Uncommon aqueous media for nitrilimine cycloadditions. II.† Computational study of the effect of water on reaction rate

Alessandro Ponti*[a] and Giorgio Molteni[b]

[a] *Istituto di Scienze e Tecnologie Molecolari, Consiglio Nazionale delle Ricerche, via Golgi 19, 20133, Milano, Italy. E-mail: ponti@istm.cnr.it; Fax: +39 02 5031 4300*
[b] *Università degli Studi di Milano, Dipartimento di Chimica Organica e Industriale, via Golgi 19, 20133, Milano, Italy*

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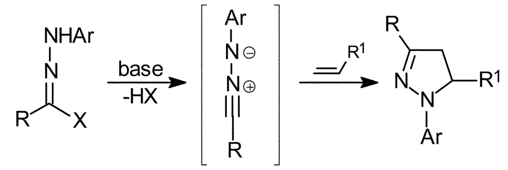
The effect of water on the 1,3-dipolar cycloaddition reaction of nitrilimines to alkenes has been studied by HF and DFT *ab initio* calculations. As solvation models we used the polarizable continuum model and a model comprising small clusters consisting of reactants hydrogen-bonded to water molecules. In addition, a combination of these two models was considered. Reactivity has been qualitatively estimated by the familiar frontier molecular orbital approach and quantitatively computed by a recent extension to the hard–soft acid–base principle involving molecular reactivity indices. The main conclusions drawn from the extensive computational results are that (i) the effect of water is in general rather small and (ii) therefore, water is not directly responsible for the large acceleration of the 1,3-dipolar cycloaddition reaction of nitrilimines to alkenes. Its role is surely minor with respect to that played by the ionic catalysts present in the reaction mixture, in agreement with the conclusions drawn in the experimental companion paper.

1. Introduction

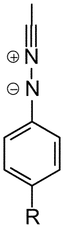
Nitrilimine cycloadditions to ethylenic dipolarophiles represent the choice method in the synthesis of variously 5-substituted-4,5-dihydropyrazoles (Scheme 1).[1] Due to the wide applications of the latter compounds in several fields of applied chemistry,[2] we developed an efficient nitrilimine cycloaddition protocol in aqueous media.[3] As reported in the companion paper (preceding article in this issue[1a]), a large increase in reaction rate has been observed for the addition of electron-rich nitrilimines to electron-poor alkenes when the reaction is carried out in a basic aqueous solution containing ionic catalysts such as sodium dodecylsulfate (SDS) and tetrahexylammonium chloride (THAC). For future reference, a selection of these experimental results is here reported (Fig. 1 and Table 1). The increase in reaction rates was deduced from reaction times and yields in comparison with those observed in chloroform.[4] To gain better insight into the mechanistic aspects, we undertook the estimation of the effect induced by water on the kinetics of nitrilimine 1,3-dipolar cycloadditions (1,3-DC) subjected to experimental study in the companion paper.[1a] Indeed, despite the usefulness of the title cycloadducts, a reliable theoretical description of nitrilimine 1,3-DCs in water is still lacking. The key concepts in this study are solvation and reactivity. It is of utmost importance to choose appropriate theoretical models for both concepts and to compare results from different models in order to draw reliable conclusions.

We considered two ways of estimating the kinetics of 1,3-DCs. The familiar frontier molecular orbital (FMO) model,[5] which focuses on the energy gap between the FMOs of the reactants, provides qualitative hints about relative reactivity. In the past decade, another approach to reactivity has been developed. This approach is based on the hard–soft acid–base (HSAB) principle[6] and on local reactivity indices[7] from density functional theory (DFT).[8] It has been successfully applied to the prediction of the favoured regioisomer in many 1,3-DCs.[9] Such method has been recently extended[10] to a quantitative measure of reactivity by computing the stabilization of the dipole–dipolarophile complex at the beginning of the reactive encounter. Indeed, in 1,3-DCs the relative energy of transition states is paralleled by the relative energy of the weakly interacting complexes forming in the early stage of the reaction.[11]



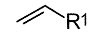
Scheme 1 General synthesis of 4,5-dihydropyrazoles.

Also for the models describing the solvent effect, we considered different approaches. Within the polarizable continuum



1

a: R = H
b: R = Me
c: R = NO_2



2

a: R^1 = COOMe
b: R^1 = *n*-Bu

Fig. 1 Structure and numbering scheme of the reactants studied in this work.

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† Part 1, preceding paper (ref. 1*a*).

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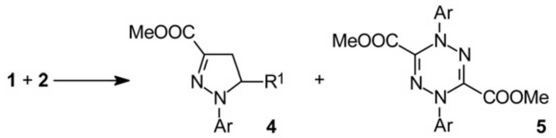
Table 1 Experimental yield of the reaction between nitrilimines **1** and dipolarophiles **2** in aqueous medium[a]



R	R^1	Reaction	Time/min	Products and yields (%)[b]		
				1	**4**	**5**
H	COOEt	**1a** + **2a**	10	—	95	—
Me	COOEt	**1b** + **2a**	10	—	95	—
NO$_2$	COOEt	**1c** + **2a**	100	—	3	—
H	*n*-Bu	**1a** + **2b**	90	5	17	42
Me	*n*-Bu	**1b** + **2b**	90	9	31	25
NO$_2$	*n*-Bu	**1c** + **2b**	360	12	—	—

[a] Ar = 4-Me-C$_6$H$_4$. [b] Isolation yields.

model (PCM),[12] the solvent effect is represented by the mutual electrostatic coupling between the molecular electron density of the reactants and a continuous medium with the dielectric constant of bulk liquid water. This approach has been recently applied to the study of the solvent effect on the activation energy of 1,3-DCs. In all cases, it turned out that the activation energy changes by a few kcal mol^{-1} (often just 1–2 kcal mol^{-1}) for polar solvents.[13] This effect seems inadequate to explain the observed large increase in the addition rate of electron-rich nitrilimines to electron-poor alkenes. Therefore, a second approach was considered, where we studied solvation clusters consisting of one reactant molecule and several hydrogen-bonded water molecules. Of course, the clusters themselves can be embedded in a polarizable continuum. As we will see, the combination of these theoretical and computational tools provides evidence supporting the interpretation of the experimental results given in the companion paper.[1a]

2. Computational details

All systems (reactant molecules and solvation clusters) were computed within the Hartree–Fock (HF) scheme; DFT calculations, which employed the hybrid functional B3LYP,[14] were carried out for the reactant molecules only. All calculations were performed using the standard 6-311 + G(d,p) basis set. In order to save computational effort, calculations were performed for methyl acrylate **2a** instead of ethyl acrylate studied in the companion paper.[1a] The geometries of the neutral reactants **1** and **2** *in vacuo* were fully optimised both at the HF and at the DFT-B3LYP level. PCM calculations of neutral systems were performed using the dielectric constant $\varepsilon = 78.39$ of bulk water and a solute cavity bounded by the electron isodensity surface[12] at 0.001 atomic units. PCM calculations were carried out at the *in vacuo* geometry both at the HF and at the DFT-B3LYP level. The mono-anions and -cations of the reactants *in vacuo* were computed at the unrestricted DFT-B3LYP level at the geometry of the neutrals; unrestricted HF calculations were discarded because of heavy spin contamination. PCM calculations of the ionic systems were performed at the unrestricted DFT-B3LYP level only.

The *in vacuo* geometries of the clusters consisting of water molecules hydrogen-bonded to **1a** and **2a** were fully optimised at the RHF level. A word about the procedure for this structural optimisation is in order at this point. First, we assumed that the largest solvent effect is due to water molecules forming "classical" hydrogen bonds with the reactant molecule. Therefore, in the case of **2a**, hydrogen bonds were considered only for the two proton-acceptor oxygen atoms of the ester group. For **1a**, in addition to the ester oxygen atoms, both nitrogen atoms in the nitrilimine moiety were considered as possible proton acceptors. Next, hydrogen bonding to each of the above proton-acceptor sites was studied by placing one or two water molecules in several different arrangements around the considered atom and optimising the geometry. Thus, a library of possible hydrogen-bonding patterns around a single atom was obtained. Up to this point, mutual interaction of the water molecules with each other and with the reactant has been neglected. Therefore, the last step was to fully optimise all possible combinations of hydrogen-bonding patterns taken from the library. Some structures turned out to be unstable, either because of steric hindrance or because of the formation of independent water dimers. Among the stable ones, we chose those of lowest energy as representative structures and named them **1aW** and **2aW**. As usual, PCM calculations of these clusters were performed at the *in vacuo* geometry. All calculations were carried out by the Gaussian98 suite.[15]

Reactivity indices[7] were computed in the usual finite difference approximation within the framework of DFT. The global indices are the molecular softness

$$S = (IP - EA)^{-1} \qquad (1)$$

and the electron chemical potential

$$\mu = -(IP + EA)/2 \qquad (2)$$

where *IP* and *EA* are the ionisation potential and electron affinity, respectively. The latter are computed as vertical differences in molecular energy between the neutral system and the mono-cation and -anion, respectively, *i.e.*

$$IP = E(\text{cation}) - E(\text{neutral}),\ EA = E(\text{neutral}) - E(\text{anion}) \qquad (3)$$

As usual, local indices are computed in atomic condensed form.[16] The well-known Fukui function[5,17] for electrophilic (f_k^-) and nucleophilic (f_k^+) attack can be written as

$$f_k^- = p_k(\text{cation}) - p_k(\text{neutral}),\ f_k^+ = p_k(\text{anion}) - p_k(\text{neutral}), \qquad (4)$$

where p_k is the electron population of atom k. In all cases, atomic populations were computed from the B3LYP electron density by the Merz–Kollman molecular electrostatic potential method.[18] B3LYP atomic populations are in excellent agreement with high-level correlated *ab initio* calculations and have modest basis set sensitivity.[19] The Merz–Kollman scheme for atomic charges has been used in most DFT studies of the regiochemistry of 1,3-DCs.[9] It has also been recently considered as an appropriate local descriptor of charge.[20] The atomic softness is finally computed as

$$s_k^{\pm} = f_k^{\pm} S \qquad (5)$$

The appropriate atomic softness has to be chosen for each atom directly participating in the reaction. The stabilization energy for the reaction between the dipole **1** and the dipolarophile **2**, where the new bonds form between atom i of **1** and atom k of **2** and between atom j of **1** and atom l of **2**, and where the dipole undergoes nucleophilic attack, can be written as[10]

$$E_{\text{stab}} = -\frac{1}{2}[\mu(\mathbf{1}) - \mu(\mathbf{2})]^2 \left(\frac{s_i^- s_k^+}{s_i^- + s_k^+} + \frac{s_j^- s_l^+}{s_j^- + s_l^+} \right) \qquad (6)$$

The superscript plus and minus signs must be exchanged when the dipole undergoes electrophilic attack.

3. Results and discussion

Nitrilimines **1** and ethylenic dipolarophiles **2** (see Fig. 1) were chosen as suitable reactants for our computational investigation since, due to their peculiar electronic features, they cover most of the reaction kinetics range shown by experiments. Two ways of estimating the reaction rate are presently considered: the well-known FMO approach, which provides a simple qualitatitive estimate of the reaction rate based on energy differences in appropriate MOs of the reactants, and the local HSAB principle, which has been recently extended to a quantitative tool for the prediction of 1,3-DC reaction rates. Since these methods are presently applied to study rate differences in very similar reactions, their reliability is improved by cancellation of systematic errors. We consider the following three solvation models. Model A: the simplest model is the PCM where the molecule is embedded in a continuous medium with the dielectric constant of bulk liquid water. Model B: solvation is modelled by the interaction of the reactant molecule with several real water molecules *in vacuo*. Such solvation clusters were investigated for **1a** and **2a** only. Among the stable clusters, we chose those of lowest energy as representative structures, as specified in the Computational details section. These optimised structures **1aW** and **2aW** are shown in Fig. 2. Model C: solvation is modelled by embedding the clusters of Model B in a continuous medium by the PCM.

3.1 FMO approach

We restrict our discussion to FMO energies obtained by Hartree–Fock method, since HF orbital energies have a well-defined physical meaning. The FMOs involved in the reaction have been carefully identified from their shape since the alkene π* MO is not always the LUMO. For the sake of conciseness, in the following we will denote the high- and low-lying FMOs as HOMO and LUMO, respectively, but the above caveat should be borne in mind. The HF FMO energy levels are pictorially reported in Fig. 3. The changes δε in HF FMO energy of both nitrilimines **1** and ethylenic dipolarophiles **2** upon solvation (Model A) are reported in Table 2 along with the solvation energy δ*E*. The HOMO and LUMO energies are affected to a small extent. Reactants **1a**,**b** and **2a**,**b** show a decrease in both FMO energies, which is larger in **1a** LUMO and **2b** HOMO. At variance, electron-poor **1c** show an increase of *ca.* 0.1 eV in both FMO energies. The solvent effect on FMO energy, as computed within Model A, can be safely estimated to be less than 0.2 eV. This is in line with Model A solvation energy which is always less than 0.5 eV. Note however that the change in FMO energy is not simply related to the solvation energy. This means that coupling to the continuum unequally affects the MO energies.

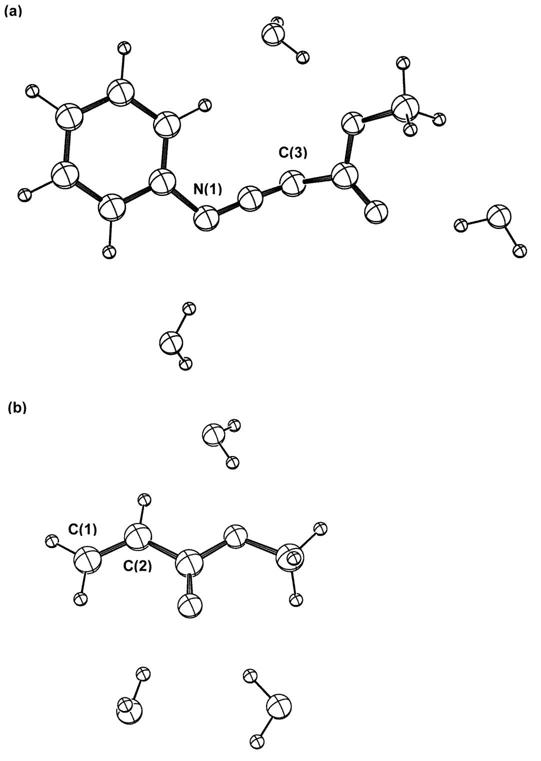


Fig. 2 Structure of the solvation clusters composed of one reactant molecule and three hydrogen-bonded water, fully optimised at the HF/6-311+G(d,p) level. (a) *N*-Phenyl-*C*-carbomethoxynitrilimine cluster, **1aW**; (b) methyl acrylate cluster, **2aW**.

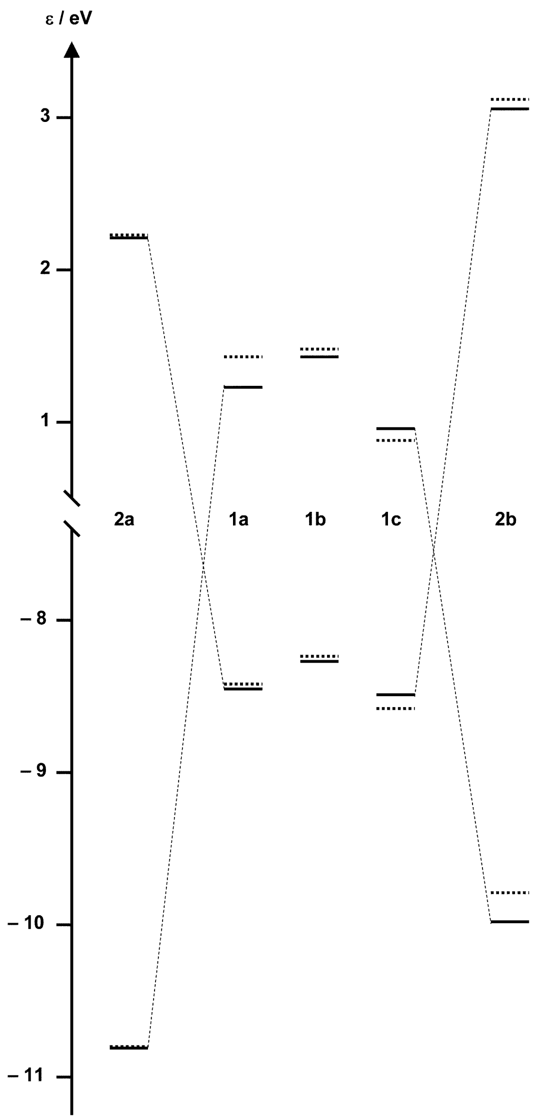


Fig. 3 HF/6-311+G(d,p) frontier molecular orbital energy ε of the studied reactants (see text for appropriate definition of these orbitals). Broken lines: reactants *in vacuo*; full lines: reactants solvated by water according to Model A (PCM).

Table 2 Effect of solvation according to Model A (PCM). HF solvation energy δ*E* (kcal mol^{-1}) and variation δε (eV) of the HF FMO energy of nitrilimines **1** and alkenes **2** (1 eV = 23.06 kcal mol^{-1})

Reactant	δ*E*/kcal mol^{-1}	$\delta\varepsilon_{\mathrm{HOMO}}$/eV	$\delta\varepsilon_{\mathrm{LUMO}}$/eV
1a	−9.2	−0.03	−0.20
1b	−7.9	−0.02	−0.05
1c	−9.8	0.09	0.08
2a	−6.7	−0.01	−0.01
2b	−1.2	−0.19	−0.06

Table 3 Effect of solvation according to Model A (PCM). Variation $\delta\Delta\varepsilon$ (eV) of the HF FMO energy gaps for 1,3-DC reaction of nitrilimines **1** with alkenes **2**

R	R^1	Reaction	Type	$\delta\Delta\varepsilon_H$	$\delta\Delta\varepsilon_L$[a]
H	COOMe	**1a** + **2a**	I	0.02	(−0.19)
Me	COOMe	**1b** + **2a**	I	0.01	(−0.04)
NO_2	COOMe	**1c** + **2a**	I	−0.10	(0.09)
H	*n*-Bu	**1a** + **2b**	II	−0.02	−0.01
Me	*n*-Bu	**1b** + **2b**	II	−0.03	0.14
NO_2	*n*-Bu	**1c** + **2b**	II	−0.14	0.27

[a] For type I reactions, $\delta\Delta\varepsilon_L$ does not affect reaction rate.

We now define the dipole–HOMO/dipolarophile–LUMO energy gap

$$\Delta\varepsilon_H = \varepsilon^{(2)}_{LUMO} - \varepsilon^{(1)}_{HOMO} \qquad (7)$$

and the dipole–LUMO/dipolarophile–HOMO energy gap

$$\Delta\varepsilon_L = \varepsilon^{(1)}_{LUMO} - \varepsilon^{(2)}_{HOMO} \qquad (8)$$

The relative values of the energy gaps $\Delta\varepsilon_H$ and $\Delta\varepsilon_L$ are the basis of Sustmann[21] classification. On the basis of the presently computed FMO energies, it turns out that cycloadditions to methyl acrylate **2a** are of type I, *i.e.* reactions only sensitive to $\Delta\varepsilon_H$, whereas cycloadditions to 1-hexene **2b** are of type II, *i.e.* reactions sensitive to both energy gaps. The variations of $\Delta\varepsilon_H$ and $\Delta\varepsilon_L$ on going from vacuum to aqueous solution, as computed within Model A, are summarized in Table 3. In cycloadditions involving electron-poor methyl acrylate **2a**, water accelerates cycloaddition to electron-poor **1c** and leaves almost unchanged reaction with **1a,b**. Reactions of electron-rich 1-hexene **2b** with **1b**,**c** show opposite water-induced changes in energy gaps. The increase in $\delta\Delta\varepsilon_L$ seems to be dominating, so that these reactions are slower in water. Reaction of **2b** with **1a** is almost unaffected. However, Model A predicts a rather small energy-gap variation (less than 0.3 eV) for all the examined cases. In the light of the above data it seems that water feebly affects 1,3-DC reaction rates within these reactivity and solvation models.

Since the PCM takes into account only the electrostatic coupling between the studied molecule and a dielectric continuum, we also considered solvation models involving water molecules hydrogen-bonded to the reactants. Due to the considerable computational effort required, we investigated only nitrilimine **1a** and methyl acrylate **2a** by this advanced model. The HF solvation energy δE and the change $\delta\varepsilon$ in HF FMO energy of **1a** and **2a** for all three solvation models are reported in Table 4.

The solvation energy steadily increases (in absolute value) by improving the solvation model. As for FMO energies, solvation model B shows a decrease for both **1a** and **2a**. The effect is in the same direction as that computed with model A, but it is much larger. Clearly, the hydrogen-bonded water molecules serve as electron-attracting groups which lower the FMO energy. The effect is larger for methyl acrylate **2a**. This may appear surprising since **2a** has no water molecule directly bonded to the reacting centres (see Fig. 2) but one should take into account the fact that in **2a** the ester moiety is more strongly conjugated to the reactive bond than in **1a**. Indeed the FMOs of **2a** have similar amplitude on the reactive alkene carbon atoms and on the carbonyl carbon and oxygen atoms, whereas the FMOs of **1a** do not extend towards the ester moiety.

Model C yields largely different results for the FMO energies of the two reactants. The HOMO energy of **1a** further decreases with respect to Model B. In contrast, the LUMO energy of **2a** is raised by about 0.4 eV, almost up to the energy computed within Model A. This can be traced back to a much larger increase of the interelectronic repulsion in **2aW** than in **1aW**. In turn, this is due to a preponderance of positive charge at the solute–solvent interface that makes the electron density of **2aW** shrink.

Clearly, the variation of the energy gap $\Delta\varepsilon_H$ for the type I cycloaddition of **1a** to **2a** (see Table 4) reflects this behaviour. The reaction between bare hydrogen-bonded clusters **1aW** and **2aW** is accelerated with respect to the reaction of the bare reactants *in vacuo*. However, the introduction of a polarizable continuum slows down the reaction of both reactants and clusters. The latter effect is larger when hydrogen-bonded water is explicitly taken into account.

We can conclude that, from the FMO standpoint, the effect of water on the reaction rate is, in general, in the sense of decreasing the reaction rate, although the effect is sensitive to the nature of the reactants. It also appears that long-range electrostatic coupling with the solvent is important. Finally, the water-induced change in FMO energy is always well below 1 eV, so that it can be concluded that the effect of water on the reaction rate is rather small.

3.2 HSAB approach

The local HSAB principle, which found a convenient theoretical framework in the DFT, provides a criterion to pick the preferred reaction path out of several possible ones.[22] Such a criterion is based on the concepts of electron chemical potential μ, which represents the escaping tendency of electrons, and of local softness s, a measure of the sensitivity of the molecular electron density to a change in μ. The electron chemical potential is the basis for a modified Sustmann's criterion[23] appropriate for the present DFT-based reactivity model: a 1,3-DC reaction is of type I when the electron chemical potential of nitrilimine dipole **1** is higher than the electron chemical potential of ethylenic dipolarophile **2**, that is, when charge is transferred from **1** to **2** upon reactive encounter. The reverse holds for a type reaction. The local HSAB principle has been recently extended to provide a quantitative measure of the stabilization in the initial critical stage of 1,3-DC reactions.[10] Consider 1,3-DC between reactants **1** and **2**, where new bonds are formed between N(1) of **1** and C(1) of **2** and between C(3) of **1** and C(2) of **2** (see Fig. 2). If charge is transferred from **1** to **2** in the initial stage of the reaction, the stabilization E_{stab} is computed by eqn. 6 with i = N(1), j = C(3), k = C(1), and l = C(2). The stabilization energy has already been shown to provide a good measure of differences in reaction kinetics of 1,3-DCs.[24]

The variation of electron chemical potential due to solvation computed with Model A is shown in Fig. 4. Solvation selectively affects the electron chemical potential: μ is lowered in

Table 4 Effect of solvation on nitrilimine **1a** and alkene **2a**. Variation of the HF solvation energy δE (kcal mol^{-1}), variation $\delta\varepsilon$ (eV) of the HOMO energy of **1a** and of the LUMO energy of **2a**, along with the variation of the FMO gap for the HOMO-dipole controlled 1,3-DC of **1a** to **2a**

Solvation model	δE(**1a**)	δE(**2a**)	$\delta\varepsilon_{HOMO}$(**1a**)	$\delta\varepsilon_{LUMO}$(**2a**)	$\delta\Delta\varepsilon_H$(**1a** + **2a**)
A	−9.2	−6.7	−0.03	−0.01	0.02
B	−11.6	−12.2	−0.22	−0.41	−0.19
C	−29.3	−34.2	−0.42	−0.02	0.39

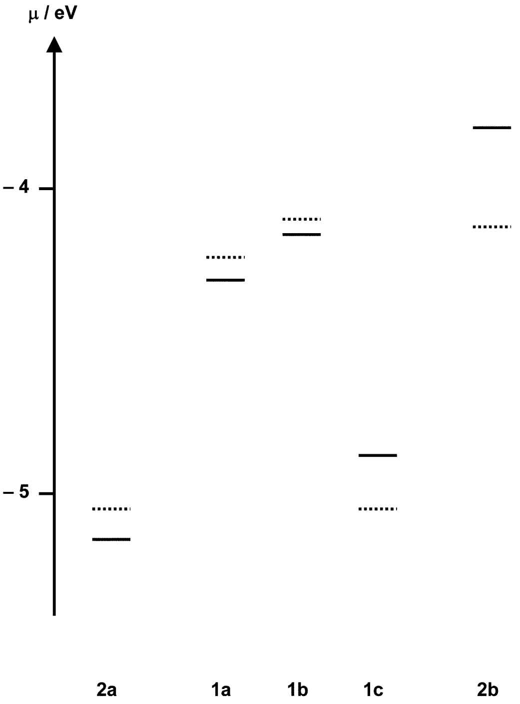


Fig. 4 B3LYP/6-311+G(d,p) electron chemical potential μ of the studied reactants. Broken lines: reactants *in vacuo*; full lines: reactants solvated by water according to Model A (PCM).

1a, **1b**, **2a** and raised in **1c** and **2b**. In Table 5 the effect of Model A solvation on the stabilization energy is shown. It is immediately apparent that the presence of water enhances the stabilization energy, and that the largest effect is predicted when the reactants have opposite electron demands (**1b** + **2a** and **1c** + **2b**). However, the stabilization energy is determined not only by the difference in electron chemical potential but also by the sensitivity of the electron density at the reacting atoms, as shown by eqn. 6. Hence, the reactivity response to solvation can be discussed as follows. The electron chemical potentials of **1a**, **1b**, **2a** undergo similar shifts so that the cycloadditions of **1a** and **1b** to methyl acrylate **2a** are accelerated because of a favourable change in atomic softness, which is particularly efficient for methyl-substituted nitrilimine **1b**. This selective behaviour can be traced back to a large increase of softness at the C(3) atom of **1b** due to solvation. Conversely the cycloaddition of **1c** to methyl acrylate **2a** is accelerated mainly because of the increase in the $[\mu(\mathbf{1}) - \mu(\mathbf{2})]^2$ term (*i.e.*, the charge transfer between the reactants is larger). The same mechanism is responsible for the small change in E_{stab} for the cycloaddition of **1a** and **1b** to 1-hexene **2b**. Finally, the largest solvation effect is shown by the reaction between **1c** and **2b** where E_{stab} is 0.58 eV more negative because of a favourable change in both terms contributing to the stabilization energy. In general, all considered reactions are favoured when carried out in water but the effect on E_{stab} is rather small, being comparable to the thermal energy at room temperature (*ca.* 0.6 kcal mol^{-1}).

In order to get a quantitative measure of the solvation effect on the reaction rate, we assume that the latter can be described by the Arrhenius equation

$$k = A\ \exp(-\Delta E^{\ddagger}/k_{\mathrm{B}}T) \tag{9}$$

where the symbols have their usual meanings. One can then compute the solvent-induced change as

$$k_{\mathrm{W}}/k_{\mathrm{V}} = \exp(-\delta E_{\text{stab}}/k_{\mathrm{B}}T) \tag{10}$$

where $k_{\mathrm{W}}/k_{\mathrm{V}}$ is the ratio of the reaction rate constant in water to that *in vacuo* at 298 K and variation of the prefactor A is neglected. The $k_{\mathrm{W}}/k_{\mathrm{V}}$ ratio (see Table 5) shows that all reactions are faster in water but also that the acceleration is modest in all considered cases. We can conclude that the combined application of DFT-based reactivity indices and PCM of solvation shows that water always accelerates the reaction rate of the title reactions and that this effect is rather small for all considered cases.

4. Conclusions

In this paper we present for the first time high-level computational results on the 1,3-DCs between several ethylenic dipolarophiles and large nitrilimines of real interest to the organic chemist. Stimulated by the experimental findings detailed in the companion paper,[1a] we focused our attention on the reactivity change observed when the reaction is carried out in aqueous media. Particular attention has been devoted to the description of the changes in electronic structure induced by water. Three solvation models have been employed, namely, the PCM, clusters involving hydrogen-bonded water molecules, and a combination of these models. As for reactivity, we used two approaches: the familiar qualitative FMO theory and a more advanced quantitative model based on molecular reactivity indices and on the HSAB principle.

The two reactivity models differ in the details of the description of the effect induced by water on the reaction rates. FMO theory predicts a small decrease in reaction rate except for the cycloaddition of the electron-poor reactants **1c** and **2a**. On the other hand, DFT-based reactivity indices show that all considered reactions are accelerated, especially when the reactants have opposite electron demands (recall, however, that both the global chemical potential μ and the local, atomic softness s_k are important in determining this behaviour). This difference can be ascribed to the consideration of the local properties of the atoms participating in the formation of new chemical bonds featured by the HSAB approach; the (approximate) description of electron correlation typical of DFT calculations might also be of importance.

Table 5 Effect of solvation according to Model A (PCM). Variation δE_{stab} (kcal mol^{-1}) of the DFT-B3LYP stabilization energy and ratio $k_{\mathrm{W}}/k_{\mathrm{V}}$ of the reaction rate constant in water to that *in vacuo* at 298 K for the 1,3-DC of nitrilimines **1** to alkenes **2**

R	R^1	Reaction	Type	δE_{stab}[a]	$k_{\mathrm{W}}/k_{\mathrm{V}}$
H	COOMe	**1a** + **2a**	I	−0.07	1.12
Me	COOMe	**1b** + **2a**	I	−0.33	1.75
NO_2	COOMe	**1c** + **2a**	I	−0.07	1.08
H	*n*-Bu	**1a** + **2b**	III	−0.18	1.35
Me	*n*-Bu	**1b** + **2b**	I/III[b]	−0.13	1.24
NO_2	*n*-Bu	**1c** + **2b**	III	−0.58	2.67

[a] For type I reactions, δE_{stab} is computed for dipole-to-dipolarophile charge transfer. For type III reactions, δE_{stab} is computed for dipolarophile-to-dipole charge transfer. [b] This reaction is type I *in vacuo*, but type III in water.

Conversely, both approaches clearly show that the effect induced by water on the reaction rate of the title reactions is rather small, since the perturbation induced by water on the electronic structure of the reactants is minor. This conclusion is supported by the agreement between very different theoretical (FMO *vs.* HSAB) and computational (HF *vs.* DFT) strategies. Comparison between the computational results and the experimental findings reported in the companion paper[1a] enables one to deduce that water is not directly responsible for the observed speed-up. Rather, the role played by the ionic catalysts SDS and THAC is crucial, in agreement with the explanation of the experimental findings proposed in the companion paper.[1a]

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