ORGANIC
LETTERS

2007
Vol. 9, No. 21
4279−4282

Computing Reliable Energetics for Conjugate Addition Reactions

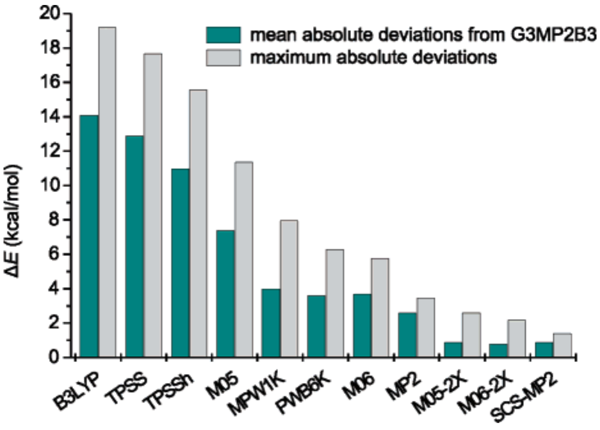
Tibor András Rokob, Andrea Hamza, and Imre Pápai*

Institute of Structural Chemistry, Chemical Research Center of the Hungarian Academy of Sciences, Pusztaszeri út 59-67, H-1025 Budapest, Hungary

papai@chemres.hu

Received August 2, 2007

ABSTRACT



The performance of various density functionals along with second-order perturbation treatments has been tested for a set of conjugate addition reactions relevant to stereoselective organocatalysis. It is shown that B3LYP predictions seriously underestimate the reaction energies, whereas two newly designed functionals (M05-2X and M06-2X) and the SCS-MP2 method provide very accurate data. These new methods represent promising alternative approaches in future mechanistic studies.

There is now ample evidence that commonly used approximated density functionals fail to predict accurate energetics for organic molecules of increasing size.[1] Recent studies clearly reveal that the most popular DFT methods give disconcertingly large errors for reaction energies[1b,f,h] and isomerization properties,[1c−e,g] which tend to add up for larger systems. The deficiencies of these methods have been related to the incorrect description of medium- and long-range nonbonded interactions,[1g] which stems from the local (or semilocal) nature of previously designed exchange-correlation functionals. These problems call for the adaptation of alternative methods in future computational studies, and fortunately, some are in fact already available.

Recently, new forms of hybrid meta-GGA-type functionals have been developed by Truhlar et al.,[2] which were shown to have improved representations of medium-range correlation energy. Of these new, highly parametrized functionals, M05-2X was found to perform remarkably well for organic molecules,[2b,3] and the M06-2X[2c] functional was shown to provide further improvements. Another appealing alternative is to apply second-order perturbation treatments[4] along with

---

(1) For recent contributions, see: (a) Schreiner, P. R. *Angew. Chem., Int. Ed.* **2007**, *46*, 4217. (b) Wodrich, M. D.; Corminboeuf, C.; Schreiner, P. R.; Fokin, A. A.; Schleyer, P. v. R. *Org. Lett.* **2007**, *9*, 1851. (c) Grimme, S.; Steinmetz, M.; Korth, M. *J. Org. Chem.* **2007**, *72*, 2118. (d) Grimme, S.; Steinmetz, M.; Korth, M. *J. Chem. Theory Comput.* **2007**, *3*, 42. (e) Schreiner, P. R.; Fokin, A. A.; Pascal, R. A.; de Meijere, A. *Org. Lett.* **2006**, *8*, 3635. (f) Wodrich, M. D.; Corminboeuf, C.; Schleyer, P. v. R. *Org. Lett.* **2006**, *8*, 3631. (g) Grimme, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 4460. (h) Check, C. E.; Gilbert, T. M. *J. Org. Chem.* **2005**, *70*, 9828.

(2) (a) Zhao, Y.; Schultz, N. E.; Truhlar, D. G. *J. Chem. Phys.* **2005**, *123*, 161103. (b) Zhao, Y.; Schultz, N. E.; Truhlar, D. G. *J. Chem. Theory Comput.* **2006**, *2*, 364. (c) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2007**, in press, DOI 10.1007/s00214-007-0310-x.

(3) (a) Zhao, Y.; Truhlar, D. G. *Org. Lett.* **2006**, *8*, 5753. (b) Zhao, Y.; Truhlar, D. G. *J. Org. Chem.* **2007**, *72*, 295. (c) Zhao, Y.; Truhlar, D. G. *J. Chem. Theory Comput.* **2007**, *3*, 289.

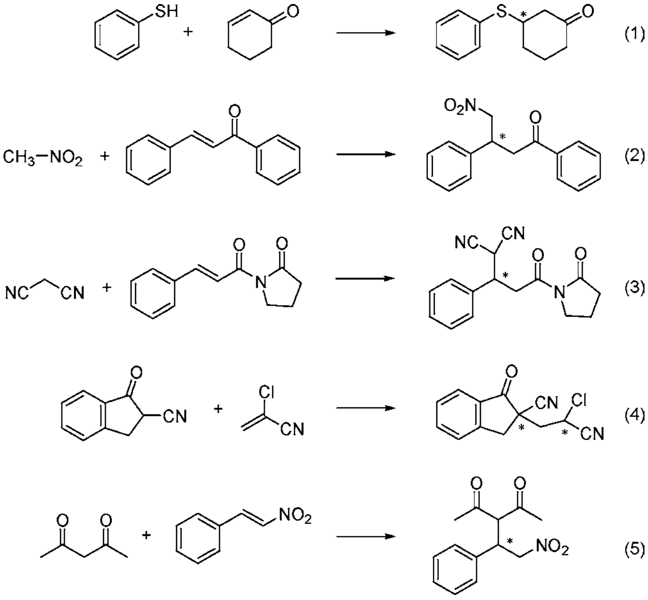
(4) Møller, C.; Plesset, M. S. *Phys. Rev.* **1934**, *46*, 618.

10.1021/ol701872z CCC: $37.00

the resolution of identity (RI) integral approximation,[5] which enables the application for larger molecules. In particular, the spin component scaled (SCS) MP2 method[6] proposed by Grimme was shown to provide very accurate energy predictions for a variety of larger systems.[7] The main goal of the present work is to demonstrate that computational mechanistic studies directed toward the development of efficient organocatalysts may greatly benefit from this methodological progress.

In this paper, we primarily focus on Michael addition reactions to electron-deficient C=C double bonds, which represent an important class of organocatalytic reactions. First, we have chosen representative reactions to assess the performance of various computational methods for reaction energies. This set includes the addition of thiophenol to cyclohex-2-enone studied earlier by Wynberg et al.[8] and four other recently examined organocatalytic addition reactions (Scheme 1).[9]

Scheme 1. Investigated Michael Addition Reactions



The functionals we have tested are the frequently used B3LYP,[10] the TPSS[11] meta-GGA functional, which is free of empirical parameters, and its hybrid version TPSSh,[12] Truhlar's MPW1K[13] and PWB6K[14] functionals, and the new M05,[2a] M05-2X,[2b] M06,[2c] and M06-2X[2c] approaches. To ensure the basis set limit in DFT calculations, we employed the large 6-311++G(3df,3pd) basis set for energy predictions. We have also tested the MP2 and SCS-MP2 methods with RI approximation and using the cc-pVTZ basis set. All the energy calculations in the present work were carried out for geometries optimized at the B3LYP/6-31G(d) level of theory. The program packages we used in our study are Gaussian 03, NWChem, and Turbomole.[15] The energy data reported in the paper correspond to relative electronic energies.[16]

The quality of approximated functionals and perturbation methods has been evaluated by comparing the predicted reaction electronic energies to those obtained from a high-level composite procedure (G3MP2B3),[17] which is expected to provide an average absolute error of around 2 kcal/mol with respect to experimental data.[16] The mean absolute deviations (MAD) and the largest absolute errors (MAX) are shown and ordered according to accuracy in Figure 1.

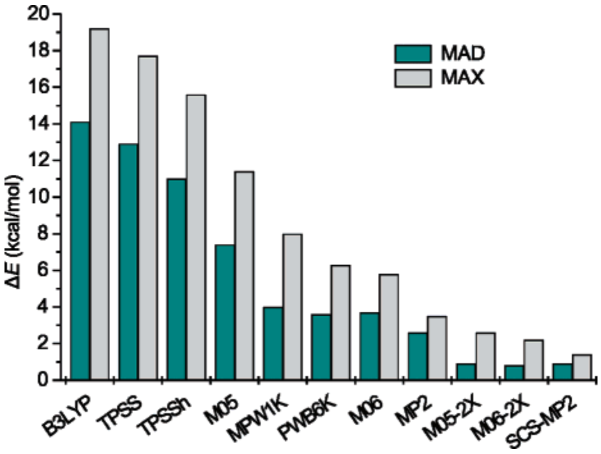


Figure 1. Mean absolute deviations (MAD) and maximum absolute deviations (MAX) (in kcal/mol) of predicted reaction energies with respect to zero-point exclusive G3MP2B3 data (see Supporting Information). The ordering is chosen according to (MAD + MAX)/2 values.

In line with previous findings, B3LYP is found to give the largest deviations from reference data. This functional

---

(5) (a) Feyereisen, M.; Fitzgerald, G.; Komornicki, A. *Chem. Phys. Lett.* **1993**, *208*, 359. (b) Weigend, F.; Häser, M. *Theor. Chem. Acc.* **1997**, *97*, 331.

(6) Grimme, S. *J. Chem. Phys.* **2003**, *118*, 9095.

(7) (a) Antony, J.; Grimme, S. *J. Phys. Chem. A* **2007**, *111*, 4862. (b) Grimme, S.; Mück-Lichtenfeld, C.; Würthwein, E.-U.; Ehlers, A. W.; Goumans, T. P. M.; Lammertsma, K. *J. Phys. Chem. A* **2006**, *110*, 2583. (c) Grimme, S. *J. Phys. Chem. A* **2005**, *109*, 3067.

(8) Hiemstra, H.; Wynberg, H. *J. Am. Chem. Soc.* **1981**, *103*, 417.

(9) (a) Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967. (b) Inokuma, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* **2006**, *128*, 9413. (c) Wang, B.; Wu, F.; Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc.* **2007**, *129*, 768. (d) Okino, T.; Hoashi, Y.; Furukawa, T.; Xu, X.; Takemoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 119. (e) Wang, J.; Li, H.; Duan, W.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4713.

(10) (a) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648. (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785. (c) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *J. Phys. Chem.* **1994**, *98*, 11623.

(11) Tao, J.; Perdew, J. P.; Staroverov, V. N.; Scuseria, G. E. *Phys. Rev. Lett.* **2003**, *91*, 146401.

(12) Staroverov, V. N.; Scuseria, G. E.; Tao, J.; Perdew, J. P. *J. Chem. Phys.* **2003**, *119*, 12129.

(13) Lynch, B. J.; Fast, P. L.; Harris, M.; Truhlar, D. G. *J. Phys. Chem. A* **2000**, *104*, 4811.

(14) Zhao, Y.; Truhlar, D. G. *J. Phys. Chem. A* **2005**, *109*, 5656.

(15) (a) Frisch, M. J. et al. *Gaussian 03*, revision B.05; Gaussian, Inc.: Wallingford, CT, 2004. (b) Bylaska, E. J. et al. *NWChem, A Computational Chemistry Package for Parallel Computers*, version 5.0; Pacific Northwest National Laboratory: Richland, Washington, 2006. (c) Ahlrichs, R., et al. *TURBOMOLE*, version 5.9.1; Universität Karlsruhe, 2007. Full references are given in Supporting Information.

(16) For further details and references, see Supporting Information.

(17) Baboul, A. G.; Curtiss, L. A.; Redfern, P. C.; Raghavachari, K. *J. Chem. Phys.* **1999**, *110*, 7650.

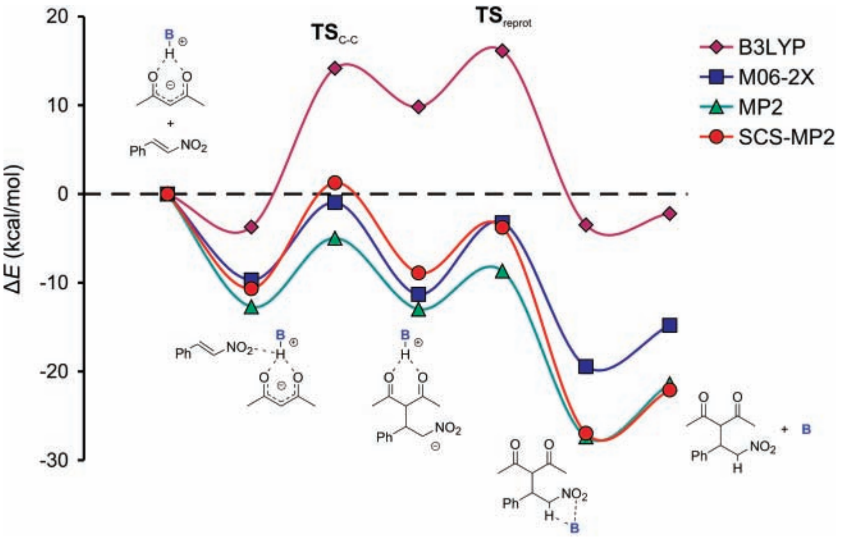


Figure 2. Calculated energy profiles for base-catalyzed Michael addition of acetylacetone to β-nitrostyrene. The energies along the reaction pathway are given relative to the first stationary point. The trimethylamine base is denoted as B. The optimized structures for the full catalytic cycle are given in the Supporting Information. Applied basis sets: TZVP (in DFT), cc-pVTZ (in MP2 and SCS-MP2).

systematically underestimates the stabilities of Michael adducts with an average error of 14.1 kcal/mol. The degree of underestimation is so severe that all these reactions that take place readily in the presence of base catalysts are predicted to be highly endergonic with B3LYP (see Supporting Information). Similar errors are obtained with the nonempirical TPSS functional, and the admixture of exact exchange energy in TPSSh provides only slight improvements. The average error of the M05 functional, which was originally designed for broad applicability, is still quite significant (7.4 kcal/mol), but its new parametrization (M05-2X) represents one of the most accurate DFT methods for the present set of reactions. The MPW1K and PWB6K models designed to improve thermochemical kinetics data appear to be more accurate than previous hybrid functionals, but they do not reach the quality of M05-2X. The M06 results indicate clear improvement over M05, whereas both M06-2X and M05-2X methods (which were parametrized for main-group compounds) perform remarkably well. Regarding the perturbation methods, the conventional MP2 procedure systematically overestimates the reaction energies (by about 3−4 kcal/mol); however, the errors are notably reduced with the SCS treatment providing results that are very close to G3MP2B3 data (MAD = 1.0 kcal/mol and MAX = 1.5 kcal/mol).

The prediction of accurate reaction energies is an indispensable requirement in theoretical mechanistic studies; however, the applied method is expected to account for the energetics of separate elementary steps as well. We have thus examined the energy profile of a model base-catalyzed reaction, namely, the addition of acetylacetone (acac) to β-nitrostyrene (eq 5 in Scheme 1) in the presence of trimethylamine (TMA) base. The involved reaction mechanism and the energy profiles obtained with two DFT approaches (B3LYP and M06-2X) and the perturbation methods are depicted in Figure 2. The basis sets employed in DFT calculations are the TZVP sets developed within the framework of DFT,[18] which were found to give very accurate energetics at reasonable computational cost for reactions shown in Scheme 1 (see Supporting Information).

According to the generally accepted mechanism of Michael additions,[8] the nucleophilic acac is activated via deprotonation by the base (B) leading to an ion pair that interacts with the electrophile, and C−C bond formation takes place ($\mathbf{TS_{C-C}}$ in Figure 2). In the next step, the adduct anion intermediate is reprotonated by BH^+ ($\mathbf{TS_{reprot}}$), and the final product is released in a dissociation process.

The main features of the M06-2X energy profile are consistent with those of perturbation methods, although one finds appreciable differences in the calculated energy barriers (±3 kcal/mol) and relative stabilities of reaction intermediates. For instance, the adduct reprotonation step is found to be notably less exothermic with M06-2X as compared to SCS-MP2 results. On the other hand, the B3LYP energy profile lies well above the other three curves, which is due to errors that accumulate along the reaction pathway. It appears that the deficiencies of the B3LYP functional induce inaccuracies not only for weak ion pair−electrophile and base−adduct interactions but also for the energetics (both kinetics and thermodynamics) of the C−C bond formation step. As a result of these errors, B3LYP calculations predict the reprotonation process to be the rate-determining step of the catalytic cycle ($\mathbf{TS_{reprot}}$ lies higher in energy than $\mathbf{TS_{C-C}}$), which contradicts with experimental findings for Michael addition reactions.[8] These results clearly confirm the conclu-

---

(18) Godbout, N.; Salahub, D. R.; Andzelm, J.; Wimmer, E. *Can. J. Chem.* **1992**, *70*, 560.

sions of recent comparative studies that suggest great precaution in using the B3LYP functional for energy predictions of larger organic molecules.

The above statement is particularly applied to computational mechanistic studies in the expanding field of organocatalysis (and probably in organometallic catalysis as well) because the system that includes the catalyst molecule and the substrates is definitely large enough to encounter the problems associated with DFT. Moreover, organocatalytic reactions are multistep processes where weak interactions play a decisive role in the stereochemical outcome of the reaction. One of the major goals of related computations is to provide insight into the details of the selectivity determining phase of the catalytic cycle.[19] Here, we show that the choice of the applied computational method may considerably affect the accuracy of selectivity predictions as well.

We have recently described two feasible reaction pathways for the enantioselective version of eq 5 promoted by a thiourea-based chiral catalyst and found that both pathways account qualitatively for the observed selectivity.[19d] Because our conclusions were based on B3LYP results, we reexamined the selectivity issue with more accurate treatments. The computed relative energies of transition states associated with the C−C bond formation step along four possible reaction channels (corresponding to routes A and B toward the (*R*) and (*S*) product isomers) are compared in Table 1.

Table 1. Predicted Selectivity Data for Enantioselective Addition of acac to β-Nitrostyrene Catalyzed by Takemoto's Bifunctional Organocatalyst[a]

	B3LYP	M06-2X	MP2	SCS-MP2
	Route A vs B			
$E(\mathrm{TS}_{\mathrm{A},R}) - E(\mathrm{TS}_{\mathrm{B},R})$	2.6 (2.7)[b]	6.1	7.1	6.1
$E(\mathrm{TS}_{\mathrm{A},S}) - E(\mathrm{TS}_{\mathrm{B},S})$	2.5 (2.9)	5.6	7.3	6.0
	Product (*R*) vs (*S*)			
$E(\mathrm{TS}_{\mathrm{A},S}) - E(\mathrm{TS}_{\mathrm{A},R})$	2.6 (2.6)	4.3	4.9	4.2
$E(\mathrm{TS}_{\mathrm{B},S}) - E(\mathrm{TS}_{\mathrm{B},R})$	2.7 (2.4)	4.9	4.8	4.3

[a] Relative energies are given in kcal/mol. $E(\mathrm{TS}_{\mathrm{X,Y}})$ denotes the total energy of transition state associated with the C−C coupling step on route X (A or B) toward product isomer Y (*R* or *S*) (see Supporting Information). Employed basis sets: TZVP in DFT, cc-pVTZ in MP2 calculations. [b] Values in parentheses correspond to B3LYP/6-311++G(d,p) calculations (ref 19d).

It is reassuring to observe that all of the applied methods consistently predict the preference of route B over A and stereoselectivity in favor of the (*R*) product, which confirms the main conclusions of our previous work. However, the energy differences obtained with M06-2X and the perturbation approaches are significantly larger than those calculated with B3LYP, which point to extremely high enantioselectivities along these reaction pathways. It is therefore very likely that additional C−C bond formation reaction channels, such as those associated with other low-lying conformations of the catalyst molecule,[19d] should be considered to fully account for experimental selectivity data. Finally, it is worth noting that the M06-2X and SCS-MP2 selectivity predictions fall rather close to each other, whereas differences between the two perturbation methods are somewhat larger.

In summary, we have shown in this paper that the basic deficiencies of the B3LYP functional give rise to serious errors for the energetics of conjugate addition reactions, which may even lead to incorrect mechanistic conclusions for related catalytic cycles. This fact, however, should not hamper theoretical mechanistic studies that involve larger organic molecules because promising new methods are available for more reliable predictions. We find that Truhlar's new functionals (M05-2X and M06-2X) and Grimme's SCS-MP2 approach provide very accurate reaction energies for conjugate additions, and they qualitatively account for mechanistic details as well.

Acknowledgment. This work has been supported by the Hungarian Research Foundation (Grant K-60549).

Supporting Information Available: Cartesian coordinates and electronic total energies of all computed species, computational details, additional data for some parts of the work, full list of authors in ref 15, and references of basis sets. This material is available free of charge via the Internet at http://pubs.acs.org.

OL701872Z

---

(19) For a selection of recent mechanistic DFT studies on organocatalytic reactions, see: (a) Yamanaka, M.; Itoh, J.; Fuchibe, K.; Akiyama, T. *J. Am. Chem. Soc.* **2007**, *129*, 6756. (b) Gordillo, R.; Houk, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 3543. (c) Bertelsen, S.; Marigo, M.; Brandes, S.; Dinér, P.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 12973. (d) Hamza, A.; Schubert, G.; Soós, T.; Pápai, I. *J. Am. Chem. Soc.* **2006**, *128*, 13151.