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New Paradigms for the Peroxy Acid Epoxidation of CC Double Bonds: The Role of the Peroxy Acid s-Trans Conformer and of the 1,2-H Transfer in the Epoxidation of Cyclic Allylic Alcohols

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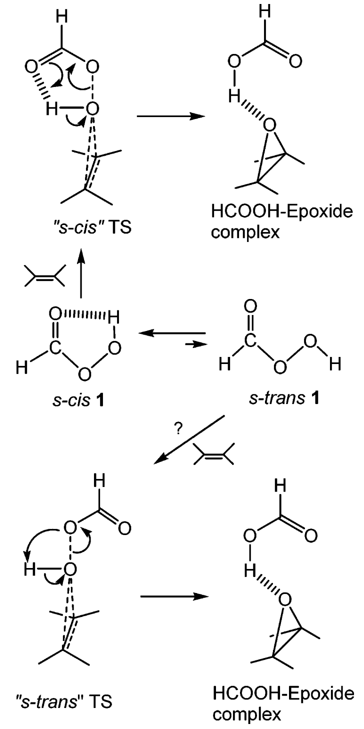
RB3LYP calculations, on reaction of performic acid with cyclic allylic alcohols, demonstrate that the less stable s-trans conformer of peroxy acids can be involved in epoxidations of C═C bonds. Transition structures (TSs) arising from s-trans performic acid retain some of the well-established characteristics of the TSs of the s-cis isomer such as the perpendicular orientation of the O−H peroxy acid bond relative to the C═C bond and a one-step oxirane ring formation. These TSs are very asynchronous but collapse directly (without formation of any intermediate) to the final epoxide−peroxy acid complex via a 1,2-H shift. Thus, our findings challenge the traditional mechanism of peroxy acid epoxidation of C═C bonds by demonstrating that the involvement of the s-trans isomer opens an alternative one-step reaction channel characterized by a 1,2-H transfer. This novel reaction pathway can even overcome, in the case of the reaction of cyclic allylic alcohols in moderately polar solvents (e.g., in dichloromethane), the classical Bartlett's mechanism that is based on the s-cis peroxy acid form and that features a 1,4-H shift. However, the latter mechanism remains strongly favored for the epoxidation of normal alkenes.

Introduction

It is well-known that peroxy acids (e.g., performic acid **1**) prefer an s-cis conformation that benefits from a strong intramolecular hydrogen-bonding interaction, with respect to the corresponding s-trans conformer (Scheme 1).[1a] It is also generally assumed that the more stable s-cis form is also the more reactive one in epoxidation reactions.[1−5] In fact, the "butterfly" transition structure (TS), proposed by Bartlett 50 years ago,[6] features an s-cis peroxy acid moiety in which the hydrogen atom is being transferred to the former carbonyl oxygen in a 1,4 process (see "s-cis" TS, Scheme 1). The equilibrium between the

SCHEME 1



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(1) (a) Erzen, E.; Koller, J.; Plesnicar, B. *J. Org. Chem.* **2001**, *66*, 5155 and references therein. (b) According to these authors, the calculated potential energy difference between s-trans (μ = 3.11 D) and s-cis (μ = 1.43 D) performic is of 2.01 kcal/mol at the B3LYP/6-311++G(d,p) level in gas phase. Our B3LYP/6-311++G(3df,2pd) calculations led to the following results: $\mu_{\text{s-cis}}$ = 1.36 D (gas), 1.45 D (benzene), 1.51 D (CH_2Cl_2) and $\mu_{\text{s-trans}}$ = 3.09 D (gas), 3.38 D (benzene), 3.67 D (CH_2Cl_2); $(G_{\text{s-trans}} - G_{\text{s-cis}})_{\text{gas}}$ = 2.48 kcal/mol, $(G_{\text{s-trans}} - G_{\text{s-cis}})_{\text{benzene}}$ = 1.77 kcal/mol, $(G_{\text{s-trans}} - G_{\text{s-cis}})_{\text{CH2Cl2}}$ = 0.62 kcal/mol. (c) Curci, R.; DiPrete, R. A.; Edwards, J. O.; Modena, G. *J. Org. Chem.* **1970**, *35*, 740.

(2) The s-cis form of neutral peroxy acids has always been assumed as the only reactive conformer in all theoretical studies on epoxidation reactions of both alkenes and allylic alcohols.[3−5]

(3) (a) Bach, R. D.; Estevez, C. M.; Winter, J. E.; Glukhovtsev, M. N. *J. Am. Chem. Soc.* **1998**, *120*, 680. (b) Bach, R. D.; Glukhovtsev, M. N.; Gonzales, C. *J. Am. Chem. Soc.* **1998**, *120*, 9902. (c) Adam, W.; Bach, R. D.; Dimitrenko, O.; Saha-Moller, C. R. *J. Org. Chem.* **2000**, *65*, 6715. (d) Bach, R. D.; Dimitrenko, O.; Adam, W.; Schambony, S. Gonzales, C. *J. Am. Chem Soc.* **2003**, *125*, 924. (e) Bach, R. D.; Dimitrenko, O. *J. Phys. Chem. A* **2003**, *107*, 4300.

(4) (a) Houk, K. N.; Liu, J.; DeMello, N. C.; Condroski, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10147. (b) Houk, K. N.; Washington, I. *Angew. Chem., Int. Ed.* **2001**, *40*, 4485. (c) Washington, I.; Houk, K. N. *Org. Lett.* **2002**, *4*, 2661.

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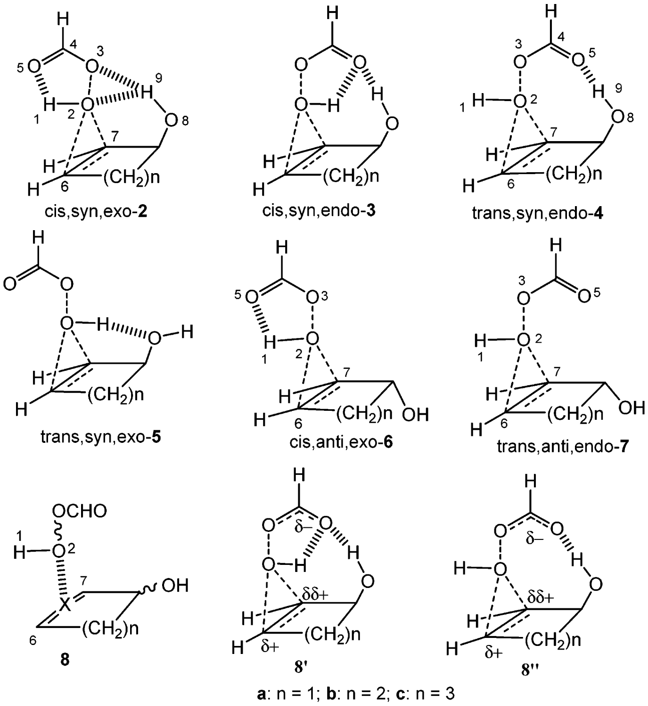
two peroxy acid conformers is certainly very fast since the energy difference between them, although remarkable, is far from being dramatic (it is on the order of a few kcal/mol[1a,b] and can be reversed in hydrogen bond acceptor solvents[1a]). These observations arise the question whether the s-trans peroxy acid form can play a role in the epoxidation reaction. It is quite evident that a transition structure (TS) derived from the s-trans peroxy acid form (e.g., "s-trans" TS, Scheme 1) should be disfavored, likewise the starting conformer, by the absence of intramolecular hydrogen bonding relative to the classical pathway via the s-cis conformer. As for competition between these two pathways, one can argue that the presence of intermolecular hydrogen-bonding interactions (either with solvent[1a,c,7] or with OH/NH_2 groups present in the alkene) can possibly revert the energy ranking of the two kinds of TSs making TSs from s-trans peroxy acids[8] compete almost on the same foot or even prevail over the corresponding TSs from s-cis peroxy acids. The two routes differ also in the mechanism of the H transfer, that is, the "s-trans" TS will necessarily produce the final epoxide via a 1,2-H shift (see "s-trans" TS, Scheme 1) at variance with the 1,4-H classical transfer.[7,9]

These observations led us to plan, in the context of our studies on the mechanism of dioxirane[10] and peroxy acid[5] epoxidation of CC double bonds, a systematic computational investigation aimed at defining the possible role played by the s-trans peroxy acid form in epoxidation reaction, and here we report the results obtained for the reactions of cyclic allylic alcohols ($n = 1-3$, Scheme 2) with performic acid. Previous computational studies[3c,5b−d] have demonstrated that the s-cis form of peroxy acids can attack allylic alcohols syn to the OH group with either an exo[11] (e.g., TS *cis,syn,exo*-**2**) or endo (e.g., TS *cis,syn,endo*-**3**) disposition of the acid relative to the alcohol.

SCHEME 2



Moreover, TSs *cis,syn,exo*-**2** (Scheme 2) lie, in the case of cyclic alcohols, at a lower energy level than both TSs *cis,syn,endo*-**3**[5b,d,12a] and TSs *cis,anti,exo*-**6**.[5b,d] Finally, preliminary studies by our group have also shown that

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[5] (a) Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M. *Tetrahedron.* **1999**, *55*, 11309. (b) Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M.; Rastelli, A. *J. Org. Chem.* **1999**, *64*, 3853. (c) Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M.; Rastelli, A. *J. Org. Chem.* **2000**, *65*, 2030. (d) Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M.; Rastelli, A. *J. Org. Chem.* **2000**, *65*, 8948. (e) Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M.; Rastelli, A. *J. Org. Chem.* **2002**, *67*, 8519.

[6] Bartlett, P. D. *Rec. Chem. Prog.* **1950**, *11*, 47 and **1957**, *18*, 111.

[7] Plesnicar et al.[1a] were the first authors to question the necessity of a "Bartlett mechanism" (reaction of the s-cis peroxy acid form and 1,4-H shift) by suggesting a possible role of the s-trans conformer (complexed with a molecule of solvent) in the oxidation of sulfides (thianthrene 5-oxide) with peroxy acids in basic (hydrogen bond acceptor) solvents. These solvents, as already emphasized several years ago by other authors,[1c] should preferentially stabilize the s-trans isomer as a result of complex formation through intermolecular hydrogen bonding interaction. The proposal by Plesnicar et al. was based on experimental and computational data but was not unambiguously substantiated with transition structure calculations.

[8] TSs involving protonated s-trans performic acid were reported by Bach et al. for the acid catalyzed performic acid epoxidation of ethylene. Protonation at the carbonyl oxygen makes the s-trans isomer much more stable than the s-cis one. However, according to authors, protonated peroxy acids do not play any role in peroxy acid epoxidation. Bach, R. D.; Canepa, C.; Winter J. E.; Blanchette, P. E. *J. Org. Chem.* **1997**, *62*, 5191.

[9] (a) We have recently demonstrated[5c] by DFT calculations that also highly distorted TSs, formally originating from s-cis performic acid, can enter the 1,2-H shift in preference to the traditional 1,4-H transfer. (b) For 1,2-H transfer in the one step olefin epoxidation by H_2O_2 see, for example: de Visser, S. P.; Kaneti, J.; Neumann, R.; Shaik, S. *J. Org. Chem***.** **2003**, 68, 2903. (c) On the basis of kinetic data it was suggested (Dankleff, M. A. P.; Curci, R.; Edwards, J. O.; Pyun, H.-E *J. Am. Chem. Soc.* **1968**, *90*, 0, 3209**)** that an "acidic" (protic) molecule (H_2O_2, protic solvent, etc.) can be involved in the activated complex of sulfide oxidation with H_2O_2. The protic molecule allows a mediated 1,2-H transfer through a cyclic TS. However, Edwards et al. also reported that sulfide oxidations with peroxy acids did not show any kinetic evidence for solvent partecipation in the transition state in the case of aprotic solvent.[1c] The latter observation stands in contrast with the recent suggestion by Plesnicar et al. that explains the decreased reactivity of peroxy acids in "basic" solvents as a result of involvement in the transition state of a complex between s-trans peroxy acid and a solvent molecule.[1a,7]

[10] Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M.; Rastelli, A. *Tetrahedron* **1998**, *54*, 6123 and **1998**, *54*, 12323.

[11] The meaning of the descriptors used are as follows: cis and trans indicate that the TS formally originates from s-cis and s-trans, respectively, conformer of performic acid; syn and anti correspond to attacks by performic acid to the double bond on the same and opposite side, respectively, relative to the hydroxy group; in endo and exo TSs the formate moiety is oriented inside and outside, respectively, relative to the allylic alcohol ring.

[12] (a) B3LYP/6-311+G(d,p) calculations showed that *cis,syn,endo*-**3a** is less stable (free energy at 298.15 K) than *cis,syn,exo*-**2a** by 2.85 kcal/mol (gas phase), 3.39 kcal/mol (benzene solution), and 3.42 kcal/mol (CH_2Cl_2 solution). Likewise *cis,syn,endo*-**3b** is less stable (free energy at 298.15 K) than *cis,syn,exo*-**2b** by 2.40 kcal/mol (gas phase), 2.87 kcal/mol (benzene solution), and 2.97 kcal/mol (CH_2Cl_2 solution). See also ref 5d for 2-cyclohexenol data. (b) The free energy (at 298.15 K) of TS *trans,syn,endo*-**4a** ($n = 1$) is lower by 7.40 kcal/mol (gas phase) and 6.43 kcal/mol (benzene solution) than that of TS *trans,syn,exo*-**5a** ($n = 1$) at the B3LYP/6-311+G(d,p) level**.** The latter transition structure is not a stationary point in dichloromethane solution (i.e., all our attempts to locate it led either to starting reactants or to products). Moreover, at the same theory level TS *trans,syn,endo*-**4b** ($n = 2$) resides at lower free energy than TS *trans,syn,exo*-**5b** by 8.2 kcal/mol in gas phase but when optimization was performed at the B3LYP/level the latter TS collapsed to the corresonding cis,syn,endo TS in which the peroxy acid acts as hydrogen bond donor. (c) As for wave functions of TSs deriving from s-trans performic acid, TSs of type **4** were always found stable (not only in the case of the reactions of cyclic allylic alcohols but also in the case of those of acyclic allylic alcohols) while wave functions of TSs of type **5** or **7** may show a slight instability. For example, the wave function of TS *trans,syn,exo*-**5a** exhibits a small RHF···UHF instability [0.25 kcal/mol, $\langle S^2\rangle = 0.163$ with the B3LYP/6-311+G(d,p) method], TS *trans,anti,exo*-**7b** ($n = 2$) is stable while TS *trans,anti,exo*-**7a** ($n = 1$) has a very small instability [0.04 kcal/mol, $\langle S^2\rangle = 0.066$ with the B3LYP/6-311+G(d,p) method].

the endo approach of the attacking s-trans peroxy acid (e.g., TS *trans*,*syn*,*endo*-**4**) is largely favored over the exo orientation (e.g., TS *trans*,*syn*,*exo*-**5**).[12b] Consequently, this paper will mostly be focused on evaluation of the competition between the "classical" cis,syn,exo TSs of type **2** and their trans,syn,endo counterparts of type **4**, for syn attacks on cyclic allylic alcohols. In both TSs **2** and **4** the peroxy acid moiety acts as hydrogen-bond acceptor either through the peroxy system as in **2** or by using the strongly basic oxygen of the carbonyl functionality as in **4**. The latter TSs should also benefit of a very favorable geometry relationship between the interacting groups (i.e., excellent alignment of the three O_8-H_9- - -O_5 centers and short OH_9- - -O_5 distance).

Computational Methods

We carried out an RB3LYP[13] study on the epoxidation of 2-cyclobutenol ($n = 1$), 2-cyclopentenol ($n = 2$), and pseudoequatorial 2-cyclohexenol ($n = 3$) with performic acid **1** by using both the small 6-31G(d) basis set as well as a larger one of triple ζ quality and with diffuse function, namely the 6-311+G(d,p) basis set. The latter basis set should be more appropriate (at least in principle) for systems rich in lone pairs and involved in hydrogen-bonding interactions,[14] such as the peroxy systems under study, and should better describe the TS polarization with partial negative charge on the formate moiety. A very careful high-level computational investigation, performed very recently by Bach et al., demonstrated that the "B3LYP variant of DFT calculations remain a useful and reasonably accurate method of choice for the study of epoxidation reactions with peroxy acid".[3e] The search for TSs was limited to concerted transition structures; i.e, only restricted B3LYP methods have been used.[3e,15,16] All gas-phase TSs reported in this paper gave a positive answer to the stability test (i.e., all TSs were found stable with the keyword Stable = Opt).[12c]

All TSs were fully optimized with the B3LYP/6-31G(d) and B3LYP/6-311+G(d,p) methods (Figures 1 and 2 display geometries obtained with the latter basis set) both in the gas phase and in solution (benzene and dichloromethane), and all of them were characterized as genuine transition structures by vibrational analysis both in the gas phase and in solution (one imaginary frequency). Bulk solvent effects on TS geometries and energies were calculated with the self-consistent reaction field (SCRF) theory using the PCM model, as implemented in the B.02 version of Gaussian 2003. The solvent cavity is composed by interlocking spheres centered on non-hydrogen atoms with radii obtained by the Barone's HF parametrization known as united atom topological model (UAHF). For the PCM-UAHF calculations the number of tesserae per atom sphere was set to 100. The data in solution include, in addition to electrostatic effects, also cavitation, dispersion, and repulsion energy.

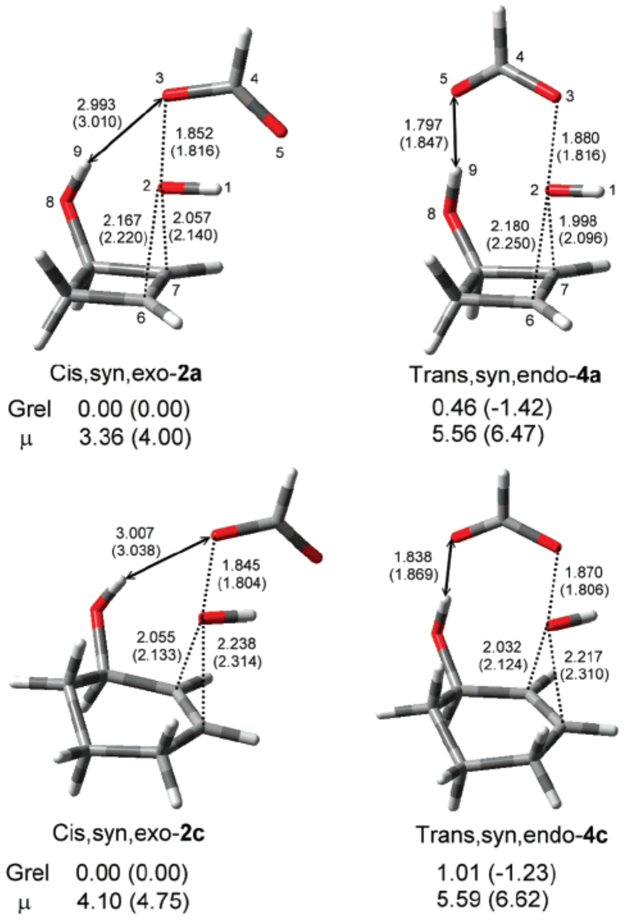

FIGURE 1. Gas-phase optimized geometries (bond lengths in Å), dipole moments (μ, debye), and relative free energies (kcal/mol) for B3LYP/6-311+G(d,p) transition structures of the epoxidation of 2-cyclobutenol (TSs **2a** and **4a**) and pseudoequatorial 2-cyclohexenol (TSs **2c** and **4c**). Data in parentheses are for full B3LYP/6-311+G(d,p) optimizations in dichloromethane solution.

Vibrational frequencies, calculated under the rigid-rotor harmonic approximation, were used unscaled[17] to compute zero-point energies, thermal corrections to enthalpy, entropy, and Gibbs free energy. Activation parameters (at 298.15 K) for all of the TSs, reported in Table 1 and Table S3 (see the Supporting Information), are referred, for the sake of homogeneity and clarity, to the more stable s-cis form of the starting peroxy acid and to the most stable allylic alcohol conformer (that one with the O−H bond pointing inside toward the double bond). The standard state of the molar concentration scale (gas

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(13) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision B.02; Gaussian, Inc.: Pittsburgh, PA, 2003.

(14) (a) Wu, A.; Cremer, D.; Plesnicar, B. *J. Am. Chem. Soc.* **2003**, *125*, 9395. (b) Xu, X.; Goddard, W. A. III. *J. Phys. Chem. A* **2004**, *108*, 2305.

(15) Bach et al. have demonstrated[3e] that the concerted synchronous spiro (perpendicular in our notation)[18] TS for epoxidation of ethylene is unambiguously supported by high level ab initio and CASSCF calculations. This study convincingly rejects the recent proposal, advanced by Leszczynski et al.[16] for the same reaction on the basis of CASSCF calculations, of a planar TS with an unsymmetrical open chain diradical structure. The conclusion by Leszczynski et al. seems to be the result of an artifact of calculations due to an incorrect choice of the active space. In fact, Bach et al. stressed that the choice of active orbitals is critical for the CASSCF approximation and that it is mandatory to recover the effects of dynamic correlation before comparing the total energies of perpendicular and planar TSs.

(16) Okovytyy, S.; Gorb, L.; Leszczynski, J. *Tetrahedron Lett.* **2002**, *43*, 4215.

(17) Rastelli, A.; Bagatti, M.; Gandolfi, R. J. *Am. Chem. Soc.* **1995**, *117*, 4965.

TABLE 1. Activation Parameters ($\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, $\Delta G^{\ddagger}$)[a] for Epoxidation of 2-Cyclobutenol, 2-Cyclopentenol, and Pseudoequatorial 2-Cyclohexenol with Performic Acid in Gas Phase and Solution (Benzene and Dichloromethane)[b] at the B3LYP/6-311+G(d,p) Level

TS	$\Delta H^{\ddagger}_{gas}$	$\Delta H^{\ddagger}_{C6H6}$	$\Delta H^{\ddagger}_{CH2Cl2}$	$\Delta S^{\ddagger}_{gas}$	$\Delta S^{\ddagger}_{C6H6}$	$\Delta S^{\ddagger}_{CH2Cl2}$	$\Delta G^{\ddagger}_{gas}$	$\Delta G^{\ddagger}_{C6H6}$	$\Delta G^{\ddagger}_{CH2Cl2}$
cis,syn,exo-**2a**	10.28	10.87	11.50	−30.08	−29.87	−29.64	19.26	19.78	20.34
trans,syn,endo-**4a**	10.21	9.78	9.34	−31.88	−31.93	−32.10	19.72	19.30	18.92
cis,syn,exo-**2b**	9.29	9.63	10.71	−30.65	−30.39	−30.16	18.43	19.13	19.71
trans,syn,endo-**4b**	9.26	8.71	8.77	−32.21	−32.64	−32.82	19.02	18.84	18.56
cis,syn,exo-**2c**	9.21	10.35	11.04	−30.67	−30.36	−30.10	18.35	19.41	20.02
trans,syn,endo-**4c**	9.45	9.75	9.25	−32.72	−32.07	−31.98	19.36	19.32	18.79
cis,anti,exo-**6b**	11.73	11.29	12.13	−28.54	−28.25	−28.16	20.24	20.36	20.53
trans,anti,endo-**7b**	15.72	14.34	14.29	−27.01	−26.70	−28.12	23.77	23.18	22.68

[a] The rigid rotor-harmonic oscillator approximation has been assumed for evaluation of the thermodynamic properties; energies in kcal/mol, entropy in cal/(mol K); $\Delta H^{\ddagger}$ and $\Delta G^{\ddagger}$ are the molar activation enthalpy and Gibbs free energy; $\Delta S^{\ddagger}$ is the molar activation entropy; these parameters are referred to the *s-cis*-performic acid, to the most stable allylic alcohol conformer and to the standard state (298.15 K) of the molar concentration scale (gas in ideal mixture at 1 mol/L, $P = 1$ atm). [b] Solution data (benzene and dichloromethane) were evaluated with the default PCM model of Gaussian 2003 by using the keywords RADII = UAHF and TSNUM = 100.

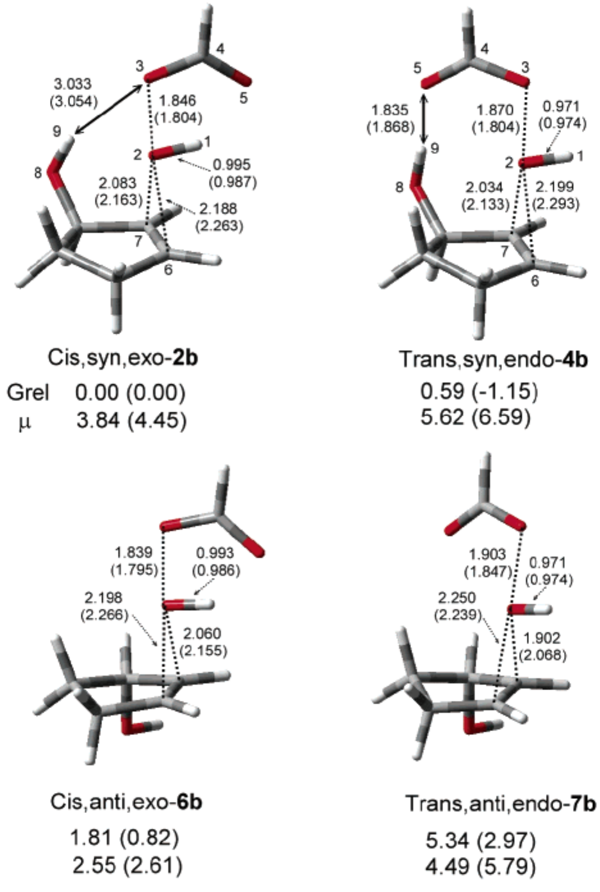

FIGURE 2. Gas-phase optimized geometries (bond lengths in Å), dipole moments (μ, debye), and relative free energies (kcal/mol) for B3LYP/6-311+G(d,p) TSs of the epoxidation of 2-cyclopentenol. Data in parentheses are for full B3LYP/6-311+G(d,p) optimizations in dichloromethane solution.

in ideal mixture at 1 mol/L, $P = 1$ atm) was used. For conversion from 1 atm standard state to 1 mol/L standard state (both for gas-phase reactions) the following contributions have been added to standard enthalpy, entropy and Gibbs free energy: $-RT$, $-R \ln R'T - R$, and $RT \ln R'T$, where R' is the value of R constant given in (L atm)/(mol K). For a reaction with A + B = C stoichiometry, the corrections for $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$, and $\Delta G^{\ddagger}$ are RT, $R \ln R'T + R$, and $-RT \ln R'T$, respectively (0.592 kcal/mol, 8.34 eu and −1.893 kcal/mol, respectively, at 298.15 K).

All IRC calculations on TSs **2** and TSs **4** were performed with the B3LYP/6-31G(d) method in the gas phase. IRC calculations on TS **2a** were also performed by using the larger B3LYP/6-311+G(d,p) basis set.

Results and Discussion

TS Geometries. Geometries of TSs originating from *s-cis*-performic acid (TSs *cis,syn,exo*-**2a**−**c** and TS *cis,anti,exo*-**6b**, Scheme 2, Figures 1 and 2, Tables S1 and S2 in the Supporting Information) exhibit the usual features already described in recent papers.[3−5] In particular, the peroxy acid moiety in these TSs is planar and adopts a “perpendicular-like” [18] orientation with respect to the C═C bond as illustrated by the values of the C_6-XO_2H_1 dihedral angle (in which X is a dummy atom located at the midpoint of the C_6−C_7 bond, see **8** in Scheme 2), that reliably describe this orientation. These values are close to 90° spanning the 83−101° range (Tables S1 and S2, Supporting Information). Formation of the two oxirane C−O bonds is concerted but not synchronous: the incipient C- - -O bond nearer to the hydroxylic group (C_7- - -O_2) is shorter than the other one (C_6- - -O_2). This observation holds both for syn TSs **2a**−**c** and anti TS **6b** and, consequently, it is not the result of hydrogen bonding interaction and cannot be attributed to the tendency of the peroxy system to get closer to the OH group and strengthen hydrogen bonding. More likely, the electrophilic attack by the peroxy system is biased toward the proximal C_7 center in order to position the positive partial charge, resulting from polarization of the breaking C═C bond, on the distal C_6 center far from the electron attracting hydroxy group (see **8′** in Scheme 2).[19]

The peroxy acid O_2−H_1 bond of cis,syn TSs **2a**−**c** is only slightly stretched (as shown by comparison of H_1−O_2 bond length in TSs **2a**−**c** with that of their competitors trans,syn TSs **4a**−**c**; Figure 2, Tables S1 and S2 (Supporting Information)), thus strongly suggesting that this bond is not involved in a pericyclic concerted “coarctate” process.[20] It stabilizes the TS by assisting the development of the partial negative charge on the formate moiety with an efficient intramolecular hydrogen bond donation. The attack by peroxy acid to the double bond can be depicted[3a,5c] as that of the electrophilic particle H−$O^{\delta+}$ assisted by the formate moiety whose major role is that of accepting electrons donated by the olefinic partner (the net charge on the attacking OH particle is very close to 0 at the TS).[19]

The fact that cyclic 1,4-H transfer does not play a vital role in the first part of epoxidation (that one from reactants to TS) makes it clear that also the s-trans peroxy acid conformer lends itself as a plausible protagonist of this reaction. This hypothesis is also supported by the fact that 1,2-H transfer is at work in olefin epoxidation by H_2O_2.[9b,c] We confirmed this prediction by locating TSs **4a**−**c** (Scheme 2, Figures 1 and 2) formally deriving from *s-trans*-**1**.[21]

In these TSs the formate moiety can easily rotate around the breaking O_2- - - O_3 bond as forces that lock up this conformer in a planar conformation (i.e., that one with $H_1O_2O_3C_4 = 180°$) are certainly weaker than the intramolecular hydrogen bonding responsible for the planarity of the s-cis form ($H_1O_2O_3C_4 = 0°$). Distortion of the $H_1O_2O_3C_4$ angle, away from the 180° value (Tables S1 and S2), allows trans,syn,endo TSs **4a**−**c** to line up the carbonyl oxygen with the O−H bond (O_5- - - -H_9−O_8 > 170°) in an optimal disposition for hydrogen bonding that is also favored by the short O_5- - - -H_9 distance (1.79−1.85 Å) and by the high basicity of the carbonyl oxygen center.[3a] As a result, the intermolecular hydrogen bonding interaction should certainly be much stronger in trans,syn TSs of type **4** than in the corresponding cis,-syn isomers of type **2** as clearly evidenced by the remarkably lower (by ~200−300 cm^{-1}) frequency of O_8−H_9 stretching vibration in TSs **4a**−**c** relative to the same frequency in TSs **2a**−**c**.[22] The energy lowering of TSs **4** with respect to TSs **2**, due to the intermolecular hydrogen bond, compensates for the presence in the latter of the peroxy acid intramolecular hydrogen bond.

Interestingly, the peroxy acid OH bond maintains a perpendicular-like orientation to the C═C bond in trans,-syn TSs too, thus confirming, once more, a remarkable tendency of the attacking OH particle to avoid as far as possible a "planar"[18] orientation. As repeatedly stressed by different authors,[3−5] the potential energy surface in the neighbors of TS, for peroxy acid epoxidation of C═C double bonds, is quite flat and consequently the geometry of peroxy acid approach can be deeply affected by the need to minimize steric crowding and to maximimize hydrogen bonding interactions. However, *the "perpendicular-like" array of the reacting moieties (O−H and C═C) at the TS core can be definitely considered as a distinctive character of this reaction*.

Asynchronicity in bond formation is higher in trans,-syn TSs than in their cis,syn counterparts and once again the shorter incipient bond is that one nearer the hydroxylic group. Following the reaction path from trans,-syn,endo TSs **4a**−**c** downhill to products, by IRC calculations [B3LYP/6-31G(d)], clearly showed the operation of the 1,2-H transfer. It also reliably demonstrated the direct connection between the trans,syn TSs and the final epoxide-formic acid complexes, thus ruling out the presence of any intermediate. However, interestingly, asynchronicity in oxirane bond formation, already significant at the TS, increases sharply at the beginning of the descent toward the products to the extent that one C- - -O bond is almost completely formed (see, for example, O_2- - -C_7 in IRC point **10a**, Figure 3) before the second one begins to close up, in a second phase, with concomitant 1,2 transfer of the hydrogen atom. Actually, the 1,2-H transfer in the reaction of s-trans **1** takes place distinctly later, along the reaction coordinate, than the 1,4-H transfer in the reaction of s-cis **1** as is convincingly demonstrated by inspection of IRC points **9a** and **10a** (Figure 3).

Comparison between these two IRC points is meaningful and informative since they feature a similar average C- - -O bond length, that is, they exhibit similar progress in oxirane ring formation. In **10a** only formation of the O_2- - -C_7 bond is well advanced (much more than that of the O_2- - -C_6 bond) while elongation of the O_2−H_1 bond is still almost negligible demonstrating that the H_1 transfer has not started yet. In **9a** asynchronicity in bond formation, although relevant, is smaller than in **10a** while progress of the H_1 transfer is already evident. IRC calculations on **4a** at the higher B3LYP/6-311+G(d,p) level fully confirmed that this TS collapses directly to the final epoxide through a 1,2-H shift in a very asynchronous process.

The comments on TS geometry data reported above hold for both 6-31G(d) and 6-311+G(d,p) geometries and for both gas phase and solution calculations (see Tables S1 and S2, Supporting Information).

All epoxidation transition structures here reported are inherently early as demonstrated by the average incipient C- - -O bond length that varies from ~2.050−2.100 Å in the gas phase at the B3LYP/6-31(d) level to ~2.200 Å in dichloromethane at the higher B3LYP/6-311+G(d,p) level. B3LYP/6-311+G(d,p) calculations predict looser (slightly earlier) TSs than those obtained with B3LYP/6-31(d) calculations, while both methods suggest that TSs

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(18) The descriptor "perpendicular" indicates a TS in which the O−H bond of the peroxy acid adopts a perpendicular orientation relative to the C═C bond [the torsion angle $C_6XO_2H_1$ (X is a dummy atom at the center of the C_6−C_7 bond, see **8** in Scheme 2) is close to 90° (that is, larger than 45°)] while in a "planar" TS this angle is close to 0° (smaller than 45°) and the O−H and C═C bonds lie in the same (or almost the same) plane.

(19) Electron transfer from allylic alcohols to performic acid, at the TS, is of the same order of magnitude (−0.3−0.4 e) for both TSs **2** and TSs **4** {TS **2a** [B3LYP/6-311+G(d,p)]: −0.40e (NPA) and −0.30e (CHELPG) in the gas phase, -0.39e (NPA) and −0.32e (CHELPG) in dichloromethane; TS **4a** [B3LYP/6-311+G(d,p)]: −0.42e (NPA) and −0.36e (CHELPG) in the gas phase, −0.37e (NPA) and −0.33e (CHELPG) in dichloromethane}. The net charge at C_6H is always more positive than that at C_7H of the cyclobutenol moiety in both TSs **2** and TSs **4** {B3LYP/6-311+G(d,p) calculations (gas phase), TS **2a**: +0.177e (NPA) and +0.160e (CHELPG) at C_6H, +0.143 (NPA) and −0.115e (CHELPG) at C_7H.; TS **4a**: +0.185e (NPA) and +0.185e (CHELPG) at C_6H, +0.125 (NPA) and −0.137e (CHELPG) at C_7H. B3LYP/6-311+G(d,p) calculations (dichloromethane), TS **2a**: +0.192e (NPA) and +0.223e (CHELPG) at C_6H, +0.108 (NPA) and −0.152e (CHELPG) at C_7H; TS **4a**: +0.174e (NPA) and +0.200e (CHELPG) at C_6H, +0.121 (NPA) and −0.142e (CHELPG) at C_7H. The net charge on the H_1O_2 group is close to 0, slightly positive and negative, respectively, according to NPA and CHELPG methods in both TSs **2** and TSs **4**{B3LYP/6-311+G(d,p) calculations, TS **2a**: −0.06e (NPA) and +0.09e (CHELPG) in the gas phase and −0.05e (NPA) and +0.08e (CHELPG) in dichloromethane; TS **4a**: −0.06e (NPA) and +0.08e (CHELPG) in the gas phase and −0.03e (NPA) and +0.09e (CHELPG) in dichloromethane.

(20) Herges, R. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 255.

(21) The presence of the first-order saddle point **4a,** on the potential energy surface of the reaction of performic acid with cyclobutenol, was confirmed by calculations with quite large basis sets [e.g., B3LYP/6-311++(3df,2pd) ($E_{\mathbf{4a}} - E_{\mathbf{2a}} = 0.76$ kcal/mol, gas phase) and B3LYP/ccp-VTZ (B3LYP/aug-ccp-VTZ//B3LYP/ccp-VTZ, $E_{\mathbf{4a}} - E_{\mathbf{2a}} = 0.84$ kcal/mol, gas phase).

(22) For example, TS **2a**: ν_{O8-H9} (gas phase) [benzene] {dichloromethane} = (3691.9 cm^{-1}) [3689.0 cm^{-1}] {3687.4 cm^{-1}} at the B3LYP/6-31G(d) level and (3768.7 cm^{-1}) [3767.1 cm^{-1}] {3766.0 cm^{-1}} at the B3LYP/6-311+G(d, p) level; TS **4a**: ν_{O8-H9} (gas phase) [benzene] {dichloromethane} = (3395.0 cm^{-1}) [3426.2 cm^{-1}] {3450.4 cm^{-1}} at the B3LYP/6-31G(d) level and (3453.4 cm^{-1}) [3492.7 cm^{-1}] {3519.7 cm^{-1}} at the B3LYP/6-311+G(d,p) level.

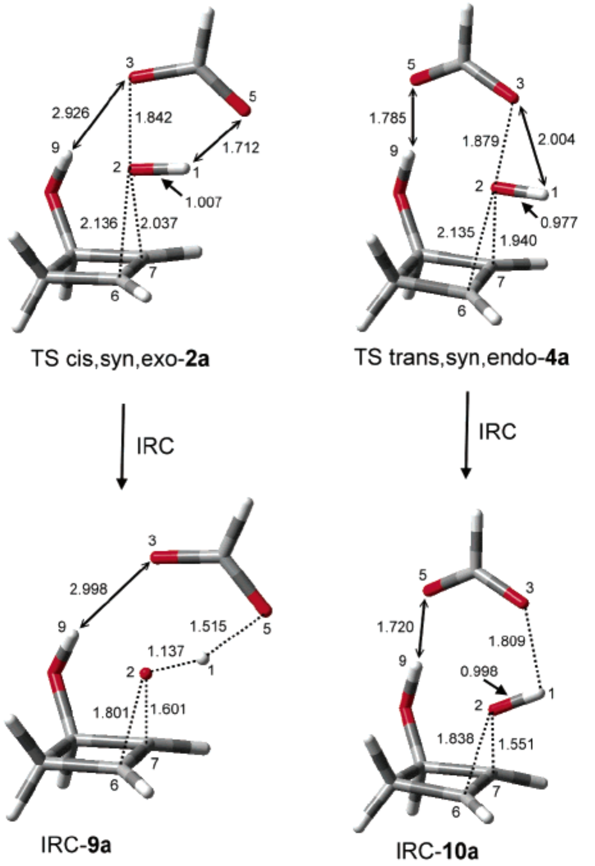

FIGURE 3. Comparison of IRC points [B3LYP/6-31G(d,p)], on the way from TSs to final epoxide, for the two competing processess in the epoxidation of 2-cyclobutenol: IRC-**9a** (reaction of the s-cis peroxy acid) vs IRC-**10a** (reaction of the s-trans peroxy acid). Progress in oxirane ring formation at IRC-**9a** is similar to that at IRC-**10a**. Bond lengths in Å.

become slightly earlier on going from the gas phase to the condensed phase as well as on increasing solvent polarity. Actually, the earliest transition structures obtained in our study are those ones predicted by the B3LYP/6-311+G(d,p) method for epoxidations in dichloromethane and, curiously, the B3LYP/6-311+G(d,p) gas-phase geometries are very similar to B3LYP/6-31(d) geometries in benzene.

In short, the novelty of the above computational data is represented by the observation that well-characterized TSs, formally originating from the s-trans conformer, lie along viable reaction paths in the case of a syn attack, assisted by hydrogen bonding interactions, by a peroxy acid to allylic alcohols. In this mechanism the 1,2-H shift replaces the classical 1,4-H shift.

However, assistance by hydrogen bonding is not mandatory for the existence of TSs derived from s-trans peroxy acids, and "trans" TSs can, in principle, be operative in the reaction of any kind of alkenes. In fact, we were able to locate true "trans" TSs also for anti attack, as exemplified by TS *trans*,*anti*,*endo*-**7b** for the reaction of 2-cyclopentenol (Figure 2), both in the gas phase and in solution. Also in the anti attack, similarly to what happens in the syn attack, the approach by *s-trans*-**1** is much more asynchronous than that by *s-cis*-**1**. Comparison between geometries of *trans*,*anti*,*endo*-**7b** and *cis*,*anti*,*exo*-**6b** illustrates this observation while IRC

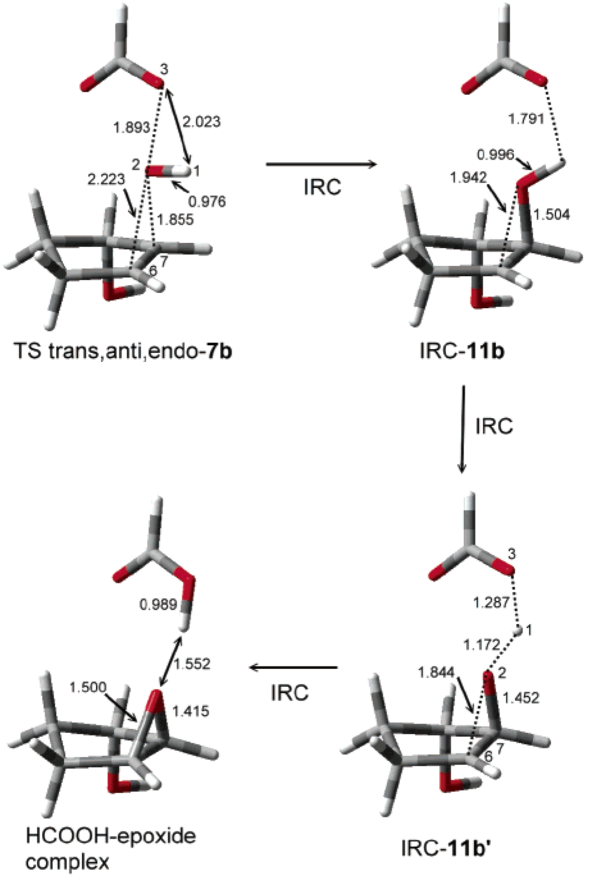

FIGURE 4. IRC following [B3LYP/6-31G(d)] from TS *trans*,*anti*,*endo*-**7b** to the final complex between formic acid and epoxide. Bond lengths in Å.

analysis confirmed that the collapse of *trans*,*anti*,*endo*-**7b** to the final complex takes place in two distinct phases, formation of the O_2-C_7 bond (see IRC-**11b**, Figure 4) followed by closure of the O_2-C_6 bond with concomitant 1,2 hydrogen transfer (IRC-**11b′**), but without the presence of any intermediate. We are in the presence of a nonconcerted one-step process.[5e]

Energetics. Tables S3 (Supporting Information) and Table 1 gather the B3LYP thermodynamic activation parameters obtained with the standard small basis set 6-31G(d) and, respectively, with the larger one 6-311+G-(d,p). Inspection of gas-phase data shows that activation enthalpies ($\Delta H^{\ddagger}_{gas}$) for the trans,syn TSs **4a**−**c** are slightly higher (0.5−0.8 kcal/mol) than those of the corresponding cis,syn TSs **2a**−**c** at the lower theory level (Table S3, Supporting Information) while they become almost identical when the basis set is expanded (Table 1). Cis,syn TSs **2a**−**c** are slightly favored by entropic factors so that, according to the activation free energies ($\Delta G^{\ddagger}_{gas}$), they should be more stable in the gas phase than trans,syn TSs **4a**−**c** by ~1.2 kcal/mol if we trust the B3LYP/6-31G(d) data (Table S3, Supporting Information) or by 0.5−1.0 kcal/mol if we assume as more reliable the B3LYP/6-311+G(d,p) results (Table 1). However, the predicted gas phase dominance of cis,syn TSs over their trans,syn counterparts is far from being dramatic, and moreover, one cannot assume gas-phase energetics as a reliable tool for predicting condensed phase competition. In fact, dipole moments of trans,syn TSs, are always larger (by about 2 D, Figures 1 and 2, Tables S1 and S2 (Supporting Information)) than those of the corresponding cis,syn isomers. The latter observation allows one to anticipate that, even if we all are aware that stabilization by solvation does not strictly parallels dipole moment values, solvation will induce a significant decrease in the energy of trans,syn TSs relative to that of their cis,syn competitors. This prediction is nicely borne out by computational data in Table 1 and Table S3 (Supporting Information) that show how reactions of *s-trans*-**1** should experience a slight decrease in activation free energies on going from the gas phase to the condensed phase while the opposite is true for the reactions of the s-cis conformer. More precisely, relative activation entropies evaluated for benzene and dichloromethane solutions are very similar to those calculated for gas phase but solvation effects adds an enthalpic favor to the trans,syn TSs with respect to their cis,syn isomers of ~1.0 kcal/mol (in benzene) and ~2.0 kcal/mol (in dichloromethane). Relative solvent effects on activation free energies, although not particularly striking, are strong enough to make the two kinds of syn TSs compete in a balanced way in benzene while in dichloromethane a reversal is observed with respect to gas phase with dominance of trans,syn over cis,syn TSs. Interestingly, calculations suggest that the relative stability of these competing TSs does not strongly depend on the ring size of the allylic alcohol, namely, it is very similar for cylobutenol and cyclopentenol while cyclohexenol seems to be slightly biased toward cis,syn TSs with respect to the other two alcohols (Tables 1 and S3 (Supporting Information)).

Things are somewhat different for competition between the "cis" and "trans" reaction channel in anti attacks that can be considered representative of attacks on alkenes. In the case of anti approach to allylic alcohols, the TSs deriving from *s-cis*-**1** (e.g., *cis*,*anti*,*exo*-**6b**) are always much more stable than those arising from *s-trans*-**1** (e.g., *trans*,*anti*,*endo*-**7b**), even if this difference is significantly attenuated by the use of a larger basis set and by solvation effects (Figure 2, Table 1, and Table S3 (Supporting Information)).[23] Thus, one can reasonably exclude a role of s-trans conformers in epoxidation of alkenes at least in the absence of specific interaction of peroxy acids with solvent or other catalysts.

Conclusion

In conclusion, we can fully maintain the traditional mechanistic picture, as recently refined by calculations,[3-5] for the epoxidations of alkenes with peroxy acids while a revision is in order for epoxidation of allylic alcohols assisted by hydrogen bonding. Our calculations provide reliable evidence that for the latter substrates there are two different competing pathways, involving, respectively, the s-cis and the s-trans peroxy acid conformer. Somewhat unexpectedly, TSs for these two kinds of processes have quite similar energies so that it is not easy to qualitatively predict which one will prevail. This observation also means that neglecting one reaction channel should not dramatically alter predictions based on quantitative ab initio calculations, thus explaining why results of previous computational investigations (based only on s-cis performic acid) on epoxidation of allylic alcohols were found to compare reasonably well with experimental data (for example with face selectivity data).[3c,5d] However, it is also quite evident that from now on theoretical investigations on allylic alcohols epoxidation must address this facet of peroxy acid reactivity and it would seem advisable to keep this possibility in mind when considering mechanisms for these reactions. Even a large out-of-plane deformation of the peroxy acid moiety does not represent an insormountable drawback for the epoxidation reaction since the process can easily go to completion through a 1,2-H tranfer in place of the usual 1,4-H shift. Given the delicate energy balance of the competing "cis" and "trans" pathways and the apparent important role played by solvent effects (due to the large difference in dipole moments) calculations aimed at pursuing chemical accuracy in reproducing and predicting peroxy acid reactivity must evaluate solvent effects as accurately as it is possible.

A final interesting remark. Abstraction of the peroxy acid proton from TSs **4** produces TSs whose geometry is similar to that of TSs located by Houk et al. for allylic alcohols epoxidations with peroxy acid anions.[4c]

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Supporting Information Available: Energy and Cartesian coordinates of all TSs and reactants at the B3LYP/6-311+G(d,p) level (gas phase and CH_2Cl_2 solution), TS geometries (gas phase and CH_2Cl_2 solution) at both the B3LYP/6-31G(d) and B3LYP/6-311+G(d,p) levels, and activation parameters (gas phase, benzene and CH_2Cl_2 solution) at the B3LYP/6-31G(d) level are reported. Enthalpy, entropy, and free energy of the starting reactants in the gas phase, benzene, and dichloromethane at both the B3LYP/6-31G(d) and B3LYP/6-311+G(d,p) levels are reported. Cartesian coordinates of the IRC points at the B3LYP/6-31G(d) level are reported. This material is available free of charge via the Internet at http://pubs.acs.org.

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[23] Aside from TSs *cis*,*anti*,*exo*-**6** and *trans*,*anti*,*endo*-**7** there are two more alternative TSs for anti attack, namely TSs cis,anti,endo and trans,anti,exo, deriving from *s-cis*-**1** and *s-trans*-**1**, respectively. We have already reported that B3LYP calculations indicate that TSs cis,-anti,endo have higher free energies than their *cis*,*anti*,*exo*-**6** counterparts in the performic acid epoxidation of 2-cyclobutenol (by ~1.6−1.8 kcal/mol)[5b] and 2-cyclohexenol (by ~2.0−2.8 kcal/mol)[5d] both in the gas phase and in solution. In the case of 2-cyclopentenol epoxidation with performic acid, the TS cis,anti,endo is less stable than TS *cis*,*anti*,*exo*-**6b** by 1.0 kcal/mol (B3LYP/6-31G(d)) and 1.5 kcal/mol (B3LYP/6-311+G(d,p)) both in the gas phase and in solution. As for TSs trans,anti,exo they reside at higher energy than the corresponding TSs *trans*,*anti*,*endo*-**7** and tend to transform into TSs cis,anti,endo by rotation of the formate moiety around the breaking O- - -O bond. Thus, the TS trans,anti,exo of the reaction of performic acid with 2-cyclopentenol could be located by using the B3LYP/6-31G(d) method as implemented in TITAN but when this structure was optimized with Gaussian it afforded the TS cis,anti,endo.