JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2007; **20:** 206–213
Published online 30 March 2007 in Wiley InterScience
(www.interscience.wiley.com) DOI: 10.1002/poc.1170

Organocatalysis: quantum chemical modeling of nucleophilic addition to α,β-unsaturated carbonyl compounds

Marius Bruvoll, Tore Hansen and Einar Uggerud*

Department of Chemistry, University of Oslo, Blindern, N-0315 Oslo, Norway

Received 14 November 2006; revised 9 January 2007; accepted 25 January 2007

ABSTRACT: One of the successful transformations within the field of organocatalysis, the organocatalytic asymmetric addition of nitromethane to α,β-unsaturated aldehydes and ketones, has been studied by quantum chemical modeling. The level of accuracy of the hybrid density functional theory method B3LYP/6-31G(d) was compared to a high level *ab initio* benchmark for this reaction. It is concluded that B3LYP/6-31G(d) performs very well for this reaction type, giving good estimates of critical energies. The reaction between acrolein and nitromethane was studied in detail. The reaction mechanism revealed an intermediate oxazolidin structure, which is currently unknown. Alkyl substitution in various positions on the amine catalyst or α,β-unsaturated carbonyl compound influences the reactivity in a predictive fashion. The iminium ion, prop-2-en-iminium, is less activated towards nucleophilic attack compared to protonated acrolein. Copyright © 2007 John Wiley & Sons, Ltd.
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KEYWORDS: organocatalysis; *ab initio* calculations; reactivity; reaction mechanism

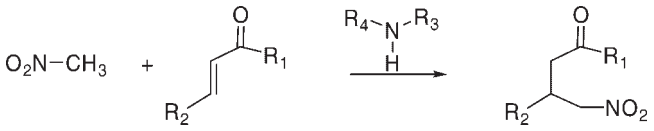
INTRODUCTION

During the last decade organocatalysis has developed to become a significant branch of organic chemistry.[1] By employing small organic molecules as catalysts, scaffolds, and templates it is possible to achieve remarkable enantioselectivity, yield, and atom-economy in important organic transformations.[2,3]

The development of new reactions and better catalysts to a large degree depends on empirism and the method of trial and error. A more rational approach would be highly advantageous in order to avoid unproductive use of time and labor. However, rational design relies on the existence of a vast portfolio of detailed mechanistic knowledge, which involves tedious and time-consuming experimental work. Some of this work is unavoidable, but there is hope it may be reduced thanks to the rapid development of more reliable quantum chemical tools for *a priori* modeling. The size and complexity of the chemical systems relevant to organocatalysis are such that the most accurate quantum chemical methods cannot be employed. Instead, more approximate schemes for solving the Schrödinger equation are used. The hybrid density functional theory approach known as B3LYP/6-31G(d) has become very popular in this respect, and it is usually used in conjunction with moderately sized or small basis sets. Quite large molecular systems can be treated and the predictive power in terms of enantioselectivity is surprisingly good judging from published literature.[4–6] This is most likely due to fortuitous cancellation of errors and not the result of high inherent accuracy of this approximate method. For this reason it would be useful to learn more about how well the method performs to different types of organocatalyzed reactions in an absolute sense.

From this short discussion it turns out that it is mandatory to investigate the strengths and inadequacies of a given computational scheme before applying it to a complex chemical problem. The performance of a computational method can be fully tested only by direct comparison with physical properties accurately determined from experiments. For a chemical reaction the most relevant measurable quantities will be barrier heights and reaction energies. Unfortunately, these quantities are usually not known for the elementary reactions in question. For example, the role of solvent and aggregation effects can make interpretation of kinetic data quite difficult. In such cases, the second best is therefore to conduct calculations for smaller model systems and compare the performance of the method against a high level *ab initio* benchmark. In this situation

**Correspondence to:* E. Uggerud, Department of Chemistry, University of Oslo, P.O. Box 1033, Blindern, N-0315 Oslo, Norway.
E-mail: einar.uggerud@kjemi.uio.no



Scheme 1

we are left with the option of studying the reaction in the gas phase. Despite this obvious limitation, the results will still be of interest in assessing the quality of the calculation. Moreover, reactivity trends in terms of substituent effects can be revealed even under the idealistic conditions of the vacuum state.

One part of the field termed organocatalysis is the nucleophilic addition to electron deficient C═C double bonds.[1] Michael acceptors are usually activated by iminium ion formation prior to nucleophilic attack. Most common Michael acceptors are α,β-unsaturated aldehydes and ketones.[7–12] We have chosen to study the addition of nitromethane to such molecules [13–16] and we will try to work along the line of direction sketched out above (Scheme 1).

The purpose of this work is mainly to assess the level of accuracy of B3LYP/6-31G(d) for this type of reaction by comparison with high level calculations. Besides this, we would like to get some insight into the most important factors which may modulate reactivity, namely the influence of the catalyst on reaction energies and barrier heights and to identify the factors influencing catalytical activity. In addition, we were interested in how alkyl substitution of the substrate molecule may affect reactivity. We would like to point out that the present work by no means is an attempt to model the complete reaction sequence of organocatalyzed nucleophilic addition in solution – a challenge we consider to be formidable.

THEORETICAL METHODS

Quantum chemical calculations

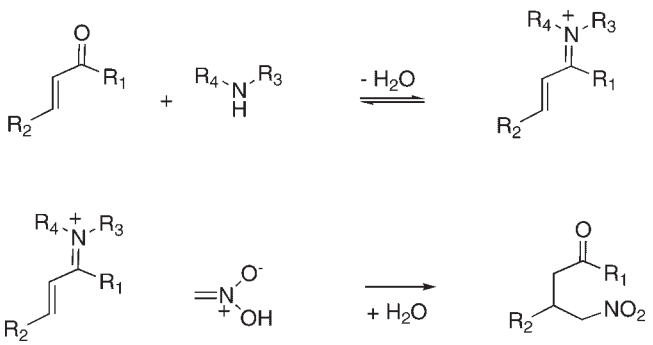
Quantum chemical calculations were carried out using the program system GAUSSIAN 03.[17] All relevant critical points (reactants, transition structures, intermediates, and products) of the potential energy surface were characterized by complete optimization of the molecular geometries using the hybrid density functional scheme B3LYP[18] with the 6-31G(d) basis set, which is abbreviated by B3LYP/6-31G(d) as well as Møller Plesset perturbation theory (MP2)[19] also with this basis set. Relative energies (B3LYP and MP2) were calculated by including unscaled zero-point vibrational energies (ZPVE). The smaller model systems were also subject of more accurate G3 or G3B3 type calculations.

We would like to emphasize that in some situations there may exist several conformers of similar potential energy. Only the one considered the most important is included in the discussion.

G3 theory[20] is a composite computational scheme which involves initial geometry optimizations at the HF/6-31G(d) level and subsequent calculation of ZPVEs at the same level of theory. Then the geometry is re-optimized at the MP2(full)/6-31G(d) level whereupon a number of single-point MP2, MP4, and QCISD(T) calculations are performed in order to obtain an energy estimate which is effectively at the QCISD(T)/G3 large level. G3B3 theory[21] uses the same higher levels as G3, except that geometries and frequencies are calculated using B3LYP/6-31G(d). Relative energies obtained by G3 and G3B3 are almost identical, provided structures are roughly the same for the structure and frequency calculations.

RESULTS

For our particular reaction, only a few mechanistic details are known from experiment.[13–15] For similar reactions catalyzed by secondary amines or amino acids under similar conditions there is good evidence for the iminium ion as the key reactive intermediate, although there are indications that iminium ion formation sometimes may be rate determining (Scheme 2, upper).[22] Furthermore, iminium ions have been observed during the course of many similar reactions.[23] Furthermore, it is assumed that the nitroalkane in question (in our case nitromethane) tautomerizes into the enol form (in our case methyleneazinic acid, **1**) prior to the key carbon–carbon bond-forming step. Usually, enolization is a limiting step, since equilibrium is in favor of the keto form. The actual reaction mechanism of nitroalkane addition in the presence of an amine may be more complex than evident from our treatment. For example, we do not yet know to what extent enolization and iminium formation are coupled to C—C formation and what role specific solvation plays. These possible shortcomings do, however, not interfere with our main mission, which is assessment of the B3LYP/6-31G(d) method. Despite this, the results of the present study should anyway be applicable and relevant to this and a wide range of similar organocatalyzed reactions.



Scheme 2

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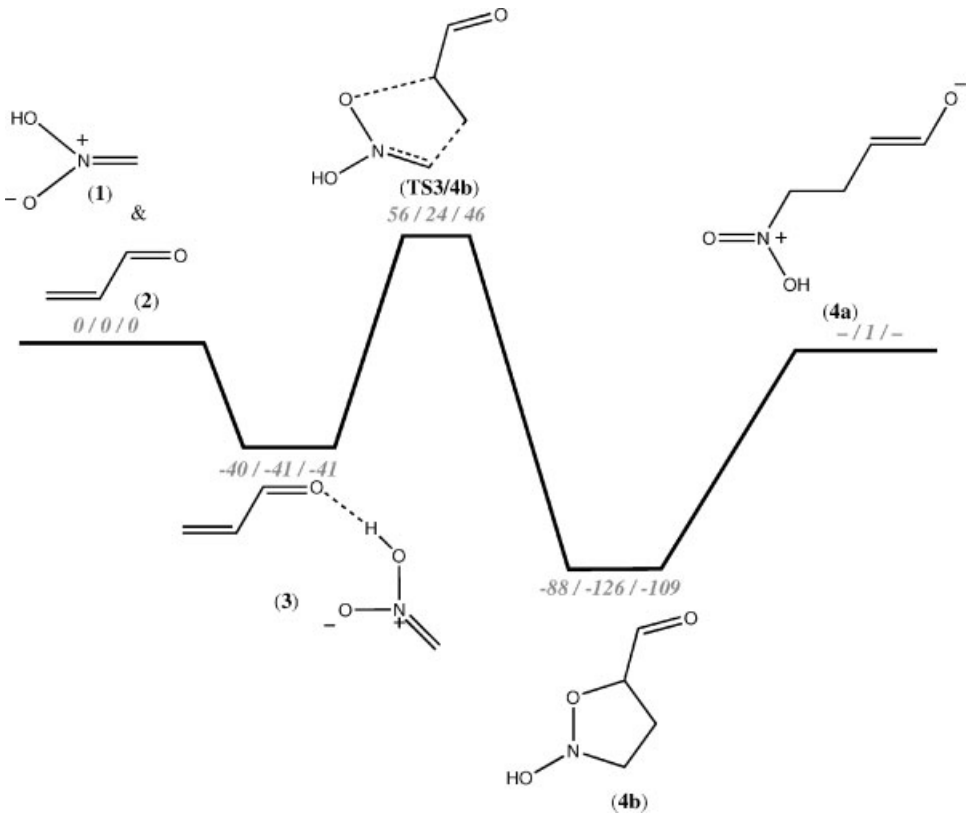

Figure 1. Potential energy diagram for the addition of methyleneazinic acid (**1**) to acrolein (**2**). The relative energies are in kJ mol^{-1} and the order is B3LYP/MP2/G3. No minimum was located corresponding to **4a** using B3LYP and HF. The latter prevented a G3 calculation

Before investigating the catalyzed reaction itself, we decided to take a look at the uncatalyzed congener. Figure 1 illustrates how direct addition of the methyleneazinic acid (**1**) to acrolein (**2**) is likely to occur. The transition structure (**TS3/4b**) is above the reactants in energy, irrespective of theoretical level, indicating that the gas phase reaction should not be observed in experiment. In between the separated reactants and the transition structure (TS) there is a hydrogen bonded intermediate (**3**), for which the chemical role is rather unimportant, but which is required to explain the local topography of this part of the potential energy surface. The intermediate (**4b**) found on the product side is more chemically significant. The five-membered ring formed, an isoxazolidin, is the result of a nucleophilic attack of the double bond in methyleneazinic acid on the β-carbon of acrolein followed by an aldol-like intramolecular ring closure. Formally, the intermediate **4b** can also be formed through a [3 + 2] cycloaddition reaction. Although the isoxalolidin skeleton is previously known,[24] the N—OH variant is new, at least to the limitation of our awareness. Since it is the minimum energy structure, it could be possible to isolate it given the suitable conditions. Opening the ring provides the open chain product **4a**, which is the anticipated addition product. It is quite unclear whether this zwitterionic structure actually has any existence in the gas phase. Neither HF nor B3LYP gives an energy minimum, which also explains why there is no entry for G3 in this case. Only with MP2/6-31G(d) a shallow potential energy minimum was located. The MP2/6-31G(d) transition structures to cyclization to the isoxazolidin (**4b**) (not indicated in the diagram) and proton transfer to the far more stable 4-nitrobutanal structure (not indicated in the diagram) are marginally above **4a**. Both are easily reached through rotations around C—C bonds corresponding to barriers of a few kJ mol^{-1}.

Not unexpectedly, protonation of acrolein activates the molecule for nucleophilic addition (Fig. 2). Comparing the data of Figs 1 and 2 shows that the barrier for the critical C—C bond-forming step decreases by approximately 100 kJ mol^{-1} upon protonation. There is a slight complication in the mechanistic picture; since it turns out there is a barrier for the association to form **7c** for B3LYP, but not for MP2. However, this finding may not be as discouraging as it appears in the first place, since both methods show that **TS6a/6b** is highest in energy and that this structure is far below the reactants in energy. The only difference is that there is a monotonic downhill path for C—C bond formation for MP2 from the association complex **6b**, while for B3LYP there is a small barrier for first passing through **TS6b/7c**. Whether this topographic detail is of big relevance to the actual reaction trajectories is questionable. We note that the isoxazolidin **7b** and a similar structure for which the C—C bond is elongated, **7c**, are of similar energy. We locate a transition structure

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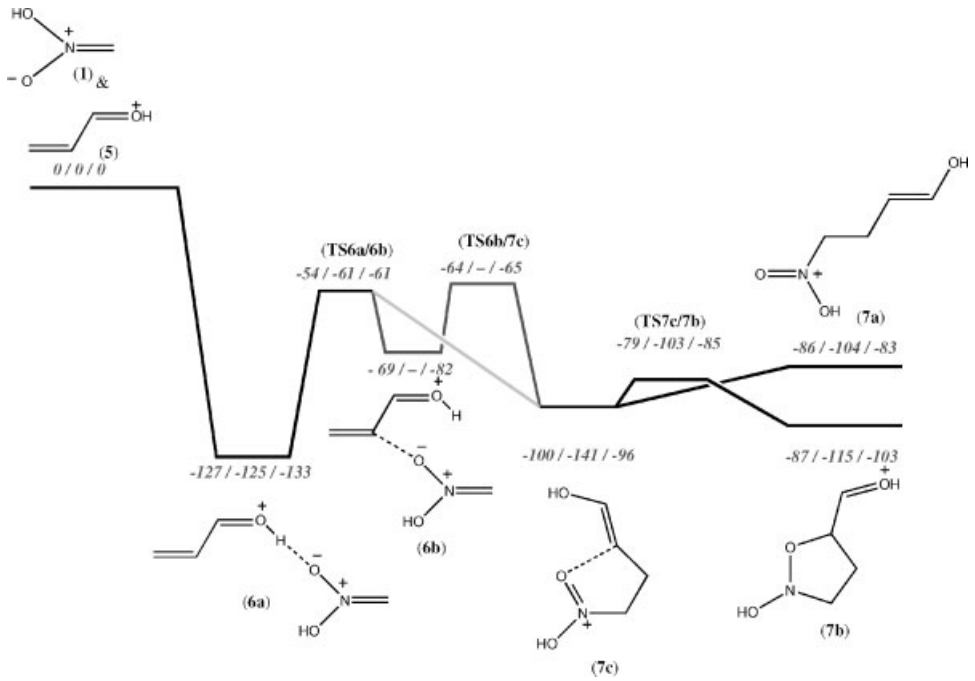

Figure 2. Potential energy diagram for the addition of methyleneazinic acid (**1**) to protonated acrolein (prop-2-en-oxonium, **5**). The relative energies are in kJ mol^{-1} and the order is B3LYP/MP2/G3B3. No minimum for **6b** or saddle point for **TS6b/7c** was located using MP2

for complete ring closure, **TS7c/7b**. The fully open chain adduct, **7a**, is also more favorable than in the non-protonated case.

The potential energy surfaces of addition to protonated acrolein (**5**) and the corresponding iminium ion, prop-2-en-iminium (**8**) are similar (Figs 2 and 3). The major difference is that the latter is somewhat less activated for C—C bond formation, although still very favorably, since all products, intermediates, and transition structures also in this case are below zero. At all levels of theory the isoxazolidin ring structure **10b** is the most advantageous. The half-open structure **10c** is a minimum with MP2, but not with B3LYP. The fully open structure **10a** was found to

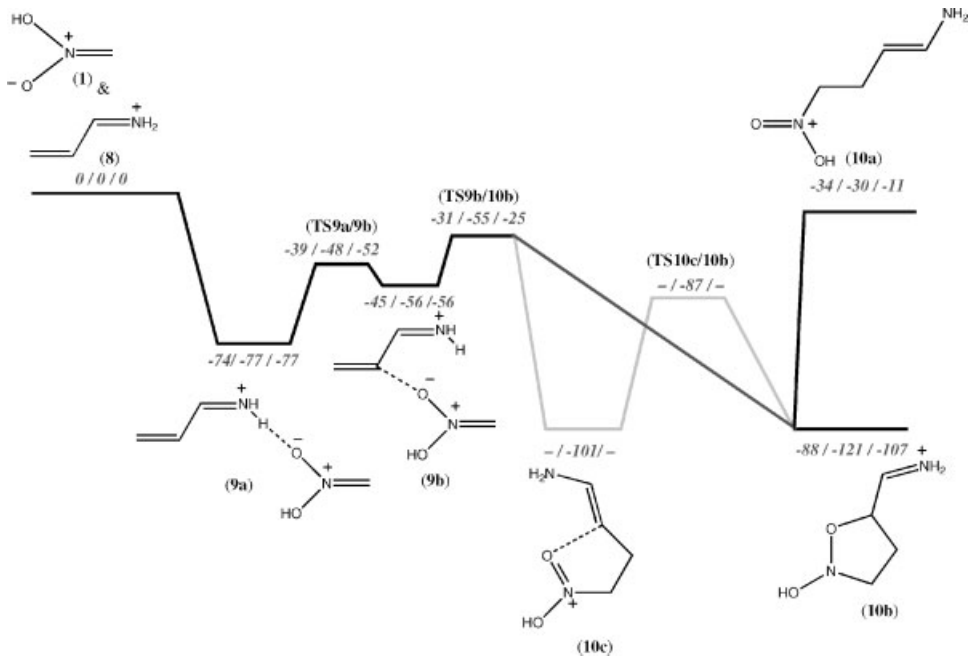

Figure 3. Potential energy diagram for the addition of methyleneazinic acid (**1**) to prop-2-en-iminium (**8**). The relative energies are in kJ mol^{-1} and the order is B3LYP/MP2/G3B3. The minimum for **10c** and the corresponding saddle point for **TS10c/10b** were only found with MP2

DOI: 10.1002/poc

be a minimum at all levels of theory employed. The key transition structures are illustrated in Figure 4.

At this stage we are in the position to estimate the performance of MP2/6-31G(d) and B3LYP/6-31G(d) by comparison to the high level extrapolations provided by G3 and G3B3. We find that the hydrogen bonded species **3**, **6a**, and **9a** give highly uniform results at all three levels. It is also clear that the relative transition structure energies calculated with B3LYP/6-31G(d) are close to the corresponding G3 and G3B3 numbers. This is encouraging. We observe that the TS for C—C formation step is underestimated by *ca*. 20 kJ mol^{-1} using MP2 compared to G3 or G3B3. We have observed the same tendency for S_N2 reactions previously.[25] The other structures B3LYP and MP2, on an average, deviate from G3 and G3B3 by the same amount. We have also seen in flat regions of the potential energy surface, a given structure may be a minimum or a saddle point depending on the level of theory. With the limited amount of data it is difficult to judge which is most correct in this respect, MP2 or B3LYP.

Despite the differences in performance of B3LYP and MP2, in particular to the fine points of C—O formation, the results give a quite consistent picture of the mechanism when applied to the models systems investigated. Protonation of acrolein increases reactivity, in agreement with the expectation. It is clear that iminium ion formation also is very favorable. The findings of the MP2 and B3LYP calculations are also in full harmony with the results obtained by assessing the isoxazolidin ring structure to be at the potential energy minimum on the product side.

In catalysis, specificity is a key issue. It is necessary to find a compound that enhances the rate of the reaction without being consumed, but this is not a sufficient criterion for being an ideal catalyst. In order to provide one specific product in large excess, a balance in reactivity has to be found. In the examples above, we noted how hydroxonium ions are very reactive. Therefore, strictly speaking, the proton is a good catalyst. However, it has been demonstrated in practice that the somewhat less reactive immonium ions are more suitable by providing a controllable environment for catalyst functionality in terms of high flexibility for structural modification of the amine used to produce the reactive iminium intermediate. It would therefore be valuable to get some insights into how various simple modifications of the amine affect the electronic environment. In addition, it is of general interest to see how alkyl substitution of the substrates modifies their reactivity.

For the above mentioned reasons we conducted B3LYP calculations of the model systems shown in Fig. 5 and Table 1. By comparing the figures in the second last column of Table 1, we observe that methyl substitution in the various positions influences reactivity in a highly predictive fashion when compared to the original unsubstituted prop-2-en-iminium (reaction 3). The largest influence is due to a methyl bonded directly to the terminal carbon, which is the electrophilic center of attack

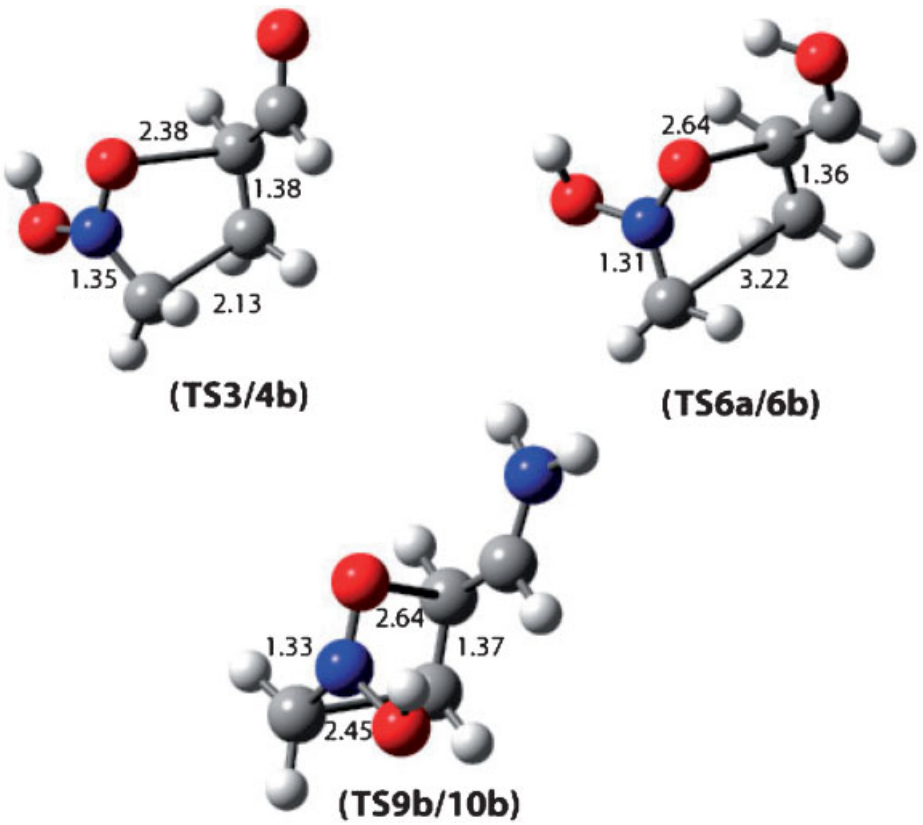

Figure 4. Transition structures of highest energy for each of the reactions described in Figs 1, 2, and 3

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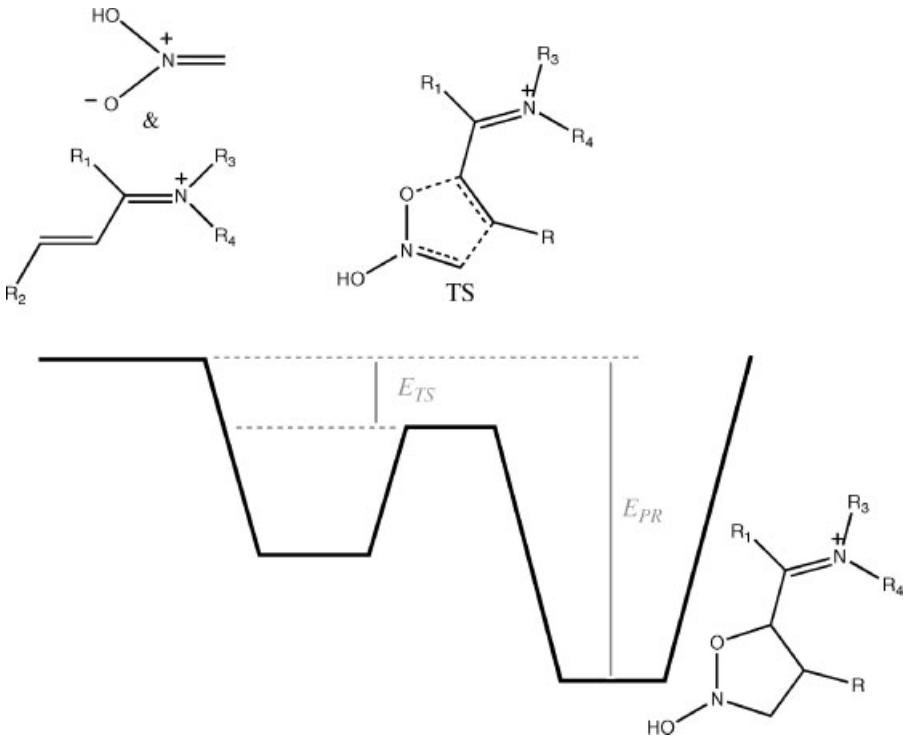

Figure 5. General potential energy diagram illustrating the influence on reactivity of methyl group substitution in the iminium ion. The data are presented in Table 1

(reaction 5). The presence of the electron-donating methyl increases the barrier substantially. Methyls bonded to the alpha carbon (reaction 4) and to the nitrogen (reaction 6) also decrease reactivity quite significantly – and the more remote substitution, the less is the effect. There is good qualitative correlation between the barrier height and the Mulliken charge of the electrophilic center (carbon no. 3) – the less positive charge, the less reactive. When we compare the effect of di- and trisubstitution (reactions 7–10), we note that the effects are additive, albeit not in the strict arithmetic sense.

The amino acid (*S*)-proline is a secondary amine, which is often used to accomplish interesting organocatalytic transformations of carbonyl compounds, being both easily available and enantiomerically pure. Even if the carbonyl substrate is not chiral, use of proline as a catalyst may induce formation of a chiral center. This phenomenon can be explained by postulating an iminium ion intermediate for which the space above and below the plane defined by the three carbon atoms bonded to nitrogen must be chemically different (see Fig. 6). By entering the upper hemisphere the nucleophile is likely to interact with the carboxylic group in the transition state, while this will not happen in the lower hemisphere. Depending on the type of the interaction with the —COOH group, this may enhance or decrease formation of the corresponding one enantiomeric product. Besides the stereochemical role played by the carboxylic group, the electron density of the substrate is affected by formation of an iminium from the substrate and the secondary amine.

Figure 6 shows the two stereoelectronically distinct transition structures located for the reaction between the proline iminium derivative of acrolein, 2-carboxy-1-propylidenepyrrolidinium (**39**). Before addressing the interactions between the nucleophile and the carboxyl group in more detail, we will first take a look at how the

Figure 6. B3LYP/6-31G(d) transition structures for the nucleophilc addition of methyleneazinic acid (**1**) to 2-carboxy-1-propylidenepyrrolidinium (**39**). The TS resulting from attack from the same side as the carboxylic acid (**TS39/40**), reaction 10A is illustrated in the left hand panel, while **TS39/40′** of reaction 10B in which the nucleophile attacks from the opposite side is shown on the right side

DOI: 10.1002/poc

Table 1. Reaction energies of nucleophilic additions to iminium ions (see Fig. 5 for reference)

Reaction no.	Product structure	R_1	R_2	R_3	R_4	E_{TS}	E_{PR}
3	**10b**	H	H	H	H	−31	−88
4	**14**	CH_3	H	H	H	−12	−85
5	**18**	H	CH_3	H	H	1	−46
6	**22**	H	H	CH_3	H	−18	−89
7	**26**	H	CH_3	CH_3	H	13	−52
8	**30**	H	H	CH_3	CH_3	−12	−90
9	**34**	H	CH_3	CH_3	CH_3	31	−51
10A (*cis*-add)	**40**	H	H	(*S*)-proline		−16	−36[a]
10B (*trans*-add)	**40'**	H	H	(*S*)-proline		−9	−90

Energies are in kJ mol^{-1} and were obtained by B3LYP/6-31G(d) including zero point vibrational energies.
A negative energy value means that the corresponding species is more stable than the separated reactants. Energies are relative to the reactants being at zero.
[a] Not cyclic.

proline ring affects the electronic properties. From Fig. 6, we notice that the transition structure for attack from the lower side (reaction 10B) is free from any steric effect of the carboxylic acid part. This result is a relative TS energy of −9 kJ mol^{-1}. This is close to the relative TS energy of reaction 8, that is, −12 kJ mol^{-1}. We therefore conclude that the electronic influences of the two secondary amines dimethyl amine and proline are very similar.

The polar tail of the nucleophile methyleneazinic acid has the potential to act as both a hydrogen donor and a hydrogen bond acceptor, and is therefore likely to interact positively with the carboxylic acid in a pre-equilibrium step, forming a hydrogen bonded dimer. For this reason alone one might eventually anticipate formation of only the product **40**. This is obviously an oversimplification and it is more likely that the C—C bond formation step itself is rate determining. In that case the relative energies of **TS39/40** and **TS39/40'** will be decisive (Fig. 5), and the key question is therefore whether the hydrogen binding is of advantage or disadvantage in this situation, a matter which is not as evident as it could appear in the first place. Only comparison of our B3LYP estimates can provide an answer. From Table 1 we see that the calculations indicate that the interaction is positive and **TS39/40** is preferred by 7 kJ mol^{-1}. This is of course not a large amount and we should be careful not to overstate the result.

CONCLUSION

The present model calculations were primarily not intended for providing accurate descriptions of a real experimental situation. The idea was to probe the accuracy of the popular and computationally inexpensive DFT method B3LYP/6-31G(d) in the bond formation step during organocatalyzed nucleophilic addition. This was achieved by comparing the results of B3LYP/6-31G(d) calculations with those of the high level method G3. In addition, we wanted to learn more about how systematic structural modification affects reactivity. In all aspects B3LYP/6-31G(d) performs surprisingly well. Important qualitative details of the potential energy surfaces are in very good qualitative agreement. Moreover, near quantitative agreement was found for the energies of intermediates and transition structures. A systematic investigation of catalyst action was conducted for both acid catalyzed reactions and iminium ion catalysis. The effect of methyl substitution in the substrate was studied and was found to decrease the reactivity, in particular at the site of electrophilic carbon being attacked.

We were also interested to see how B3LYP/6-31G(d) is able to predict enantioselectivity. In this regard it is important that non-bonding interactions are treated correctly to reproduce largely steric effects. Hydrogen bond interactions appear to be quite well described with B3LYP/6-31G(d) for the present systems. This is in agreement with Tsuzuki and Lüthi.[26] However, these authors report a general tendency for underestimating this type of intermolecular interaction. The same authors report that B3LYP also underestimates the attractive part of alkyl/alkyl interactions. In this respect PW91 is better. Despite these shortcomings, the prospect of getting useful mechanistic insight for the purpose of rational design of catalyst for enantioselective reactions seems very good.

Acknowledgements

We are grateful for a generous grant of computing time from NOTUR (The Norwegian High Performance Computing Consortium).

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