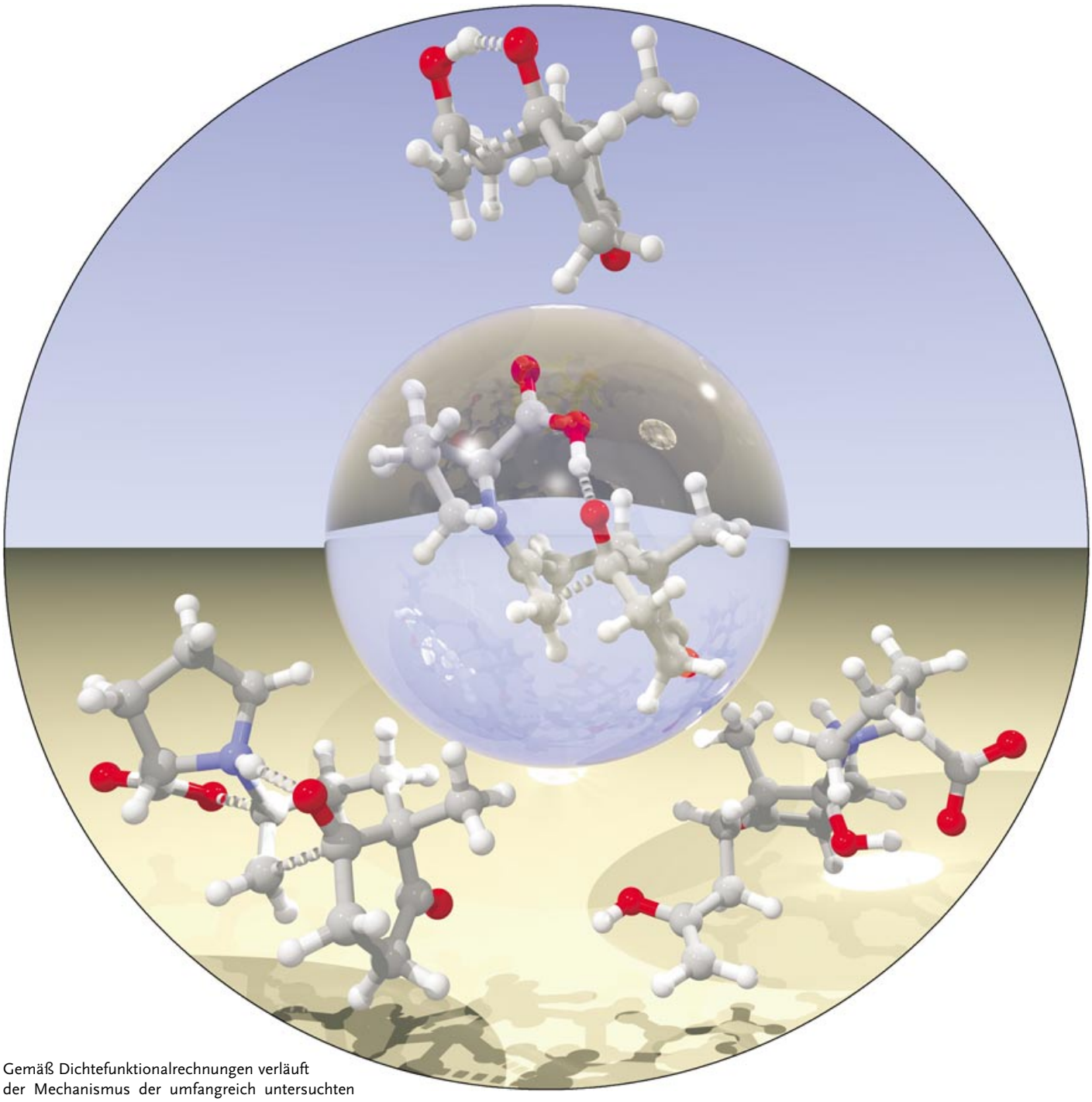
Zuschriften



Gemäß Dichtefunktionalrechnungen verläuft der Mechanismus der umfangreich untersuchten Hajos-Parrish-Eder-Sauer-Wiechert-Reaktion, einer prototypischen asymmetrischen organokatalytischen Umwandlung, über eine Prolinenamin-Zwischenstufe (in der Mitte abgebildet), die eine konzertierte Aldolcyclisierung unter Protonenübertragung eingeht. Weiteres erfahren Sie in der Zuschrift von K. N. Houk und F. R. Clemente auf den folgenden Seiten.

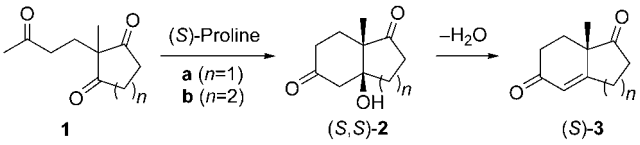
DOI: 10.1002/ange.200460916

Density Functional Calculations

Computational Evidence for the Enamine Mechanism of Intramolecular Aldol Reactions Catalyzed by Proline**

*Fernando R. Clemente and K. N. Houk**

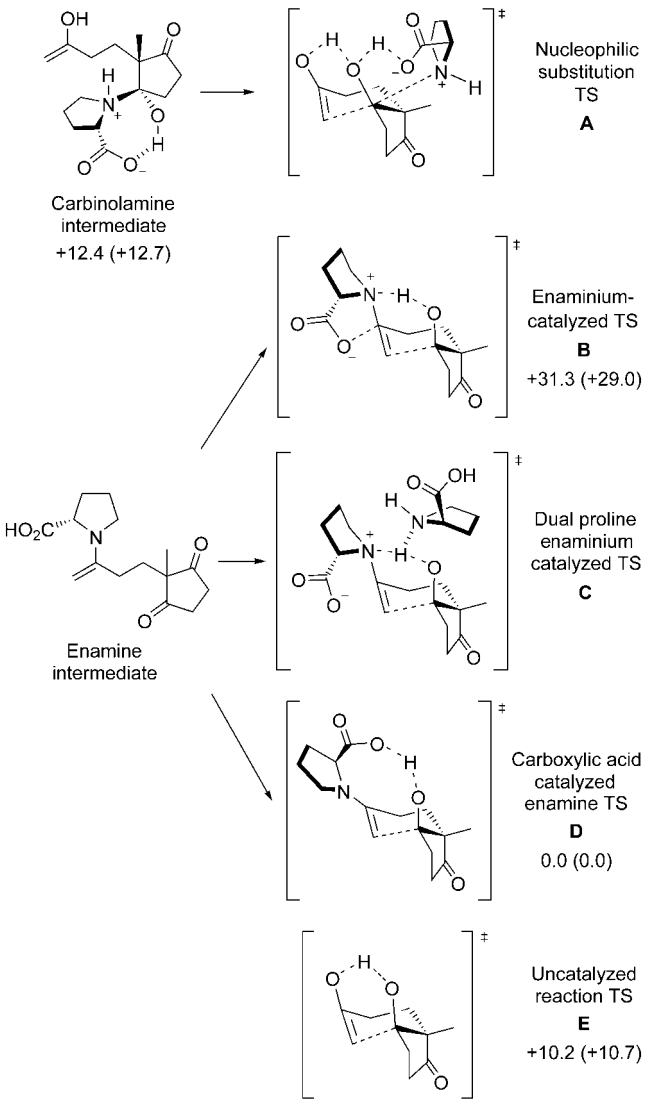
The first examples of enantioselective intramolecular aldol cyclizations catalyzed by proline (Scheme 1) were independently reported by Hajos and Parrish[1] and by Wiechert and co-workers[2] in 1971. Useful synthetic intermediates, such as the Wieland–Miescher ketone (**3b**) are easily obtained by this reaction. This reaction constitutes a cornerstone in the emergent field of enantioselective organocatalysis. A variety of C–C bond-forming reactions have been achieved with chiral organocatalysis in recent years.[3]



Scheme 1. Enantioselective intramolecular aldol cyclization.

In spite of the classic status of this reaction, the mechanism remains controversial. Herein we provide definitive theoretical evaluation of the various mechanisms proposed for the reaction; by computation of all six steps in the reaction we show how the reaction conditions may influence the rate-determining step and the stereoselectivity.

In their original paper,[1b] Hajos and Parrish proposed two mechanisms (Scheme 2): **A**, which requires the formation of a carbinolamine intermediate followed by nucleophilic substitution at this center by the enol form of the acyclic carbonyl; and **B**, with an enaminium intermediate and C–C bond-formation accompanied by N-H-O hydrogen transfer and nucleophilic assistance by the carboxylate group of proline. Hajos still argues for mechanism **A**,[1c] on the basis of his experiments with ^{18}O-labeled water where no incorporation of ^{18}O in the products was observed.[1b] However, List et al. have reinvestigated these experiments recently under carefully controlled conditions, and they found efficient (>90%) ^{18}O incorporation.[4]



Scheme 2. Relative energies (E + ZPE, kcal mol^{-1}; ZPE = zero-point energy) of proposed proline-catalyzed aldolization transition states. Values in parentheses include solvation energies in DMSO using the PCM/UAKS model.

In the 1980s, Agami supported the mechanisms involving enamine intermediates[5] on the basis of accumulated experience in amine catalysis of similar reactions.[6] Mechanism **B** was criticized, since it involves a protonated enamine that must reduce the nucleophilicity of the C=C bond. They proposed mechanism **C**, which involves a second molecule of proline to assist in the hydrogen transfer.[5] While model **C** was supported by the observation of a kinetic nonlinear effect, List and co-workers have reported evidence that show the absence of nonlinear effects in these reactions and support a one-proline mechanism.[7]

Mechanism **D** involves an enamine intermediate with concerted C–C bond formation and proton transfer from the carboxylic acid group to the carbonyl acceptor. This transition state, initially proposed by Jung in a review in 1976,[8] was

[*] Dr. F. R. Clemente, Prof. Dr. K. N. Houk
Department of Chemistry and Biochemistry
University of California
Los Angeles, CA 90095-1569 (USA)
Fax: (+1) 310-206-1843
E-mail: houk@chem.ucla.edu

[**] We are grateful to the National Institute of General Medical Sciences, National Institutes of Health for financial support of this research, and the National Computational Science Alliance, the National Science Foundation, and UCLA Academic Technology Services for computer resources. F.R.C. thanks Fundación Ramón Areces (Spain) for a postdoctoral fellowship.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  DOI: 10.1002/ange.200460916

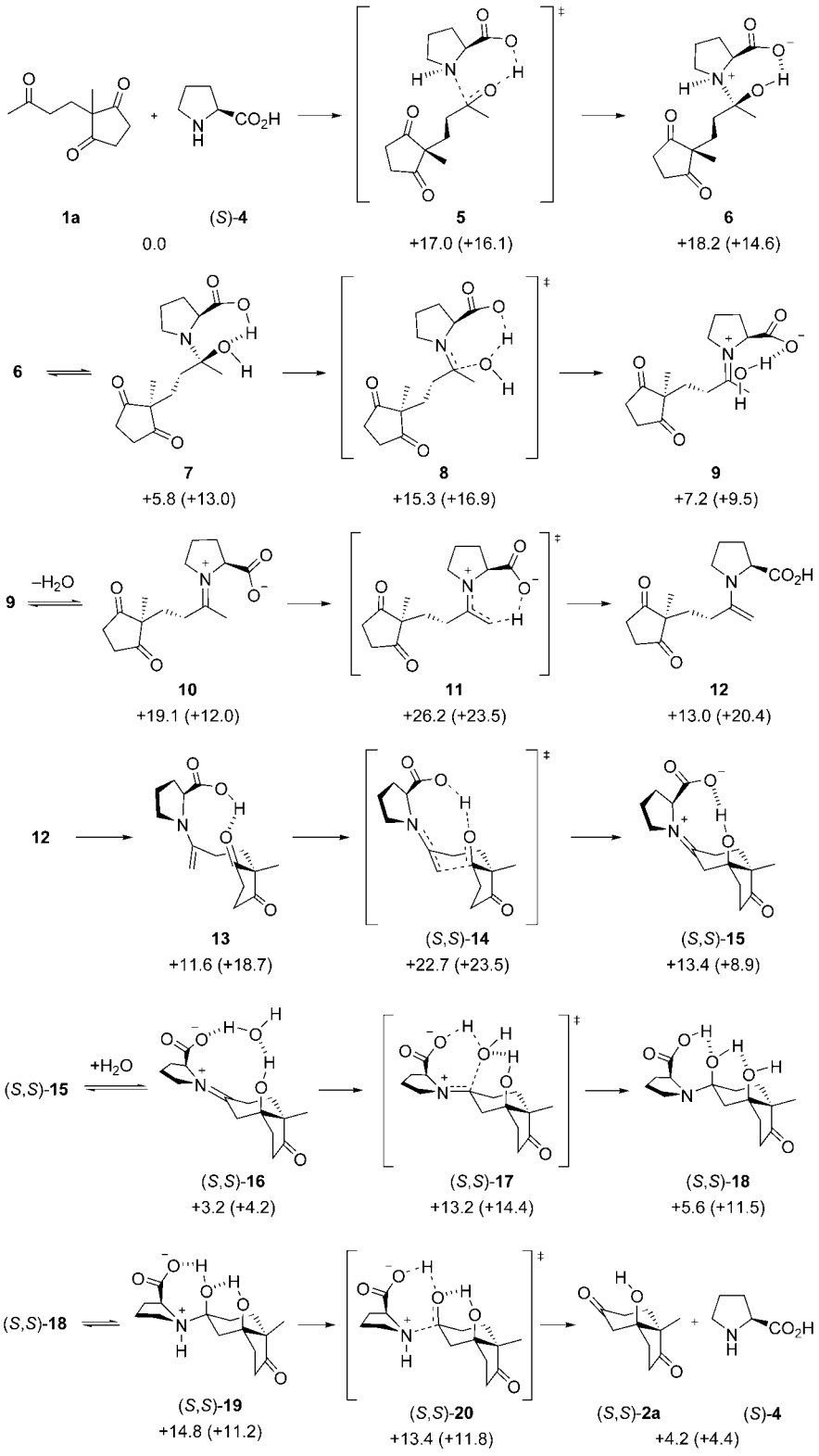
almost abandoned in favor of mechanism **C** until 2000. In their pioneering work on enantioselective proline catalysis of intermolecular aldol reactions, List, Barbas, and co-workers proposed a model similar to **D**.[9] Our preliminary computational studies on the origins of the stereoselectivity of the intramolecular aldol reactions depicted in Scheme 1 also support mechanism **D**, since transition states computed for this reaction provide a satisfactory explanation of the stereochemical outcome.[10]

We have located the transition structures for the C–C bond-forming step of the different mechanisms proposed (Scheme 1), which is the presumed rate-determining step for the transformation. All the geometries were fully optimized with GAUSSIAN[11] at the B3LYP/6-31G(d) level followed by frequency calculations to determine the nature of the stationary points. The reported energies come from B3LYP/6-31 + G(d,p) energy calculations on the geometries optimized at the lower level.[12] Free energies of solvation were computed as the energy difference of HF/6-31 + G(d,p) single point energy calculations in DMSO (PCM model[13] and UAKS radii)[11b] and in the gas-phase on the DFT gas-phase geometries.

The relative energies of the different transition states or intermediates are given in Scheme 2. The carboxylic acid catalyzed enamine mechanism (**D**) is energetically the most favorable. The transition structure for C–C bond formation by this mechanism is more than 10 kcal mol^{-1} lower in energy than the corresponding one for the uncatalyzed process (**E**). Mechanism **B**, which involves the zwitterionic form of the enamine (enaminium), is disfavored by about 30 kcal mol^{-1} over mechanism **D**. The nucleophilic substitution TS (**A**) could not be located, and all our optimization attempts led to structures similar to **E**, the uncatalyzed process. However, the carbinolamine intermediate preceding this C–C bond-forming TS is more than 12 kcal mol^{-1} higher in energy than TS **D**. It is thus expected that a structure such as TS **A**, if it exists, would be even higher in energy than this intermediate.

The enhanced nucleophilicity of the enamine C=C bond together with the activation of the carbonyl electrophile by the carboxylic acid constitute the basis of the catalytic activity of the amino acid acting through mechanism **D**. Protonation of the enamine nitrogen atom (**B**) drastically reduces the reactivity of the C=C bond. On the other hand, the mechanism originally supported by Hajos (**A**) appears very unlikely since the carbinolamine intermediate is already higher in energy than the transition structure for the uncatalyzed process (**E**).

Scheme 3 depicts the proposed pathway for the enantioselective aldol cyclization of **1a** catalyzed by (*S*)-proline involving the formation of an enamine intermediate (**12**) and



Scheme 3. Proposed pathway for the (*S*)-proline-catalyzed cyclization of **1a** into (*S*,*S*)-**2a** with the relative gas-phase energies (kcal mol^{-1}). Values in parentheses include solvation energies in DMSO using the PCM/UAKS model.

carboxylic acid catalysis in the C–C bond-forming step ((*S*,*S*)-**14**). Boyd and co-workers have reported a similar study but for the intermolecular reaction.[14] The last stage in the formation of enamine intermediate **12** is the intramolecular deprotonation by the carboxylate group (**11**). This process and the subsequent C–C forming step have equal energies in solution and represent the rate-determining steps (Figure 1). The C–C bond forming step ((*S*,*S*)-**14**) is the stereochemistry-determining step of the reaction. The preferential formation of the *S*,*S* enantiomer was rationalized in an earlier computational study from our research group.[10]

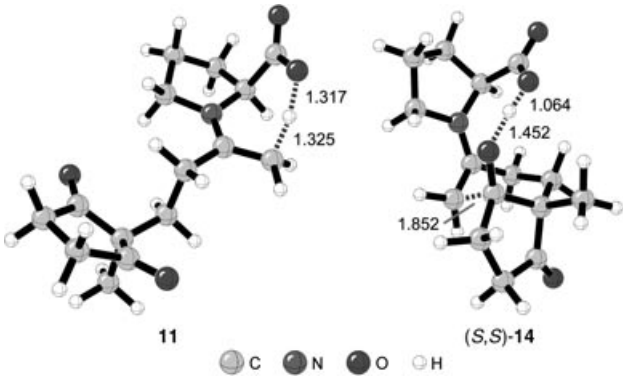


Figure 1. B3LYP/6-31G(d)-optimized transition-state geometries of the rate-determining steps for enamine formation (**11**) and aldol cyclization ((*S*,*S*)-**14**). Interatomic distances are given in Å.

After the formation of the C–C bond, the hydrolysis of iminium (*S*,*S*)-**15** is achieved in a series of easy steps that leads to the release of the aldol product (*S*,*S*)-**2a** and recovery of the catalyst. These steps are analogous, but in reverse order, to those at the beginning corresponding to the formation of iminium intermediate **10**. As expected, the most difficult step in the hydrolysis of (*S*,*S*)-**15** is the nucleophilic attack of water ((*S*,*S*)-**17**). This step will compete with the reversal of the C–C bond-forming step ((*S*,*S*)-**14**) at a low concentration of water. This result has significance on the stereoselectivity.

Recent experimental work,[4,7] together with these computational studies, have established the previously controversial mechanism of aldol reactions catalyzed by proline.

Received: June 9, 2004

Keywords: aldol reaction · asymmetric catalysis · density functional calculations · proline · reaction mechanisms

[1] a) Z. G. Hajos, D. R. Parrish, German Patent DE 2102623, July 29, **1971**; b) Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615–1621; c) Z. G. Hajos, http://preprint.chemweb.com/orgchem/0209001.

[2] a) U. Eder, G. Sauer, R. Wiechert, German Patent DE 2014757, Oct. 7, **1971**; b) U. Eder, G. Sauer, R. Wiechert, *Angew. Chem.* **1971**, *83*, 492–493; *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496–497.

[3] Reviews: a) P. I. Dalko, L. Moisan, *Angew. Chem.* **2001**, *113*, 3840–3864; *Angew. Chem. Int. Ed.* **2001**, *40*, 3726–3748; b) E. R. Jarvo, S. J. Miller, *Tetrahedron* **2002**, *58*, 2481–2495.

[4] B. List, L. Hoang, H. J. Martin, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5839–5842.

[5] For a review of their work, see C. Agami, *Bull. Soc. Chim. Fr.* **1988**, *3*, 499–507.

[6] a) T. A. Spencer, H. S. Neel, T. W. Flechtner, R. A. Zayle, *Tetrahedron Lett.* **1965**, 3889–3897; b) H. Molines, C. Waksel-man, *Tetrahedron* **1976**, *32*, 2099–2103; c) K. L. Brown, L. Damm, J. D. Dunitz, A. Eschenmoser, R. Hobi, C. Kratky, *Helv. Chim. Acta* **1978**, *61*, 3108–3135.

[7] L. Hoang, S. Bahmanyar, K. N. Houk, B. List, *J. Am. Chem. Soc.* **2003**, *125*, 16–17.

[8] M. E. Jung, *Tetrahedron* **1976**, *32*, 3–31.

[9] a) B. List, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **2000**, *122*, 2395–2396; b) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas III, *J. Am. Chem. Soc.* **2001**, *123*, 5260–5267.

[10] S. Bahmanyar, K. N. Houk, *J. Am. Chem. Soc.* **2001**, *123*, 12911–12912.

[11] a) Gaussian98 (Revision A.9), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **1998**; b) solvation calculations performed with Gaussian03: Gaussian03 (Revision B.05), M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **2003**.

[12] Reported energies include zero-point energy corrections at the same level of the geometry (B3LYP/6-31G(d)) scaled by 0.9806: A. P. Scott, L. Radom, *J. Phys. Chem.* **1996**, *100*, 16502–16513.

[13] a) B. Mennucci, R. Cammi, J. Tomasi, *J. Chem. Phys.* **1999**, *110*, 6858–6870; b) M. Cossi, G. Scalmani, N. Rega, V. Barone, *J. Chem. Phys.* **2002**, *117*, 43–54.

[14] K. N. Rankin, J. W. Gauld, R. J. Boyd, *J. Phys. Chem. A* **2002**, *106*, 5155–5159.

