ORGANIC LETTERS

2010
Vol. 12, No. 22
5162−5165

Theoretical Investigation of the Rubicordifolin Cascade

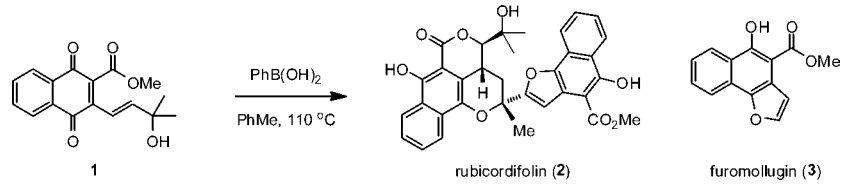
Jean-Philip Lumb,*,† Jamin L. Krinsky,‡ and Dirk Trauner§

Department of Chemistry, University of California, Berkeley, California 94720, United States

jplumb@stanford.edu

Received September 10, 2010

ABSTRACT



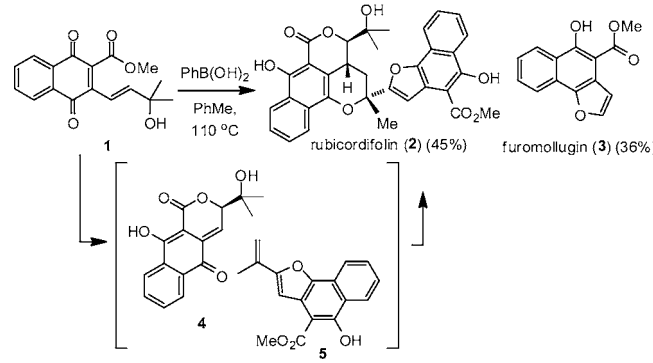
1 rubicordifolin (**2**) furomollugin (**3**)

The results of a theoretical investigation on the complex cascade reaction leading to the natural product rubicordifolin are reported. These computations analyze the discrete transformations that are required during the conversion of the vinyl naphthoquinone starting material into the natural product, including two pseudopericyclic cyclizations as well as a diastereoselective, hetero-Diels−Alder reaction.

Over the past several years we have been interested in the synthesis of an unusual class of pseudodimeric naphthoquinones isolated from the medicinal plants *Rubia cordifolia* and *R. oncotricha*.[1,2] Our syntheses have been based on presumed biosynthetic pathways, guided largely by the surprising fact that these highly oxidized natural products are isolated in racemic form. Early on in the development of this program, we reported that vinyl quinone **1** undergoes a remarkable transformation in the presence of phenylboronic acid at elevated temperatures, providing rubicordifolin (**2**) and furomollugin (**3**) in yields of 45% and 36%, respectively (Scheme 1).[2a]

Initially, we proposed that an *endo*-selective, [4 + 2] cycloaddition between *o*-quinone methide **4** and vinylnaphthofuran **5** could account for the formation of **2** as a single diastereomer. However, certain aspects of this hypothesis merited further investigation. These included the precise manner in which **1** is converted into **4** and **5**, as well as an explanation for the exquisite diastereocontrol in the cycloaddition.[3]

Scheme 1. Synthesis of Rubicordifolin (**2**) and Furomollugin (**3**)



With the aim of shedding light onto the mechanism of this reaction we initiated a theoretical investigation into the behavior of **1**. Herein we report the results of these

† Present address: Department of Chemistry, Stanford University.

‡ Present address: Molecular Graphics and Computation Facility, University of California, Berkeley.

§ Present address: Department of Chemistry, University of Munich.

(1) For a review of bioactive natural products derived from *Rubia* see: Chauhan, S.; Singh, R. *Chem. Biodiversity* **2004**, *1*, 1241.

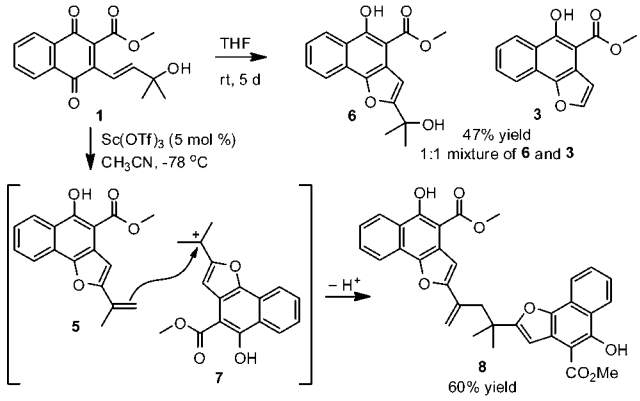
(2) (a) Lumb, J. P.; Trauner, D. *J. Am. Chem. Soc.* **2005**, *127*, 2870. (b) Lumb, J. P.; Choong, K. C.; Trauner, D. *J. Am. Chem. Soc.* **2008**, *130*, 9230.

(3) Despite the absence of products arising from exo- or regioisomeric transition states in the crude reaction mixture, their formation cannot be unequivocally excluded in light of the incomplete mass balance of the reaction.

10.1021/ol102157d
Published on Web 10/25/2010

calculations[4] which, in conjunction with experimental findings, have led us to revise our proposed mechanism for the formation of **2**. The relatively new M06−2X[5] functional was used for geometry optimizations and frequency calculations, in conjunction with the 6-311+G(d,p) basis set.[6] When possible, the energies of optimized structures were recalculated by using the double hybrid functional B2PLYP-D,[7] which includes a second-order perturbative component and an empirical dispersion correction; results for this method are given in parentheses. Reported energies for both methods were corrected for zero-point energy calculated at the M06−2X level, and isomeric sets were constructed so that energies could be directly compared to that of compound **1** (**1** is defined as two molecules of **1** and one molecule of H_2O). All values are reported in kcal/mol.

Scheme 2. Reactivity of Vinylnaphthoquinone **1**



First we discuss the proposed formation of dienophile **5** and furomollugin (**3**). Vinylnaphthoquinone **1** underwent spontaneous cyclization to provide a 1:1 mixture of **3** and **6** when left as a dilute solution in THF for extended periods at room temperature (Scheme 2).[2a] All attempts to improve upon the selectivity or yield of this process by changing solvent, temperature, or pH resulted in either decreased yields of **3** and **6** or intractable mixtures. Importantly, exposure of **1** to a variety of Lewis acids, including complexes of Mg, Ti, Al, or Sn, consistently resulted in near instantaneous formation of **3** and **6**, albeit in low isolated yields. The sole exception was the action of $Sc(OTf)_3$ in CH_3CN, which afforded dimer **8** in 60% yield. These results are significant when discussing the role that phenylboronic acid plays in the synthesis of **2** (vide infra).

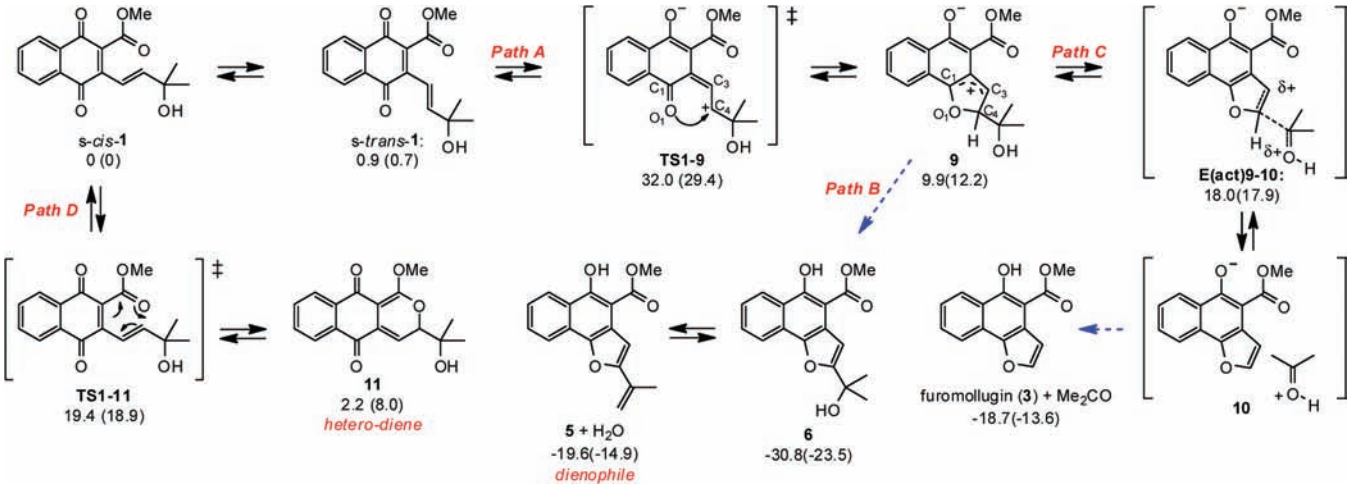
Computational results suggest that the formation of **3** and **6** occurs via a reversible cyclization of *s-trans*-**1** to form zwitterion **9** (Scheme 3, path A), passing over a sizable energy barrier of 32.0(29.4) kcal/mol. In transition state **TS1-9**, significant twisting about the C_3-C_4 double bond places a formally empty p-orbital at C_4 in the best natural bond orbital (NBO)[8] resonance form. According to a NLMO[9] analysis, the C_1-O_1 π-bond donates 2.7% of its electron pair to C_4, while an O_1 lone pair donates 7.9% of its electron density. This suggests that the transformation of **1** to **9** is more accurately described as a pseudopericyclic cyclization, by the arrow pushing mechanism illustrated in Scheme 3, than as a classical Nazarov-type cyclization.[10]

Once formed, zwitterion **9** can undergo either of two irreversible transformations (Scheme 3, paths B and C). In path B, a presumably intermolecular proton transfer generates **6**, which is 30.8(23.5) kcal/mol downhill relative to *s-cis*-**1** (the kinetics of this step were not modeled). In path C, a retro-hydroxyalkylation initially affords ion-pair **10**. Following proton transfer, this path yields furomollugin (**3**) and one molecule of acetone, which are favored enthalpically over s-*cis*-**1** by 18.7(13.6) kcal/mol. The energy of activation $E_{(act)}$**9**−**10** for the formation of ion pair **10** was estimated to be 18.0(17.9) kcal/mol by optimizing the reactant **9** and the dissociation transition state using a PCM water solvation model.[11] We assume that the relative energy barriers of pathways B and C are energetically similar given that formation of **3** and **6** appears to be irreversible, and that these two products are formed in near equimolar quantities when starting from vinylquinone **1** (Scheme 2).

While formation of **9** by this mechanism is predicted to be feasible at the elevated temperatures required to generate rubicordifolin (**2**), transition state **TS1-9** is prohibitively high in energy to explain the ambient-temperature reactivity of **1** in THF (Scheme 2).[12] The presence of adventitious acid was not ruled out in the latter case,[13,14] and thus the above calculations were repeated with protonation at the quinone carbonyl.[15] Under acid catalysis, the activation energy required for the formation of **9** decreases to 7.8(6.0) kcal/mol, while $E_{(act)}$**9**−**10** decreases to 11.2(11.1) kcal/mol (with a THF PCM solvent correction). This is consistent with the experimental observation that the rate of formation of **3** and **6** is greatly increased in the presence of either Brønsted or Lewis acids.[14]

(4) Frisch, M. J., et al. *Gaussian 09*, Revision A.2, Gaussian, Inc., Wallingford, CT, 2009. Complete citation in the Supporting Information.
(5) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc.* **2008**, *120*, 215.
(6) (a) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.* **1980**, *72*, 650. (b) McLean, A. D.; Chandler, G. S. *J. Chem. Phys.* **1980**, *72*, 5639.
(7) (a) Grimme, S. *J. Chem. Phys.* **2006**, *124*, 034108. (b) Schwabe, T.; Grimme, S. *Phys. Chem. Chem. Phys.* **2007**, *9*, 3397.
(8) Reed, A. E.; Curtiss, L. A.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899.
(9) For Natural Localized Molecular Orbital (NLMO) analysis see: (a) Reed, A. E.; Weinhold, F. *J. Chem. Phys.* **1985**, *83*, 1736. (b) Hübler, K.; Hunt, P. A.; Maddock, S. M.; Rickard, C. E. F.; Roper, W. R.; Salter, D. M.; Schwerdtfeger, P. *Organometallics* **1997**, *16*, 5076.
(10) For a recent computational analysis of pseudopericyclic cyclizations see: Duncan, J. A.; Calkins, D. E. G.; Chavarha, M. *J. Am. Chem. Soc.* **2008**, *130*, 6740, and references cited therein.
(11) Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, *105*, 2999. Only the activation energy is given here because the T.S. energy is not directly comparable with the other (gas-phase) results.
(12) Since the reaction mixture was exposed to ambient light, a radical mechanism could account for the room temperature cyclization of **1**. For a related, photoinduced cyclization of vinyl quinones see: Iwamoto, H.; Takuwa, A.; Hamada, K.; Fujiwara, R. *J. Chem. Soc., Perkin Trans. 1* **1999**, *5*, 575. A light-induced radical mechanism in the formation of rubicordifolin seems unlikely, however, since the reaction vessel was thoroughly wrapped in aluminum foil prior to thermolysis.
(13) Butyric acid is a known impurity of "aged" THF: Coetzee, J. F.; Chang, T.-H. *Pure Appl. Chem.* **1985**, *57*, 633, and references therein.
(14) For a related room temperature, acid mediated cyclization of vinyl-*p*-quinones see: Taing, M.; Moore, H. W. *J. Org. Chem.* **1996**, *61*, 329.
(15) See the Supporting Information for a complete analysis of protonated **1**.

Scheme 3. Proposed Mechanism for the Formation of Furomollugin (**3**) and Coupling Partners **11** and **5**[a]



[a] The various pathways accessible to vinylquinone **1** are denoted in red above the appropriate arrows. Arrows that are in blue represent irreversible steps in the formation of furomollugin (**3**) and coupling partners **11** and **5**.

The final step in the formation of dienophile **5** is the dehydration of naphthofuran **6** (Scheme 3). Experimental and computational results suggest that this process is reversible given that calculated **6** is enthalpically favored over **5** (and one molecule of H_2O) by 11.2(8.6) kcal/mol, and that exposing **6** to the reaction conditions does not produce **5**. Since phenylboronic acid is required for the formation of rubicoridfolin (**2**), and since byproducts such as dimer **8** are absent from the crude reaction mixture (Scheme 2), we believe that this reagent facilitates the reversible dehydration of **6** under mild conditions.[16]

Next, we turn our attention to the identity and formation of the key heterodiene coupling partner. Initially we assumed that phenylboronic acid, serving as a Lewis acid, facilitated cyclization of **1** and subsequent demethylation of the carbomethoxy group to generate coupling partner **4** (Scheme 1).[2a] However, this hypothesis now seems unlikely, given the propensity of **1** to rapidly cyclize to **3** and **6** in the presence of Lewis acids.

On the other hand, the noncatalyzed cyclization of s-*cis*-**1** to generate **11** is predicted to be endothermic by ~2 kcal/mol[17] and to pass over an energy barrier, **TS1-11**, of only 19.4(18.9) kcal/mol (Scheme 3, path D). Therefore, at elevated temperatures **1** is predicted to exist in equilibrium with **11**. Interestingly, the propensity for **1** to cyclize to **9** vs **11** appears to be sensitive to pH. The noncatalyzed value of **TS1-11** is 12.6(10.5) kcal/mol lower than **TS1-9**, whereas under acid catalysis, **TS1-9** is favored by ~2 kcal/mol. This suggests that careful maintenance of a neutral pH is required for the formation of **11** and thus the natural product.

Given the ease with which **11** is formed, we conclude that its irreversible hydrolysis to generate **4** must either be slower than the formation of **9** and **5** or inoperative in order to allow for the formation of **9** and thus **5**.[18] Alternatively, **11** could serve as a suitable diene for the key hetero-Diels−Alder cycloaddition with **5**, wherein hydrolysis of the resulting adduct would then generate **2** (vide infra).[19]

Taken together, the results presented above suggest that the formation of coupling partners **11** and **5** proceeds via reversible cyclization of **1** to **11** concomitant with the rate-limiting formation of intermediate **9**. Intermolecular proton transfer would then provide **6**, which in the presence of a suitable boron reagent[20] transiently generates **5**. The dehydration of **6** is predicted to be significantly faster than the conversion of **1** to **9**,[16] which is a requirement in order for sufficient quantities of **11** to be present to react with **5**.

With an understanding of the various equilibria accessible to **1**, we turned our attention to the key hetero-Diels−Alder cycloaddition. As previously discussed, we initially proposed that *o*-quinone methide **4** underwent an *endo*-selective cycloaddition with vinyl naphthofuran **5** to directly afford rubicordifolin (**2**) (Scheme 1).[2a] While this Diels−Alder reaction is predicted to be accessible under the reaction conditions,[21] **11** is more likely the [4 + 2] coupling partner based on the results presented above. Accordingly, we evaluated an alternative sequence of events in which the **11**/**5** cycloaddition precedes hydrolysis (Scheme 4). In this case the pathway through *endo*-**TS12** is

(16) The dehydration of 2-(benzofuran-2-yl)propan-2-ol mediated by phenylboronic acid was modeled by using a THF PCM solvent correction. The activation energy is 20.5 kcal/mol and the transformation is endothermic by 8.3 kcal/mol. See the Supporting Information for details.

(17) Note that the B2PLYP-D value of 8.0 kcal/mol suggests that the M06−2X value of 2 kcal/mol represents a lower limit in the energetic difference between **1** and **11**.

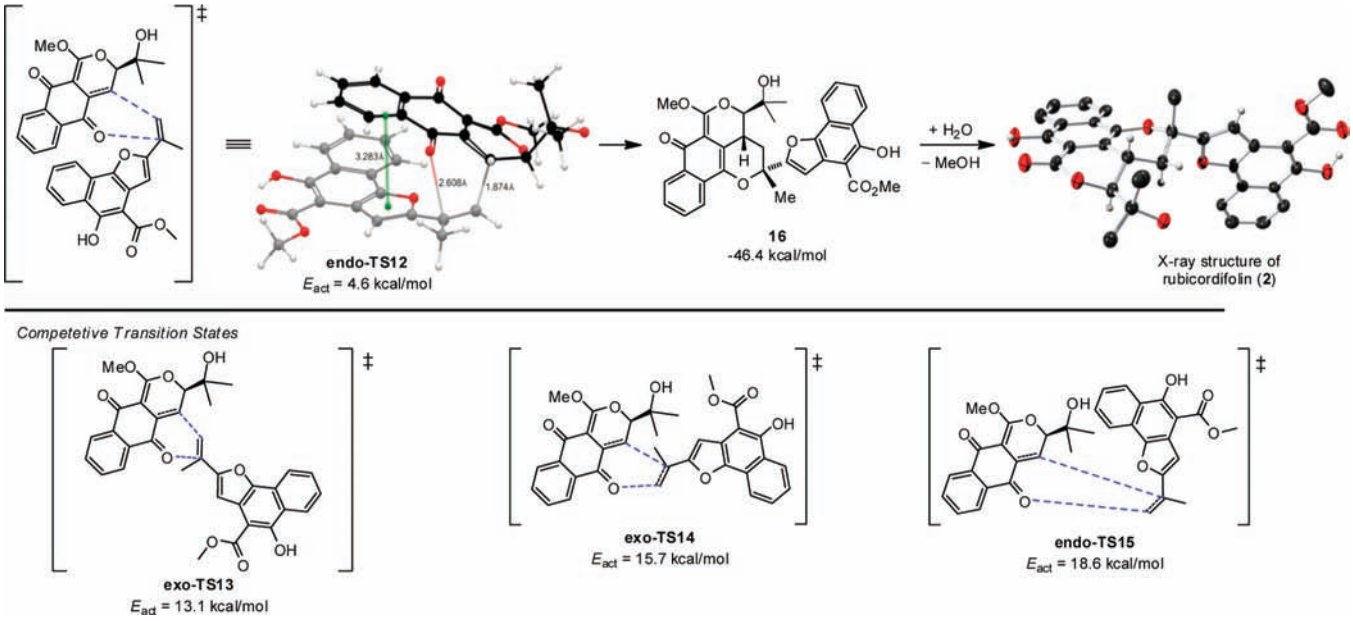
(18) The corresponding carboxylic acid of **1** has been evaluated as a potential reactive intermediate. See the Supporting Information for a detailed discussion.

(19) For a related cyclization/[4 + 2] cycloaddition cascade see the synthesis of torreyanic acid: Li, C.; Johnson, R. P.; Porco, J. A. *J. Am. Chem. Soc.* **2003**, *125*, 5095.

(20) At elevated temperatures, phenylboronic acid is believed to exist in equilibrium with phenyl boroxine and 3 equiv of H_2O: Chen, F.; Kina, A.; Hayashi, T. *Org. Lett.* **2006**, *8*, 341. For a review of boronic acids in catalysis see: Ishihara, K.; Yamamoto, H. *Eur. J. Org. Chem.* **1999**, *3*, 527.

(21) See the Supporting Information for the **4**/**5** cycloaddition.

Scheme 4. Analysis of the Key, Hetero-Diels-Alder Cycloaddition

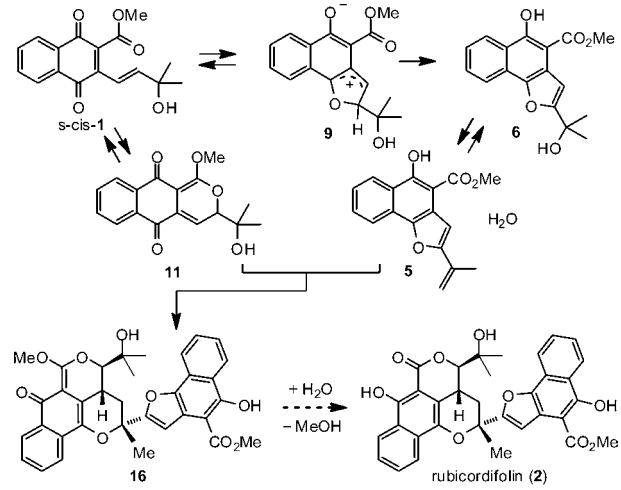


remarkably facile (E_{act} = 4.6 kcal/mol) and favored over *exo*-**TS13** by 8.5 kcal/mol. Regioisomeric transition states **TS14** and **TS15** are disfavored by 11.1 and 14.0 kcal/mol, respectively. Irreversible hydrolysis of adduct **16**, either under the reaction conditions or upon workup, would then lead to rubicordifolin (**2**).

It appears that a favorable π-stacking interaction between **11** and **5** in the [4 + 2] transition state plays a critical role in determining the stereochemical outcome of the cycloaddition (Scheme 4). In **TS12** the two coupling partners are separated by roughly 3.3 Å, which is well within the 3.6 Å threshold generally accepted for intermolecular interactions.[22b] Interestingly, in preliminary studies with the B3LYP functional, π-stacking was not observed, and at this level of theory *exo*-**TS13** was slightly favored over *endo*-**TS12**.[5,22] The relative stereochemistry of **2** has now been confirmed by single-crystal X-ray diffraction analysis (Scheme 4) and is consistent with the relative stereochemistry resulting from *endo*-**TS12**. Consequently, we conclude that π-stacking provides a sufficient energetic stabilization to dictate the stereochemical course of the cycloaddition, and thus the observed configuration of the natural product.

On the basis of the results presented herein, we propose a revised mechanism that accounts for the remarkable formation of rubicordifolin (**2**) in a single synthetic operation starting from naphthoquinone **1** (Scheme 5). Importantly, this proposal does not require the orchestration of two, irreversible reaction steps in the formation of the natural product, but instead, predicts the reversible formation of both coupling partners from two reservoirs, which are in turn separated by the rate-determining step of the reaction.

Scheme 5. Overall Reaction Mechanism



Acknowledgement. We thank Pfizer Inc. for sponsoring an ACS predoctoral fellowship for J.P.L. All computations were performed at the UCB Mol. Graphics and Comp. Facility on equipment purchased with funds from NSF Grant CHE-0840505.

Supporting Information Available: The synthetic procedure and spectroscopic data for compound **8**, crystallographic data for **2** (CIF), and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL102157D

(22) For examples of B3LYP acting poorly in modeling dispersion forces see: (a) Šponer, J.; Riley, K. E.; Hobza, P. *Phys. Chem. Chem. Phys.* **2008**, *10*, 2595. (b) Ujaque, G.; Lee, P. S.; Houk, K. N.; Hentemann, M. F.; Danishefsky, S. J. *Chem.—Eur. J.* **2002**, *8*, 3423. (c) Zhao, Y.; Truhlar, D. G. *J. Chem. Theory Comput.* **2006**, *2*, 1009.