2 displacement by the solvent.[14,21] In addition, the same order of magnitude was found for the inverse nucleophile α-secondary isotope effects measured in the S_N2 substitution reactions of benzyl- and alkyl-arenesulfonates and benzyl-bromides with anilines, and were taken as evidence for the higher degree of bond making and the 'tightness' of the transition state.[15e] Our results are therefore consistent with a 'tight' S_N2-'like' transition state where the 'smaller'-deuterated nucleophilic-solvent inserts closer, with respect to the lighter analogue, to the reactive center of the tertiary carbon atom of the intermediate resulting to a higher degree of C–O bond formation. Of further support to the above proposal is the fact that if a distant interaction of the nucleophile with the tertiary carbon center had been involved, then a secondary isotope effect in favor of the CH_3-bearing alcohols should have been measured. This is clearly not the case. If such a contribution was present, then it must be obscured by the steric hindrance of the tight transition state. To account for the consistency of the inverse nucleophile-solvent isotope effects found in the present study, we conclude that the 'tight' transition state includes a higher degree of C–O bond making accompanied by a lesser degree of C–N bond breaking.

In conclusion, we have reported here for the first time on experimental nucleophile-solvent isotope effects, determined during the nucleophilic interception of an intermediate, with the structural characteristics of a diaziridinium imide, in the reaction of *N*-phenyltriazolinedione with simple alkenes. The nucleophile-solvent isotope effects were found to be consistently inverse and were taken as evidence for a 'tight' S_N2-'like' transition state, where the 'smaller' deuterated nucleophilic-solvent interacts from a closer distance with the electrophilic center of the intermediate and faces less steric hindrance than its lighter solvent competitor. At this stage of the work, the present results give a qualitative description and in the next steps we will seek further support from theoretical calculations with regard to a more detailed structure of the transition state.

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18. (a) Appropriate resonances for the calculation of solvent isotope effects were taken (ppm): 2-methylpropene: 3.62 (s, $–NCH_2–$), 3.25 (–OMe); 2-methyl-2-butene: 4.20 (q, –NCH–), 3.23 (–OMe); 2,3-dimethyl-2-butene: 3.26 (–OMe), 1.23 ($–OCMe_2$); (b) Calculated molar ratios $[\mathrm{ene}]/[\mathrm{trap}]_{\mathrm{total}}$: 2-methylpropene: 0.42 (CH_3OD/CD_3OD); 0.68 (CH_3OH/CD_3OH); 2-methyl-2-butene: 0.29 (CH_3OD/CD_3OD); 0.34 (CH_3OH/CD_3OH); 2,3-dimethyl-2-butene: 0.15 (CH_3OD/CD_3OD); 0.14 (CH_3OH/CD_3OH).
19. In such a case we could have uneven competition between the two nucleophile-solvents because of: (i) a possible primary isotope effect during -H(D) transfer, and (ii) a secondary isotope effect during the nucleophilic addition through hyperconjugation, both of which would have favored the –OH bearing solvent.
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