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Thermodynamic parameters $\Delta\Delta H^{\#}$ and $\Delta\Delta S^{\#}$ as probes for the transition state in the reaction of *N*-phenyltriazolinedione with alkenes in nucleophilic solvents

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Dedicated to the memory of Professor Christopher S. Foote

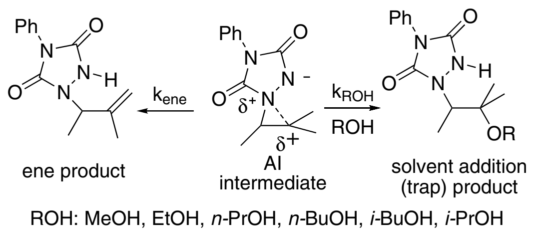
Abstract—The thermodynamic parameters, $\Delta\Delta H^{\#}$ and $\Delta\Delta S^{\#}$, were determined for the interception of an intermediate, with the structural characteristics of an aziridinium imide, by nucleophilic solvents during the reaction of 2-methyl-2-butene with *N*-phenyltriazolinedione. The experimentally measured parameters were found to be in favor of an S_N2-'like' transition state and showed strong dependence on the bulkiness of the incoming molecule of the nucleophile-solvent.

The ene[1] reactions of triazolinediones (TADs),[2] singlet oxygen ($^1O_2$),[3] and nitrosoarene (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] This issue remains open for additional structural studies in the future.

It has been reported that reaction of *N*-phenyltriazolinedione (PTAD) in nucleophilic protic solvents affords, in addition to the ene adduct, a second alkoxy product that was proposed to be the result of the nucleophilic addition of the solvent to the diaziridinium imide intermediate.[12] In the above study it was suggested that both of these final products originate from a common intermediate and that the formation of the solvent adduct is under entropic control. In order to throw further light on the solvent addition path, we continued work on this subject by measuring the thermodynamic parameters $\Delta\Delta H^{\#}$ and $\Delta\Delta S^{\#}$, for the reaction of simple alkyl-substituted alkenes with PTAD in several alcoholic solvents that differ in their bulkiness. The idea was that in a nucleophilic, S_N2-'like', interception of an intermediate by the solvent it would be possible to detect the effect of the bulkiness of the incoming nucleophile-solvent. For clarity with the interpretation of the results we used the proposed diaziridinium imide intermediate as a model.

In this context, we carried out the reactions of PTAD with 2-methyl-2-butene, in six alcoholic solvents of varying alkyl chain length and branching (Scheme 1).

In a typical experiment, to a 10^{-1} M solution of 2-methyl-2-butene in the appropriate solvent equilibrated



ROH: MeOH, EtOH, *n*-PrOH, *n*-BuOH, *i*-BuOH, *i*-PrOH

Scheme 1. Ene and solvent addition (trap) products in the reaction of 2-methyl-2-butene with *N*-phenyltriazolinedione in alcoholic solvents.

Keywords: Ene reactions; Triazolinediones; Thermodynamic parameters; Solvent addition.

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to the desired temperature, solid PTAD (90% of the stoichiometric molar ratio) was added at once, 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. Next, the ^{1}H NMR of the crude mixture was taken.[13] For each solvent the reaction was performed at least at three different temperatures. From the molar ratio of the two products, from ^{1}H NMR integral ratios of the appropriate peaks for each temperature, we plotted ln{[ene]/[trap]} as a function of $1/T$. From the best fit straight line, the $\Delta\Delta H^{\#}$ and $\Delta\Delta S^{\#}$ parameters were calculated for each solvent using the Arrhenius equation:

$$\begin{aligned}\ln k &= \ln(k_{\text{ene}}/k_{\text{ROH}}) = \ln(k_{\text{ene}}/k_{\text{trap}}) = \ln\{[\text{ene}]/[\text{trap}]\}\\ &= -\Delta\Delta G^{\#}_{\text{ene,trap}}/RT = -(\Delta\Delta H^{\#}_{\text{ene,trap}} - T\Delta\Delta S^{\#}_{\text{ene,trap}})/RT\\ &= (-\Delta\Delta H^{\#}_{\text{ene,trap}}/R)1/T + \Delta\Delta S^{\#}_{\text{ene,trap}}/R.\end{aligned}$$

It is noticeable that the correlation coefficients found for all the tested alcoholic solvents were very close to unity (>0.99). The values obtained from ^{1}H NMR were also verified by gas chromatography and were found to be very similar, together with good correlation coefficients. The values for each solvent tested are depicted in Table 1.

For clarity with regard to the numbers included in Table 1, we should note that $\Delta\Delta H^{\#} = \Delta H^{\#}_{\text{ene}} - \Delta H^{\#}_{\text{trap}}$ (thermodynamic stability factor) favors the formation of the solvent addition product over the ene product, whereas $\Delta\Delta S^{\#} = \Delta S^{\#}_{\text{ene}} - \Delta S^{\#}_{\text{trap}}$ (entropic factor) favors the formation of the ene over the solvent addition product (monomolecular for the ene vs bimolecular for the solvent addition-trapping sequence).

At the first sight, inspection of Table 1 reveals that there is good agreement between the NMR and GC values obtained. The dependence of both the thermodynamic parameters on the size changes in the alcoholic solvent is also evident. The values of both parameters were found to have decreased gradually with increasing solvent bulk.

Table 1. $\Delta\Delta H^{\#}$ and $\Delta\Delta S^{\#}$ thermodynamic parameters for the reaction of trimethylethylene with PTAD in different alcoholic solvents[a,b]

Entry	Solvent (ROH)	Method	$\Delta\Delta H^{\#}$ (kcal/mol)	$\Delta\Delta S^{\#}$ (eu)
1	MeOH	NMR	6.8 ± 0.1	22 ± 1
		GC	6.9 ± 0.1	22 ± 1
2	EtOH	NMR	5.2 ± 0.1	19 ± 1
		GC	5.1 ± 0.1	19 ± 1
3	*n*-PrOH	NMR	4.6 ± 0.1	17 ± 1
		GC	4.6 ± 0.1	17 ± 1
4	*n*-BuOH	NMR	3.7 ± 0.1	14 ± 1
		GC	3.6 ± 0.1	14 ± 1
5	*i*-BuOH	NMR	3.1 ± 0.1	15 ± 1
		GC	3.2 ± 0.1	15 ± 1
6	*i*-PrOH	NMR	1.7 ± 0.1	10 ± 1
		GC	1.4 ± 0.1	9 ± 1

[a] The values included in the table are average values of two independent runs for each method used.

[b] The values from ^{1}H NMR spectra were calculated from integral ratios of the appropriate peaks and those from GC chromatograms were calculated from the respective % area ratios after their normalization for the MW of the two products.

In entries 1–4, there is a good comparison of the gradual reduction of $\Delta\Delta H^{\#}$ values as a function of the increased linear chain length of the added nucleophilic solvent. Starting from MeOH (entry 1), the solvent adduct (trap product) was found to be favored by $\Delta\Delta H^{\#}$ ~7 kcal/mol. With EtOH (entry 2) this preference drops to ~5 kcal/mol, while with an extra –CH_2– group added to the alkyl chain (*n*-PrOH, entry 3) a $\Delta\Delta H^{\#}$ value of ~4.5 kcal/mol was measured, falling to ~3.6 kcal/mol preference for *n*-BuOH addition over the adduct formation.

The last two entries (5 and 6) offer a comparison of branched alcoholic solvents (*i*-BuOH and *i*-PrOH, respectively). When the alkyl chain branching is at the opposite end from the solvent nucleophilic center (oxygen atom at the hydroxyl group) there is only a small difference in the $\Delta\Delta H^{\#}$ values found, as is evident on comparing those calculated for *n*-BuOH versus *i*-BuOH (~3.6 kcal/mol vs ~3.2 kcal/mol, respectively). In contrast, when the alkyl chain branching is closer to the nucleophilic center of the solvent as in *i*-PrOH (secondary alcohol) there is a dramatic decrease in the preference for solvent addition over ene adduct formation (i.e., ~1.6 kcal/mol).

The above differences in $\Delta\Delta H^{\#} = \Delta H^{\#}_{\text{ene}} - \Delta H^{\#}_{\text{trap}}$ values correlate satisfactorily with the bulkiness of the alkyl chain of the nucleophilic solvent. The bulkier the nucleophile-solvent the less preference for the solvent addition product over ene adduct formation. According to the Hammond postulate, the preference for solvent adduct formation should come from greater stabilization of the transition state of the solvent interaction with the AI intermediate. This stabilization is more pronounced in the case of smaller nucleophilic solvents (i.e., MeOH), which offers a less crowded transition state. In other words, the interaction of MeOH with the target tertiary carbon center in the AI intermediate is stronger or more tight (more pronounced or a closer interaction). Such an interaction between the solvent molecule and the AI intermediate is more difficult to achieve as the chain length or branching near the nucleophilic center increases, presumably because of repulsive steric interactions between the incoming molecule of the solvent and the substituents at the tertiary carbon atom of the intermediate. This distant interaction leads to a less stabilized transition state for the solvent addition path in comparison to the transition state leading to the formation of the ene adduct.

In the final column of Table 1, the $\Delta\Delta S^{\#} = \Delta S^{\#}_{\text{ene}} - \Delta S^{\#}_{\text{trap}}$ values also decreased gradually as the size of the nucleophilic solvent increases. In this context, in the case of the smaller nucleophile, MeOH (entry 1), the larger $\Delta\Delta S^{\#}$ value was found to reveal a higher symmetry requirement (or organization) of the transition state leading to the solvent adduct over ene adduct formation. This large (22 eu in favor of the ene over solvent adduct formation) difference in $\Delta S^{\#}$ should owe its magnitude to the monomolecularity of the ene adduct transition state (intermolecular reorganization after AI intermediate formation and relatively more positive $\Delta S^{\#}_{\text{ene}}$) versus the bimolecularity of the solvent addition transition state (intermolecular organization of the solvent molecule with the AI intermediate, therefore a relatively more negative $\Delta S^{\#}_{\text{trap}}$).[12]

The above difference in $\Delta\Delta S^{\#}$ decreases gradually with increasing alkyl chain length. Accordingly, in EtOH (entry 2), $\Delta\Delta S^{\#}$ was found to be ~19 eu, in *n*-PrOH ~17 eu, and ~14 eu for *n*-BuOH (entry 4). Again no dependence of the $\Delta\Delta S^{\#}$ value was noticed when the alkyl branching in the solvent molecule was away from the nucleophilic center, as was evident from the values obtained for *n*-BuOH and *i*-BuOH (14 eu and 15 eu, entries 4 and 5, respectively). In contrast, the biggest decrease was found in the case of *i*-PrOH (entry 6) where a value of $\Delta\Delta S^{\#}$ ~10 eu was measured. Again, alkyl branching close to the nucleophilic center of the solvent molecule results in the smallest $\Delta\Delta S^{\#}$ difference, as was also found for the $\Delta\Delta H^{\#}$ value.

The above advanced differences in $\Delta\Delta S^{\#}$ values as a function of alkyl chain length-bulkiness of the nucleophilic solvent is attributed to the more 'strict' (or 'tight') organization of the transition state leading to solvent adduct formation with smaller nucleophiles (higher symmetry demand) and to the more 'loose' (or 'soft') organization in the case of longer or branched nucleophiles (less symmetry demand). Higher $\Delta\Delta S^{\#}$ values were obtained in less crowded bimolecular transition states, whereas more crowded transition states gave rise to lower values.

The values found for the $\Delta\Delta H^{\#}$ and $\Delta\Delta S^{\#}$ parameters discussed above support an S_N2-'like' transition state leading to the formation of the solvent addition product, as is depicted in Figure 1.

Since the AI intermediate, and thus the succeeding transition state, is surrounded by the alcoholic solvent, proton transfer from a solvent molecule to nitrogen is reasonably assumed to be involved in the same step. This idea led us to the proposition of a solvent adduct-forming step through a transition state that involves two molecules of the nucleophilic solvent that interact tightly with the AI intermediate as depicted in Figure 1.

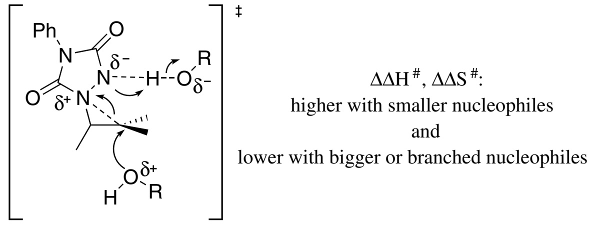

Figure 1. Transition state for the nucleophilic interception of the AI intermediate by an alcoholic solvent molecule, leading to the formation of the solvent addition (trap) product.

The involvement of the second solvent molecule is expected to contribute to both thermodynamic parameters in several ways. First to $\Delta\Delta H^{\#}$ because (i) of the N–H bond formation (transition state stabilization factor in favor of solvent adduct formation) and at the same time, (ii) of a destabilized contribution coming from the remaining partially negatively charged alkoxy-moiety of the solvent molecule. More substituted alcoholic solvents should impose a more pronounced destabilization because of the +I inductive effect of the alkyl-substituents.[14] Our opinion is that the measured $\Delta\Delta H^{\#}$ differences are a mean value of the above contributing factors.

The involvement of the second solvent molecule is also expected to have a contribution to $\Delta\Delta S^{\#}$, because of the decreased efficiency, for the bulkier solvent molecules, to be aligned (or conjugated) with the negatively charged nitrogen atom during the transition state, again because of the steric interactions involved. Such interactions are expected to lower the overall measured $\Delta\Delta S^{\#}$, thus lowering the degree of organization in the transition state during solvent addition.[15]

In summary, we have reported here experimentally determined thermodynamic parameters $\Delta\Delta H^{\#}$ and $\Delta\Delta S^{\#}$ for the reaction of trimethylethylene with PTAD in alcoholic solvents, which have helped to gain detailed information about the geometry of the transition state leading to the nucleophilic solvent addition product. This systematic study together with the acquired information could be an initiative for further structural and, hopefully synthetic studies for the ene reaction. Currently we are working toward this direction extending the study with other simple alkyl-substituted alkenes.

Acknowledgments

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13. All the solvent addition products were isolated chromatographically and fully characterized by ^{1}H, ^{13}C NMR, and FT IR spectroscopy and by ESI MS spectrometry. Their spectra are in agreement with their structures and will be reported in detail in a full paper. Selected spectral data for the MeOH adduct, *1,1-dimethyl-2-[4-phenyl-1,2,4-triazoline-3,5-dionyl]-propyl methyl ether*; ^{1}H NMR ($CDCl_3$, 250 MHz): 1.23 (s, 3H, CH_3), 1.31 (s, 3H, CH_3), 1.33 (d, $J = 6.89$ Hz, 3H, CH_3), 3.26 (s, 3H, OCH_3), 4.19 (q, $J = 6.89$ Hz, 1H, CH), 7.32–7.55 (m, 5H, aromatics), 7.79 (s, br, 1H, NH); ^{13}C NMR ($CDCl_3$, 62.9 MHz): 12.2, 21.5, 22.7, 49.5, 58.8, 78.0, 125.6, 128.0, 129.1, 131.5, 151.5, 152.4; FT IR (KBr, ν cm^{-1}): 3201, 2987, 1767, 1691, 1502, 1431, 1085, 839, 770, 643; ESI MS: calculated for $C_{14}H_{19}N_3O_3$ $[M] = 277.32$. Found: $[M+H]^+ = 278.43$ (100). Elemental analysis calculated for $C_{14}H_{19}N_3O_3$: C, 60.63; H, 6.91; N, 15.15. Found: C, 60.71; H, 6.92; N, 15.13.
14. This inductive effect though is in favor of the addition of the first solvent molecule to the tertiary carbon atom.
15. Such low organization is valid also for the first interacting molecule in the case of a bulky solvent.