

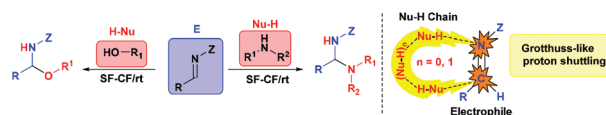
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## The role of proton shuttling mechanisms in solvent-free and catalyst-free acetalization reactions of imines

V. J. Lillo, J. Mansilla and J. M. Saá\*

Catalyst-free and solvent-free reactions of the type  $\text{NuH} + \text{E} \rightarrow \text{Nu-EH}$  are NuH-catalyzed processes in which Grotthuss-like proton shuttling plays a key role.



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## PAPER

### The role of proton shuttling mechanisms in solvent-free and catalyst-free acetalization reactions of imines†

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Proton transfer is central to the understanding of chemical processes. More so in addition reactions of the type  $\text{NuH} + \text{E} \rightarrow \text{Nu-EH}$  taking place under solvent-free and catalyst-free conditions. Herein we show that the addition of alcohols or amines (the NuH component) to imine derivatives (the E component), in 1 : 1 ratio, under solvent-free and catalyst-free conditions, are efficient methods to access *N,O* and *N,N*-acetal derivatives. In addition, computational studies reveal that they are catalyzed reactions involving two or even three NuH molecules operating in a cooperative manner as H-bonded  $\text{NuH} \cdots (\text{NuH})_n \cdots \text{NuH}$  associates (many body effects) in the transition state through a concerted proton shuttling mechanism (addition of alcohols) or stepwise proton shuttling mechanism (addition of amines), thereby facilitating the key proton transfer step.

## Introduction

One of the great challenges in today's organic chemistry resides at the interface with sustainability.<sup>1</sup> In fact, governments around the world are launching actions for the so-called chemical substitution, thereby meaning "the replacement or reduction of hazardous substances or processes..."<sup>2</sup> for which purpose emerging R&D research programs on the science of sustainability are being implemented.<sup>3</sup> Clearly, organic chemists have a key role to play in this area, namely that of inventing<sup>4</sup> new processes characterized not only by their chemical efficiency,<sup>5</sup> but also by their environmental proficiency, where Green Chemistry lies.<sup>6</sup> Even though, for the most part only technological approaches have been devised so far,<sup>7</sup> we strongly believe that fundamental organic chemistry may still provide novel, far-reaching solutions to these problems,<sup>8</sup> for which purpose complementary computational-experimental approaches are being recommended.<sup>9</sup> Unfortunately, though, computational approaches for analysing solvent-free and catalyst-free chemistry are an unsolved, challenging problem.

With this general objective in mind, we focused our attention on the study and viability of solvent-,<sup>10</sup> and catalyst-free<sup>11</sup> (SF-CF)<sup>12</sup> reactions of the general type  $\text{NuH} + \text{E} \rightarrow \text{Nu-EH}$  characterized by two main chemical events, namely the trans-

fer of a proton from NuH to E,<sup>13</sup> and the formation of a C-C or heteroatom-C bond, both of which could be rate-determining. Prior to studying complex multistep processes (Mannich, Friedel-Crafts, amidoalkylation and related reactions) in their racemic and enantioselective versions,<sup>14</sup> we first concentrated on studying the apparently trivial textbook addition reactions of alcohols and amines (the NuH component) to imines and imine derivatives (the E component) in an effort to obtain *N*-substituted *N,O*-acetals and *N*-substituted *N,N*-acetals under SF-CF conditions. We were curious to learn when and how proton transfer<sup>15</sup> could take place under SF-CF conditions as, in the absence of an external solvent, one might expect just two alternative behaviours. On the one hand, one could expect that the transfer of a proton from NuH to E could take place in the rate-determining step of a concerted or stepwise process,<sup>16</sup> in which case, as required for a general acid mechanism,<sup>17</sup> the so-called *libido rule* should work out.<sup>18</sup> However, this condition leads one to the paradoxical conclusion that a catalytic effect is needed when no catalyst is apparently available. On the other hand, one could call upon a Grotthuss-like proton-jumping mechanism if proton transfer were to occur after the rate-determining attack of a chain of NuH units ( $\text{NuH} \cdots (\text{NuH})_n \cdots \text{NuH}$ ) upon the E component.<sup>19</sup> Curiously enough, a survey of the literature revealed only some scattered reports regarding this category. Such is the case of the addition of alcohols, or water, to ketenes already reported in 1967 by Pracejus *et al.*, and in 1968 by Satchell *et al.* which provided sound kinetic evidence proving the involvement of  $(\text{ROH})_n$  chains working as a catalyst.<sup>20</sup> Kinetic and computational evidences have also been found for the involvement of  $(\text{ROH})_n$

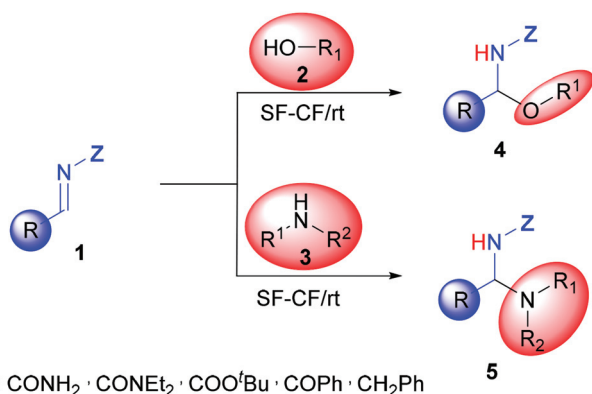
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associates in the addition of alcohols to keteneimines,<sup>21</sup> and to isocyanates as well.<sup>22</sup>

Accordingly, two relevant questions arose at the start, namely: (1) Could we expect to end up with viable synthetic methodology by simply mixing the NuH and E components in a 1 : 1 ratio under SF-CF conditions? And (2) are catalyst-free NuH + E → Nu-EH reactions truly uncatalyzed reactions? To answer both questions, we selected a variety of imine derivatives **1** (Z = CONH<sub>2</sub>, CONEt<sub>2</sub>, COO<sup>t</sup>Bu, CPh, CH<sub>2</sub>Ph, and R = alkyl, aryl or heteroaryl groups) for studying their reactions with alcohols **2** or amines **3** with the expectation of learning about the essentials of SF-CF chemistry (Scheme 1), as well as finding sustainable solutions<sup>23</sup> for textbook reactions such as the formation of *N*-substituted *N,O*-acetals **4** (Nu = OR<sub>1</sub>),<sup>24,25</sup> or *N*-substituted *N,N*-acetals (aminals) **5** (Nu = NR<sub>1</sub>R<sub>2</sub>).<sup>26</sup> Actually, *N,O*-acetals **4** are present in the scaffold of several bioactive natural products like zampanolide,<sup>27</sup> irciniastatins,<sup>28</sup> pederin,<sup>29</sup> and pederin-type compounds,<sup>30</sup> whereas *N,N*-acetals **5** are also present in natural communesins<sup>31</sup> and pharmacologically valuable acetals like quinethazone.<sup>32</sup>

We would like now to report that the above SF-CF reactions take place smoothly by simply mixing NuH and E in a 1 : 1 ratio (see below for detailed conditions in some specific cases) at room temperature, provided that at least one of the two components was a liquid. Moreover, according to computational data (see below), the addition of alcohols **2** or amines **3** to imines **1**, have both been found to be catalytic in nature. The reaction with alcohols **2** involves a general acid-general base catalysis,<sup>33</sup> in which the cooperative action<sup>34</sup> of a NuH... (NuH)<sub>*n*</sub>...NuH H-bonded chain facilitates a proton shuttling mechanism operating in concert with O-C bond formation, as in many other relevant enzymatic reactions.<sup>35–37</sup> As for previous cases the catalytic effects do not seem to be due to solvation effects.<sup>20–22</sup> On the other hand, the reaction with amines **3** involves a multi-step mechanism, the H-bonded chain eventually undergoing a Grotthuss-type proton jumping thereby facilitating the key proton transfer to the imine terminal nitrogen atom.<sup>38</sup>



**Scheme 1** Acetalization reactions of imine derivatives **1** with alcohols **2** and amines **3**.

## Results and discussion

At the start two experimental issues were of major concern to us, namely the well-known hydrolytic lability of the imines and imine derivatives **1**,<sup>39</sup> but also the mutual solubility of the NuH and E chosen for study.<sup>40</sup> Initial studies under strictly anhydrous conditions were successful, though somewhat costly. Fortunately, despite the former advice, we eventually found that under SF-CF conditions there was no need to take recourse to anhydrous reactants (alcohols **2** or amines **3**), nor to rigorously dried equipment, as reaction times and chemical yields were identical under both anhydrous and standard conditions. In fact, all reactions reported here have been carried out at room temperature in open air using standard equipment, by adding the NuH to freshly prepared imine derivatives **1** (Z = CONH<sub>2</sub>, CONEt<sub>2</sub>, COO<sup>t</sup>Bu, CPh, and R = alkyl, aryl or heteroaryl groups), or commercially available *N*-benzyl benzylideneimine **1e** in a 1 : 1 ratio.<sup>41</sup> The mixture was then stirred for a period of time during which, in a number of cases,<sup>42</sup> intense thickening developed until the whole mixture collapsed into a thick, solid mass impossible to stir any further, which was then elaborated for the isolation of adducts **4** or **5**.<sup>43</sup>

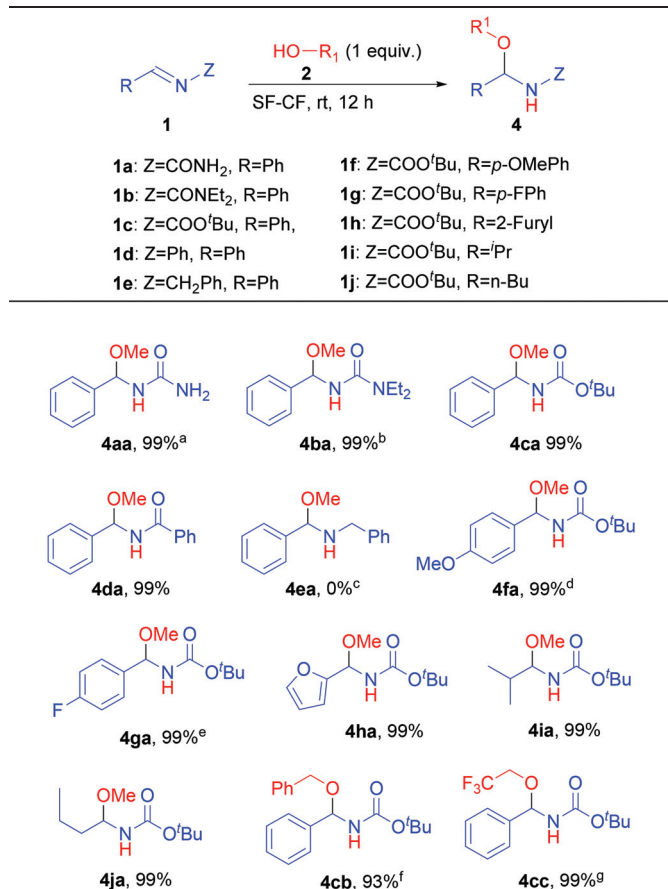
### Addition of alcohols **2** to imines **1** under SF-CF conditions

Except for *N*-benzyl imine **1e**, the reaction of *N*-aminocarbonyl, *N*-alkoxycarbonyl and *N*-acyl imine derivatives **1** with alcohols **2** (R<sub>1</sub> = alkyl) proceeded smoothly thus giving rise to the corresponding *N*-substituted *N,O*-acetals **4** in near to quantitative yield in most cases (Table 1). Extra amounts of methanol (**2a**) were required to force the solubility of solid imines such as *N*-aminocarbonyl imine **1a**, and *N*-alkoxycarbonyl imines **1f** and **1g**. In fact, no limitations other than the mutual solubility of imines **1** and alcohols **2** appear to restrict the applicability of this SF-CF methodology.

Thus, as illustrated in Table 1, a variety of *N*-aminocarbonyl, *N*-alkoxycarbonyl and *N*-acyl imines derived from alkyl, aryl and heteroaryl aldehydes have been successfully employed with alcohol partners such as methanol **2a**, benzyl alcohol **2b** or 2,2,2-trifluoroethanol **2c**, the latter giving rise to a much faster reaction no doubt due to its increased acidity. Special mention should be made of the fact that even imines derived from alkyl aldehydes behave normally under our SF-CF conditions,<sup>44</sup> as revealed by the high yields obtained of *N*-alkoxycarbonyl substituted *N,O*-acetals **4ia** and **4ja**.

### Addition of amines **3** to imines **1** under SF-CF conditions

As illustrated in Table 2, the corresponding SF-CF reactions of *N*-aminocarbonyl, *N*-alkoxycarbonyl and *N*-acyl imine derivatives **1** with a variety of primary and secondary amines **3a–i**, in 1 : 1 ratio in all but one case (see below), took place in very short reaction times, thereby giving rise to the corresponding *N*-substituted *N,N*-acetals (aminals) **5**, which were isolated as oils or solids in near to quantitative yields. As for the case of

**Table 1** Scope of the SF–CF addition of alcohols **2** to imines **1**<sup>a</sup> 10 equiv. of MeOH required; 1 h reaction time. <sup>b</sup> 72 h reaction time.<sup>c</sup> No reaction detected after 3 days. <sup>d</sup> 3 equiv. of MeOH required.<sup>e</sup> 5 equiv. of MeOH required. <sup>f</sup> 40 h reaction time. <sup>g</sup> 1 h reaction time.

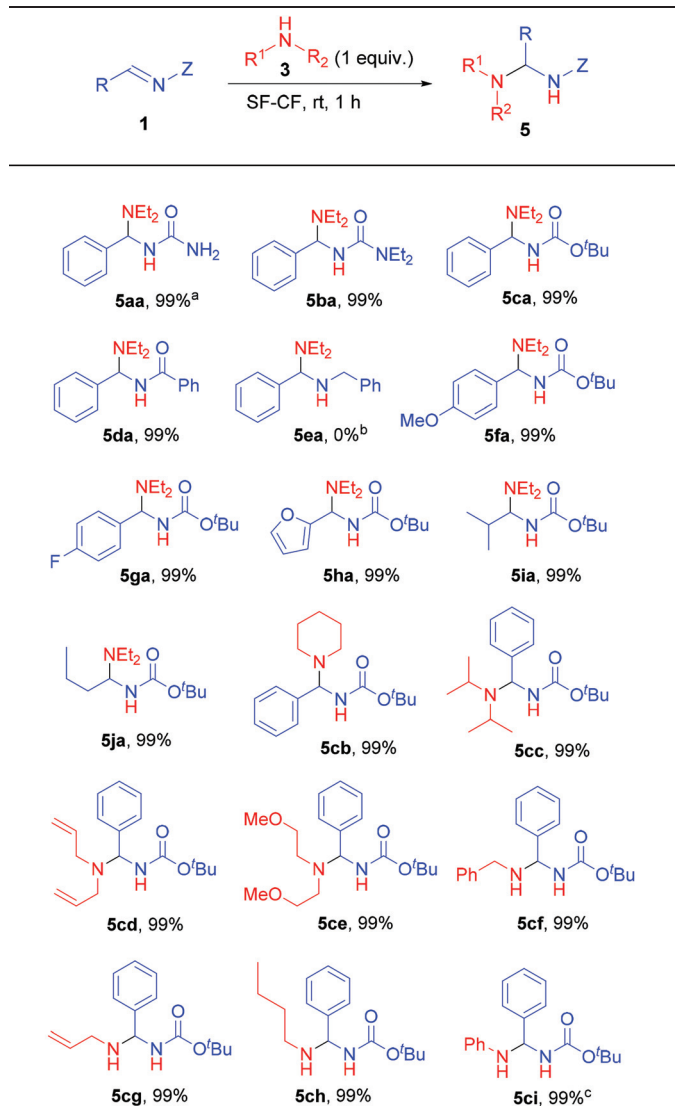
alcohols, the addition of amines to *N*-benzyl benzylideneimine **1e** did not proceed (Table 2).

All kinds of alkylidene, arylidene or heteroarylidene *N*-acyl, *N*-alkoxycarbonyl and *N*-aminocarbonyl imines (**1a–i**) were employed successfully as illustrated in Table 2.

It is worth remarking that except for imine **1a** which required 2 equivalents of diethylamine **3a** to achieve solubilization, strict 1 : 1 imine : amine mixtures were employed for the remaining cases. Even solid imine derivatives **1f** and **1g** behaved normally when treated in a 1 : 1 ratio with liquid diethylamine **3a**, thereby giving rise to amins **5fa** and **5ga**.

Concerning the scope of the amines capable of undergoing this chemistry it should be mentioned that we have found no limitations as the above SF–CF reactions worked fine with both secondary **3a–e** and primary amines **3f–h** and, surprisingly, even with aniline **3i**.

A relevant feature of the above SF–CF reactions was the very fast evolution of the addition of amines **3** compared to the addition of alcohols **2**. Sequential snapshots in Fig. 1 illustrate this feature for the specific case of **1b** + **3a**.

**Table 2** Scope of the SF–CF addition of amines **3** to imines **1**<sup>a</sup> 2 equiv. Et<sub>2</sub>NH needed. <sup>b</sup> No reaction detected after 3 days. <sup>c</sup> 3 hours reaction time.**Fig. 1** Pictures taken at 0, 10 and 60 min illustrating the thickening process of the **1b** + **3a** reaction mixture (1 : 1 ratio).

## Computational analysis

In trying to learn how the above SF–CF reactions involving proton transfer could actually work out, we planned a computational approach, conscious that kinetic approaches would be



far from trivial. However, no well-established method has been reported to model solvent-free reactions by means of a computational treatment. A crude approximation to gauge solvent-free reactions calls for considering them as small clusters  $[n \times (\text{NuH} + \text{E})]$  of the reactant molecules. Accordingly, we felt that, at least for their initial stages where the reaction is still a liquid mixture, a quantum mechanical study of small clusters ( $n > 1$ ) in parallel with the standard analysis of a pair of reactant molecules ( $n = 1$ ) could provide valuable mechanistic insights.<sup>45</sup> So, at the start, we treated a single pair of reactant molecules within a density functional theory (DFT) protocol and planned to confront this data with that of small clusters ( $n = 2$  and  $n = 3$ ) of the reactant molecules. For these purposes, we decided to use Truhlar's M06-2X functional<sup>46</sup> with the basis set 6-31+G(d,p), as implemented in the Gaussian G09 package of programs.<sup>47</sup> Since even small clusters require massive resources as they are time-consuming processes, our computational analysis has been applied to clusters of four reactant molecules such as those in clusters  $2 \times (1 + 2)$ , and six reactant molecules such as those in clusters  $3 \times (1 + 2)$ . In addition, as a reasonable approximation for the SF-CF liquid-phase chemistry (involving  $\text{NuH} + \text{E}$  mixtures of unknown dielectric constant) we felt that we should explore the above reactions, at least for  $n = 1$  and  $n = 2$ ,<sup>48</sup> with PCM for a spanning variety of dielectric constants such as those of dichloromethane, acetonitrile, methanol or diethylamine.<sup>49</sup> In some cases simplified models of imine derivatives **1** have been employed in computation, as follows. Authentic **1a** and **1e** were used for computational studies, as well as the *N,N*-dimethyl derivative (instead of the *N,N*-diethyl analog) of **1b**, and the methoxycarbonyl derivative (instead of the *tert*-butoxycarbonyl analog) of **1c**. Our model for **3a** (diethylamine) was dimethylamine. The numbering system has not been changed though, to avoid confusion.

### Computational analysis of the addition alcohols **2** to imines **1**

Experimental observations had led us to recognize fundamental differences between *N*-benzyl benzylideneimine **1e** (this compound did not react) and *N*-aminocarbonyl, *N*-alkoxycarbonyl and *N*-acyl imine derivatives. So, in the search for the basic principles of the addition reaction under SF-CF conditions, we first examined the gas phase reaction of **2a** (methanol) with the above-mentioned models of **1a**, **1b**, **1c** and **1e** and later in liquid phases such as dichloromethane, acetonitrile and methanol having a variety of dielectric constants (Table 3). From these studies we learned that the addition of **2a** (methanol) takes place in all cases in a concerted fashion through a four-membered ring transition structure, exhibiting quite large energy barriers in both the gas phase and solution phases (Table 3).

We considered though that these large values were incompatible with both the easy evolution experimentally observed for **1a–c** and the lack of reactivity of **1e** as well. Fortunately, we soon found that these reactions were catalyzed by a second molecule of the NuH reactant **2a** acting as a general acid–base catalyst in providing a proton to the imine nitrogen and simul-

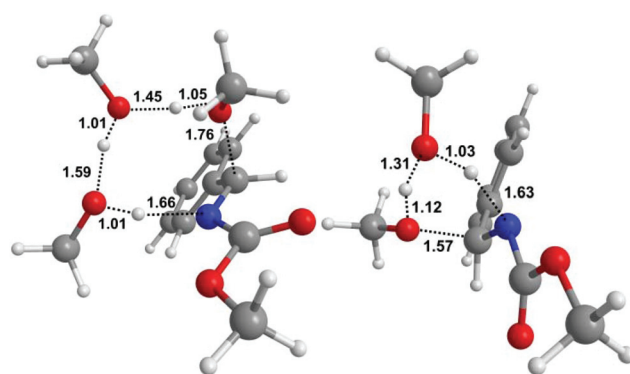
**Table 3** Energy barriers ( $\Delta\Delta G^\ddagger$ , kcal mol<sup>−1</sup>) found for the gas phase (M06-2X/6-31+G\*\*) and liquid phases (M06-2X(PCM = solvent)/6-31+G\*\*) addition of 1–3 methanol (**2a**) molecules to imines **1a–e**<sup>a</sup>

Entry	Gas phase	CH <sub>2</sub> Cl <sub>2</sub>	CH <sub>3</sub> CN	MeOH
<b>1a</b> + MeOH	43.03	43.14	42.89	42.91
<b>1a</b> + 2MeOH	25.72	29.96	31.13	29.26
<b>1a</b> + 3MeOH	20.76	27.84	29.27	27.34
<b>1b</b> + MeOH	40.34	42.21	43.55	40.80
<b>1b</b> + 2MeOH	27.18	31.58	34.03	31.31
<b>1b</b> + 3MeOH	19.54	28.88	31.00	28.34
<b>1c</b> + MeOH	40.40	35.15	38.73	38.74
<b>1c</b> + 2MeOH	27.01	29.26	29.24	29.24
<b>1c</b> + 3MeOH	17.12	24.87	25.60	25.21
<b>1e</b> + MeOH	45.92	49.20	47.65	47.66
<b>1e</b> + 2MeOH	31.35	33.98	33.54	33.71
<b>1e</b> + 3MeOH	25.63	32.03	32.63	32.82

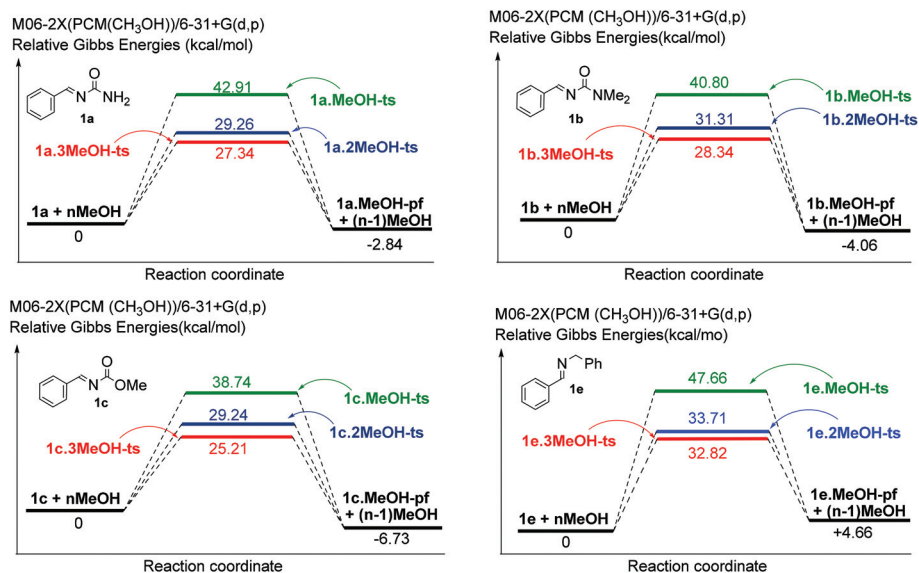
<sup>a</sup> The models actually employed in computations were: **1a**, **1b** (the *N,N*-dimethyl derivative instead of the *N,N*-diethyl derivative), **1c** (the methoxycarbonyl derivative instead of the *t*-butoxycarbonyl derivative), and **1e**.

taneously removing a proton from the attacking methanol molecule to the imine carbon atom, *i.e.* catalysis involving the attack of a  $\text{NuH} \cdots (\text{NuH})_n \cdots \text{NuH}$  H-bonded chain ( $n = 0$ ) where a proton shuttling mechanism concerted with O–C bond formation operates through a six-membered ring transition structure (Fig. 2, left) as confirmed by IRC analysis,<sup>50</sup> the result being a remarkably strong catalytic effect which lowered the above energy barriers in the gas phase by more than 13 kcal mol<sup>−1</sup>.<sup>51</sup>

However, assuming the origin of the condensed phase of our SF-CF reactions [**1** + **2a** (methanol)], we considered that the catalytic effect should be best modelled with appropriate PCM (methanol) calculations. The PCM data in methanol (in all cases more than 9 kcal mol<sup>−1</sup> lowering of the energy barriers, as shown in Scheme 2 and Table 3) is particularly relevant in considering the (major) importance of the so-called concerted proton shuttling operating at the addition of methanol (**2a**) to imines **1** under SF-CF conditions *vs.* the (minor) solvation effects.



**Fig. 2** Transition state structures (M06-2X(PCM = methanol)/6-31+G\*\*) of **1c-2MeOH-ts** (left) and **1c-3MeOH-ts** (right) revealing the double and triple shuttling mechanism, respectively. Distances given in angstroms.

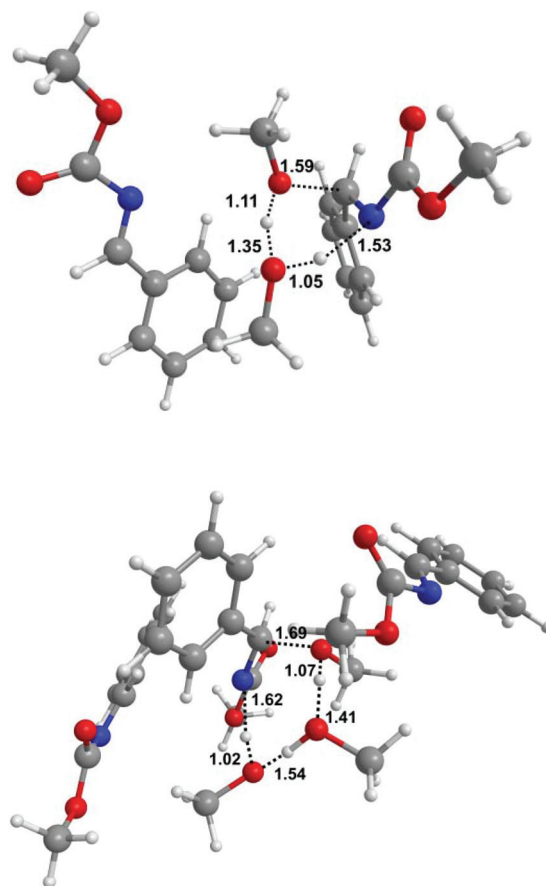


**Scheme 2** Reaction profiles of the addition reaction of methanol (2a) to **1a**, **1b**, **1c** or **1e**. Relative Gibbs free energies of M062X/6-31+G\*\*//PCM (MeOH) calculations. Values in kcal mol<sup>-1</sup>.

Interestingly, we found that a third reactant molecule **2a** (methanol) can intervene in the process, in which case the concerted proton shuttling mechanism takes place through an eight-membered ring transition structure (Fig. 2, right), as eventually confirmed by IRC analysis.<sup>52</sup> The extra energy lowering (from 0.89 to 4.3 kcal mol<sup>-1</sup>, Table 3) computed for these cases proves the involvement of NuH...NuH...NuH H-bonded triads in the addition of alcohols to imine derivatives under SF & CF conditions. Initial studies of proton shuttling mechanisms involving four reactant alcohol molecules (twelve membered-ring transition structures) failed, however.

It is worth remarking that the catalytic effect induced by this cooperative triple shuttling mechanism was found to be operative not only for *N*-aminocarbonyl imines **1a** and **1b**, and *N*-alkoxycarbonyl imines **1c** but also for simple alkylamines such as *N*-benzylimine **1e**, its role being manifested in an extra lowering of the energy barriers in all cases, for both the gas phase and solution phases too, as illustrated in Scheme 2 and Table 3. Notice however that, despite the kinetic advantage provided by the cooperative action of NuH...(NuH)<sub>n</sub>...NuH chains of alcohols in the above proton shuttling mechanisms, computation predicts that the addition of methanol to *N*-benzyl benzylideneimine **1e** should not take place as it is an endothermic process ( $\Delta G = +4.46$  kcal mol<sup>-1</sup>, Scheme 2), in complete agreement with experiment (**1e** remains unchanged in the presence of methanol **2a**).

What is still more interesting, we have found that the above concerted proton shuttling mechanisms, and therefore their catalytic effects, operate also in clusters of reactant molecules, as illustrated for the case of  $n \times (\mathbf{1a} + \mathbf{2a})$  and  $n \times (\mathbf{1c} + \mathbf{2a})$ ,  $n$  being 2 or 3 (Fig. 3). Table 4 comparatively illustrates the energy barriers found in the gas phase and liquid phase calculations.<sup>48</sup>



**Fig. 3** Transition state structures (M06-2X/6-31+G\*\*) of clusters  $2 \times (\mathbf{1c-MeOH})\text{-ts}$  (upper) and  $3 \times (\mathbf{1c-MeOH})\text{-ts}$  (lower) revealing the double and triple shuttling mechanism in the clustered systems. Distances given in angstroms.



**Table 4** Energy barriers ( $\Delta\Delta G^\ddagger$ , kcal mol<sup>-1</sup>) found for the gas phase (M06-2X/6-31+G\*\*) and liquid phase (M06-2X(PCM = solvent)/6-31+G\*\*) addition of methanol (**2a**) to imines **1a** or **1c** in clusters

Entry	Gas phase	CH <sub>2</sub> Cl <sub>2</sub>	CH <sub>3</sub> CN	MeOH
1×( <b>1a</b> + MeOH)	43.03	43.14	42.89	42.91
2×( <b>1a</b> + MeOH)	29.03	35.06	36.69	36.53
3×( <b>1a</b> + MeOH)	25.43	nd	nd	nd
1×( <b>1c</b> + MeOH)	40.40	35.15	38.73	38.74
2×( <b>1c</b> + MeOH)	27.70	33.75	34.54	34.52
3×( <b>1c</b> + MeOH)	24.91	nd	nd	nd

nd: not determined.

The analysis of clusters although limited in scope clearly backs these conclusions too. We believe this is a strong support to confirm the fact that the kinetic effect provided by concerted proton shuttling mechanisms should manifest in addition reactions of the general type E + NuH (alcohols) under SF-CF conditions whatever the dielectric constant of the condensed phase reaction might be.

It is also worth pointing out that hydrolysis products (aldehydes) were not observed in periodic <sup>1</sup>H NMR controls carried out in all cases examined (**1a-d** and **1e**), despite the fact that a concerted proton shuttling mechanism should also be operative for hydrolysis (NuH = H<sub>2</sub>O). Eventually, we were able to prove by computation (M06-2X/6-31+G\*\*) that in all cases studied (**1a**, **1b**, **1c** and **1e**) the barriers for addition of water through a proton shuttling mechanism were higher than those found for the addition of methanol whatever the dielectric constant (Table 5),<sup>53</sup> in complete agreement with experiment.<sup>50</sup>

#### Computational analysis of the addition of amines 3 to imines 1

As found for the addition of alcohols **2**, the SF-CF additions of amines **3** to imine derivatives **1a-c** appear to be also catalysed processes involving proton shuttling mechanisms. Catalysis is proved (Table 6) by the fact that the energy barrier for the reaction of **1** + Me<sub>2</sub>NH was found to be, in all cases (**1a**, **1b**, **1c**), and under all circumstances (gas phase or condensed phases such as Et<sub>2</sub>NH, CH<sub>2</sub>Cl<sub>2</sub>, CH<sub>3</sub>CN or CH<sub>3</sub>OH of quite different dielectric constants), much higher than those of **1** + *n*Me<sub>2</sub>NH (*n* = 2 or 3).

Regarding the shuttling mechanisms, computations have revealed striking differences between the two processes

**Table 5** Energy barriers ( $\Delta\Delta G^\ddagger$ , kcal mol<sup>-1</sup>) found for the gas phase (M06-2X/6-31+G\*\*) and liquid phase (M06-2X(PCM = solvent)/6-31+G\*\*) addition of two methanol (**2a**) or water molecules to imines **1a-c**

Entry	Gas phase	CH <sub>2</sub> Cl <sub>2</sub>	CH <sub>3</sub> CN	MeOH
<b>1a</b> + 2MeOH	25.72	29.96	31.13	29.26
<b>1a</b> + 2HOH	34.30	39.33	36.00	36.02
<b>1b</b> + 2MeOH	27.18	31.58	34.03	31.31
<b>1b</b> + 2HOH	30.19	34.67	37.75	35.01
<b>1c</b> + 2MeOH	27.01	29.26	29.24	29.24
<b>1c</b> + 2HOH	28.87	32.59	32.58	32.59

**Table 6** Energy barriers ( $\Delta\Delta G^\ddagger$ , kcal mol<sup>-1</sup>) found for the gas phase (M06-2X/6-31+G\*\*) and liquid phase (M06-2X(PCM = solvent)/6-31+G\*\*) addition of 1, 2 or 3 dimethylamine molecules to imines **1a-c**

Entry	Gas phase	Et <sub>2</sub> NH	CH <sub>2</sub> Cl <sub>2</sub>	CH <sub>3</sub> CN	MeOH
<b>1a</b> + Me <sub>2</sub> NH-ts	30.72	28.18	27.47	26.86	26.89
<b>1a</b> + 2Me <sub>2</sub> NH-ts1	11.55	14.67	15.54	15.80	15.77
<b>1a</b> + 2Me <sub>2</sub> NH-ts2	19.74	17.62	15.68	14.40	14.44
<b>1a</b> + 3Me <sub>2</sub> NH-ts1	15.07	20.21	21.69	22.71	22.65
<b>1a</b> + 3Me <sub>2</sub> NH-ts2	19.11	18.70	17.69	16.14	16.16
<b>1b</b> + Me <sub>2</sub> NH-ts	28.47	28.92	26.71	28.16	25.45
<b>1b</b> + 2Me <sub>2</sub> NH-ts1	10.11	16.16	15.79	18.63	15.89
<b>1b</b> + 2Me <sub>2</sub> NH-ts2	18.29	19.92	16.31	17.98	15.29
<b>1b</b> + 3Me <sub>2</sub> NH-ts1	13.38	20.59	21.36	24.58	21.84
<b>1b</b> + 3Me <sub>2</sub> NH-ts2	18.23	20.89	19.02	N.C. <sup>a</sup>	N.C. <sup>a</sup>
<b>1c</b> + Me <sub>2</sub> NH-ts	26.05	24.28	23.46	22.82	22.84
<b>1c</b> + 2Me <sub>2</sub> NH-ts1	11.60	13.78	14.64	15.16	15.14
<b>1c</b> + 2Me <sub>2</sub> NH-ts2	14.87	13.24	11.07	9.88	9.91
<b>1c</b> + 3Me <sub>2</sub> NH-ts1	14.38	18.94	20.78	21.50	21.48
<b>1c</b> + 3Me <sub>2</sub> NH-ts2	11.78	11.16	11.35	9.90	9.97

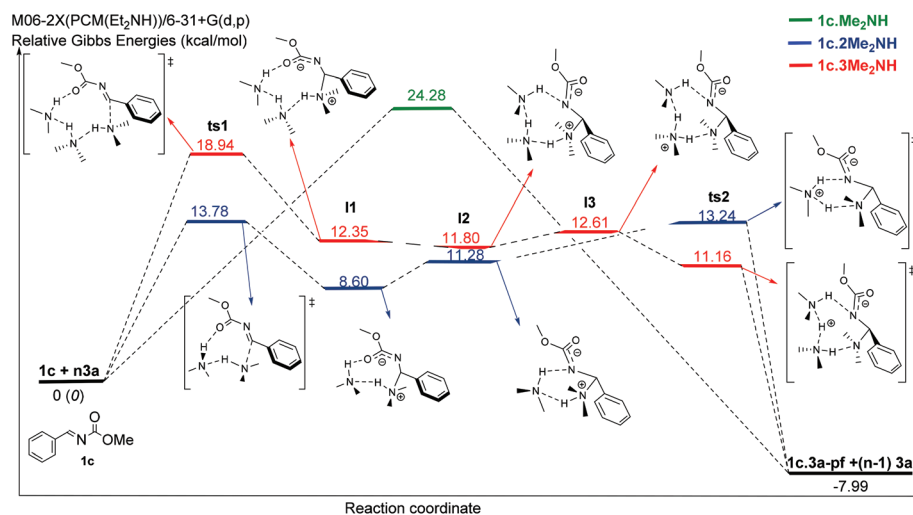
<sup>a</sup> N.C. = no convergence reached.

(alcohol vs. amine additions) that need to be specified and discussed. Thus, in striking contrast to the concerted nature of the SF-CF addition of alcohols, our computational analysis shows that the SF-CF addition of amines **3** to imine derivatives **1a-c** takes place in all cases through stepwise processes (**1e** did not react due to the endothermic character of the reaction) involving an initial attack of a NuH... (NuH)<sub>*n*</sub>...NuH H-bonded associate (*n* = 0 or 1; NuH = Me<sub>2</sub>NH) to the imine grouping (**ts1**), eventually followed by an intramolecular hydrogen transfer *via* proton shuttling (**ts2**) (Scheme 3 and Fig. 4).

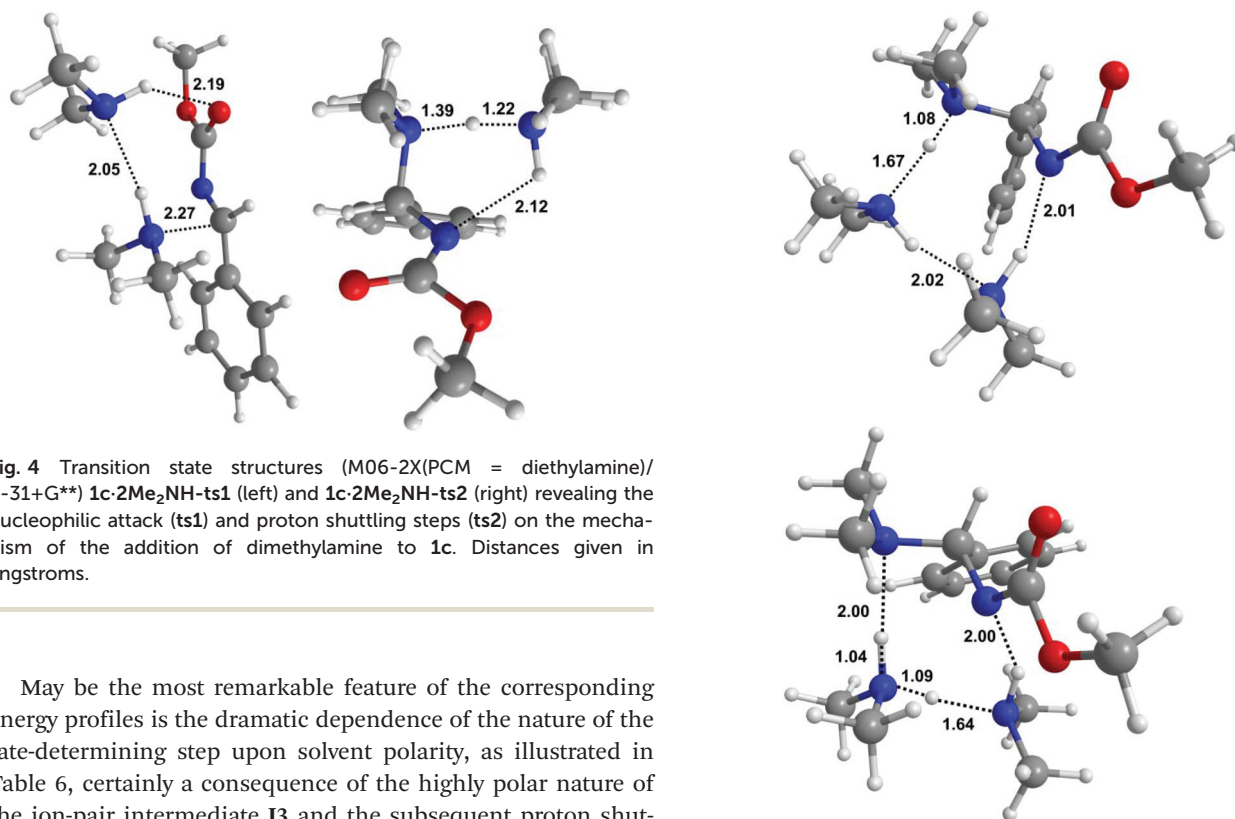
It should be emphasized though that either one of the above processes (**ts1** or **ts2**) can be rate-determining as this issue depends on three variables: the *n* value, the substrate polarity and the condensed phase dielectric constant. Specifically, for aggregate dimers (NuH... (NuH)<sub>*n*</sub>...NuH, *n* = 0) the initial attack (**ts1**) leads to (Scheme 3 and Table 6) a conformationally flexible, zwitterionic intermediate **I** (two relevant conformations **I1** and **I2** are shown)<sup>50</sup> which subsequently undergoes an intramolecular hydrogen transfer (**ts2**) through proton shuttling thereby leading to the final *N,N*-aminal derivatives **5**, a process that recalls the so-called Grotthuss mechanism.

In all cases studied when *n* = 0, the IRC analysis of **ts2** reveals the existence of a hidden intermediate,<sup>54</sup> namely the ion-pair resulting from the first proton jump from the zwitterion **I2**.<sup>55</sup>

Interestingly, for those cases where *n* = 1, the zwitterionic intermediate **I** (two conformations **I1** and **I2** are shown) is not the starting point to launch the shuttling process. Instead, the point of departure is the full ion pair species **I3**, now a real intermediate observed by computation in all cases studied (gas phase and liquid phases such as Et<sub>2</sub>NH, CH<sub>2</sub>Cl<sub>2</sub>, CH<sub>3</sub>CN or CH<sub>3</sub>OH of quite different dielectric constants) (Fig. 5).



**Scheme 3** Reaction profiles of the addition reaction of dimethylamine (**3a**) to **1c** (in  $\text{Et}_2\text{NH}$ ). Relative Gibbs free energies of M06-2X(PCM = diethylamine)/6-31+G(d,p) are given.



**Fig. 4** Transition state structures (M06-2X(PCM = diethylamine)/6-31+G\*\*) **1c.2Me<sub>2</sub>NH-ts1** (left) and **1c.2Me<sub>2</sub>NH-ts2** (right) revealing the nucleophilic attack (**ts1**) and proton shuttling steps (**ts2**) on the mechanism of the addition of dimethylamine to **1c**. Distances given in angstroms.

May be the most remarkable feature of the corresponding energy profiles is the dramatic dependence of the nature of the rate-determining step upon solvent polarity, as illustrated in Table 6, certainly a consequence of the highly polar nature of the ion-pair intermediate **I3** and the subsequent proton shuttling through the transition structure **ts2**.

In light of the above considerations, we focused our analysis on the initial stages of the additions of amines **3** to imines **1a–c** as described by PCM calculations with diethylamine as solvent (Table 6 and Scheme 3). Thus, proton shuttling (**ts2**) appears to be the rate-determining step for **1** + **2Me<sub>2</sub>NH** additions,<sup>56</sup> whereas the initial attack of H bonded associates ( $\text{NuH} \cdots (\text{NuH}) \cdots \text{NuH}$ ) upon the C=N grouping (**ts1**) is that for **1** + **3Me<sub>2</sub>NH** additions.<sup>57</sup> Notice too that at difference with the addition of

**Fig. 5** Relevant structural details (M06-2X(PCM = diethylamine)/6-31+G\*\*) of the zwitterionic intermediate **1c.3Me<sub>2</sub>NH-I2** (upper), and the ion-pair intermediate **1c.3Me<sub>2</sub>NH-I3** (lower) resulting from **1c** +  $\text{NuH} \cdots (\text{NuH})_n \cdots \text{NuH}$ ,  $n = 1$ .

alcohols **2**, the addition of amines **3** is energetically favored for **1** + **2Me<sub>2</sub>NH** over **1** + **3Me<sub>2</sub>NH** additions and therefore only double proton shuttling mechanisms are predicted.

## Conclusions

Solvent-free and catalyst-free reactions of the type NuH + E → Nu-EH (NuH = alcohols or amines, E = N-carbonyl imines) have been computationally and synthetically explored. Both addition reactions are experimentally viable operations under solvent-free and catalyst-free (SF-CF) conditions, by working at room temperature with 1 : 1 mixtures in most cases. In spite of the fact that no external catalysts are present, both operations have been shown to be catalysed processes according to computation in the gas phase (M06-2X/6-31+G(d,p)) and condensed phases (M06-2X(PCM = solvent)/6-31+G(d,p)). Catalysis is provided by the own NuH (alcohols or amines) molecules acting in a cooperative manner (many-body effects) as H-bonded associates NuH...[NuH]<sub>n</sub>...NuH (*n* = 0–1) thereby inducing a significant lowering of the reaction energy barriers. Specifically, the addition of alcohols (the NuH component) has been found to involve a concerted process in which two or even three NuH molecules actively cooperate (many-body effect) through a proton shuttling mechanism to facilitate proton transfer. In striking contrast, the addition of amines (the NuH component) involves stepwise, NuH-catalyzed processes in which only two NuH molecules participate. We believe that these observations, together with those already cited,<sup>20–22</sup> confirm the relevance of the catalytic role that substrates (NuH) can play in the realm of catalysis.

Proton shuttling mechanisms of proton transfer under SF-CF conditions, whether concerted or stepwise, may also operate for complex reaction systems involving all kind of homo or hetero NuH...[NuH]<sub>n</sub>...NuH associates. Their discovery will surely facilitate the development and understanding of relevant sustainable chemistry in their racemic and enantioselective versions. We are working towards this goal.

## Conflicts of interest

There are no conflicts to declare.

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