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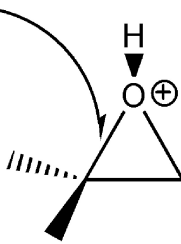
Note

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*J. Org. Chem.*, **2007**, 72 (1), 295-298 • DOI: 10.1021/jo061863z

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Predicted bond length (Å)		
B3LYP	1.790	
CCSD	1.599	
M05	1.602	
M05-2X	1.607	
MP2	1.598	
TPSSh	1.661	

Basis set: 6-311++G(d,p)

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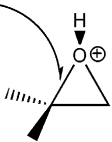
# How Well Can New-Generation Density Functionals Describe Protonated Epoxides Where Older Functionals Fail?

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In a recent article, Carlier et al. (*J. Org. Chem.* **2006**, *71*, 1592) examined the prediction of several DFT functionals and showed that the most popular density functional, B3LYP, and 15 others fail badly for the prediction of the structure of protonated 2-methyl-1,2-epoxypropane. In this note, we compare the performance of several recently developed density functionals for the calculation of structures and energetics of protonated cyclic ethers, including epoxides. We found that several of the newly developed DFT methods perform better than B3LYP or any of the other 17 functionals examined by Carlier. We conclude that a recently published functional, M05-2X, has greatly improved performance for an unsymmetrical protonated epoxide, and we recommend this functional for studies that involve protonated epoxides and protonated ethers.

Epoxides are important reactive intermediates in industry and in organic synthesis because their three-membered heterocyclic rings provide a desirable combination of reactivity, stereoselectivity, flexibility, and atom economy.<sup>1–9</sup> Due to their importance in synthesis and because they are carcinogens, many computational studies<sup>10–27</sup> have been carried out to assist in

understanding reaction mechanisms involving epoxides. A very recent study of the 12 protonated epoxides and other cyclic ethers in Figure 1 by Carlier et al.<sup>25</sup> showed that the most popular density functional, B3LYP,<sup>28–30</sup> fails badly for the prediction of the C2–O bond lengths of asymmetrically substituted protonated epoxides (such as 5-H<sup>+</sup>), as compared to the wave function theory (WFT), in particular, MP2<sup>31</sup> and CCSD.<sup>32</sup> Carlier et al. also surveyed the performance of 17 other density functionals of the generalized gradient approximation (GGA) and hybrid GGA types for the prediction of the C2–O bond length and the ring-opening energetics for 5-H<sup>+</sup>, and 15 tested density functionals in their study do poorly for 5-H<sup>+</sup>. Carlier et al. did not provide results for some newly developed density functionals,<sup>33–40</sup> such as meta-GGAs and hybrid meta-GGAs. The purpose of this note is two-fold. First, we survey the performance of several new-generation density functionals for these protonated epoxides and other cyclic ethers. Second, based on the survey, we recommend the best density functional for studies of organic systems involving protonated epoxides and cyclic ethers.

We classify density functionals as follows: GGAs depend only on spin density,  $\rho_\sigma$ , and its reduced gradient,  $s_\sigma$ ; meta-

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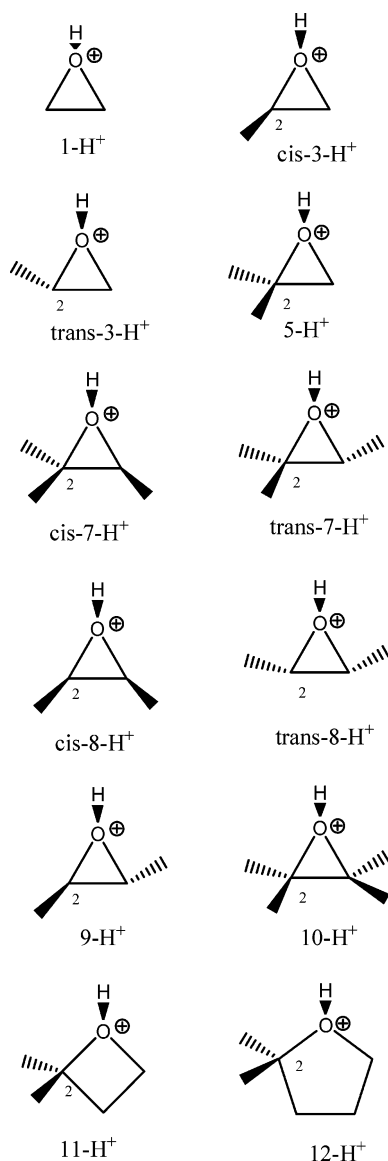


FIGURE 1. Twelve protonated epoxides and cyclic ethers.

GGAs also depend on spin kinetic energy density, and hybrid GGAs and hybrid meta-GGAs also include some percentage of Hartree–Fock exchange. The functionals we assessed in this note include two functionals, namely, PBE<sup>41</sup> (a GGA) and TPSS<sup>33</sup> (a meta-GGA) optimized primarily to theoretical constraints and also their hybrids, PBEh<sup>42</sup> and TPSSh.<sup>43</sup> We also include four density functionals designed for kinetics: MPW1K,<sup>44</sup> MPWB1K,<sup>35</sup> BMK,<sup>36</sup> and PWB6K,<sup>37</sup> among which MPW1K is a hybrid GGA, whereas MPWB1K, BMK, and PWB6K are hybrid meta-GGAs. We also tested seven general-purpose density functionals: two hybrid GGAs, B97-1<sup>38</sup> and B97-2;<sup>39</sup> four hybrid meta-GGAs, MPW1B95,<sup>35</sup> PW6B95,<sup>37</sup>

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TABLE 1. Ring-Opening Energies (kcal/mol) and Bond Lengths (Å) for 5-H<sup>+</sup> <sup>a</sup>

theory	$\Delta H_0$	C2–O	C1–O	ref	mean error <sup>b</sup>
Results from Carlier et al.					
CCSD	−4.4	1.599	1.504	25	
MP2	−1.5	1.598	1.514	25	0.005
B3LYP	−8.7	1.790	1.480	25	0.108
mPW1PW91	−8.0	1.644	1.485	25	0.032
mPW1PBE	−7.9	1.642	1.483	25	0.032
PBE	−7.7	1.773	1.492	25	0.093
Nonempirical DFT Methods and Their Hybrids					
PBEh	−7.9	1.634	1.484	this work	0.027
TPSS	−4.6	1.716	1.506	this work	0.060
TPSSh	−5.0	1.675	1.500	this work	0.040
Semiempirical DFT Methods for Kinetics					
BMK	−6.3	1.657	1.479	this work	0.041
MPW1K	−7.9	1.596	1.474	this work	0.017
MPWB1K	−6.7	1.581	1.473	this work	0.025
PWB6K	−6.9	1.582	1.473	this work	0.024
Semiempirical General-Purpose DFT Methods					
B97-1	−8.0	1.723	1.487	this work	0.071
B97-2	−8.1	1.657	1.485	this work	0.038
M05	−8.4	1.602	1.486	this work	0.011
M05-2X	−6.6	1.607	1.496	this work	0.008
M06-L	−8.2	1.731	1.476	this work	0.080
MPW1B95	−6.9	1.609	1.481	this work	0.016
PW6B95	−7.2	1.633	1.485	this work	0.027

<sup>a</sup> The 6-311++G(d,p) basis set is employed for all calculations in this table.  $\Delta H_0$  is the zero-point inclusive ring-opening energy, that is, the ring-opening energy at 0 K. <sup>b</sup> Mean unsigned error in the two bond lengths, as compared to CCSD.

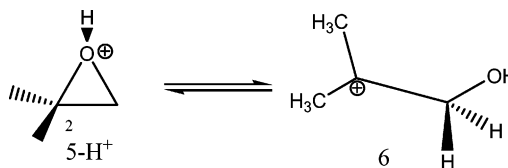


FIGURE 2. Ring-open reaction of protonated 2-methyl-1,2-epoxypropane.

M05,<sup>45</sup> and M05-2X,<sup>40</sup> and one meta GGA, M06-L.<sup>46</sup> We employed the 6-311++G(d,p)<sup>47</sup> polarized and augmented triple- $\zeta$  basis set.

Table 1 summarizes the results for the 5-H<sup>+</sup> compound. In addition to the functionals mentioned above, from ref 25 we include B3LYP,<sup>28–30</sup> PBE,<sup>41</sup> and the two functionals that performed best, mPW1PW<sup>48</sup> and mPW1PBE<sup>41,48</sup> (which are nearly the same because the PBE and PW91 correlation functionals are very similar<sup>49</sup>). The energy of ring opening (Figure 2),  $E_{ro}$ , is defined as

$$E_{ro} = E_0(6) - E_0(5-H^+) \quad (1)$$

where  $E_0$  is the ground state energy, consisting of electronic energy (including nuclear repulsion) at equilibrium plus zero-

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point vibrational energy, which was computed in the harmonic approximation. We use the CCSD/6-311++G(d,p) results of Carlier et al.<sup>25</sup> as reference data for the discussion below.

Table 1 shows that PBEh gives better energetics and C2–O bond lengths than the B3LYP functional, and PBEh also performs better than the PBE GGA. Moving up “Jacob’s ladder”<sup>50</sup> from PBE (second rung, GGA) to TPSS (third rung, meta-GGA), both energetics and bond lengths get improved for the ring-open reaction of 5-H<sup>+</sup>. TPSSh performs better for bond length but slightly worse for energetics than TPSS.

Among the four functionals designed for kinetics, BMK overestimate the C2–O bond length, whereas MPW1K, MPWB1K, and PWB6K underestimate it, and MPWB1K gives the best energetics.

Among the tested general-purpose semiempirical functionals, B97-1, B97-2, and M06-L do poorly for calculating the C2–O bond length, but M05, M05-2X, and MPW1B95 give very good predictions of the C2–O bond length. Among them, M05-2X gives the best prediction for the energetics and the C1–O bond length. The performance of M05-2X is comparable to the correlated WFT MP2 method. Results in Table 1 show that the new-generation DFT methods M05-2X, M05, and MPW1B95 give the best results for the prediction of the structure of 5-H<sup>+</sup>, with mean unsigned errors of 0.008, 0.011, and 0.016 Å, respectively, as compared to a mean unsigned error of 0.104 Å average over the 18 functionals considered in ref 25.

The conclusions in Table 1 are not sensitive functions of basis set or zero-point energy. The Supporting Information gives results with another basis set without zero-point energy that confirm this.

Table 2 summarizes the results for all 12 protonated species in Figure 1 with the 6-311++G(d,p) basis set. The results for MP2 and B3LYP are taken from Carlier et al.<sup>25</sup> We tabulated two statistical errors, mean signed error (MSE) and mean unsigned error (MUE, same as mean absolute deviation), for the C2–O bond lengths and C1–O (Cn–O) bond lengths using the CCSD results as reference. For the C2–O bond lengths, MP2 gives the smallest MSE and MUE. The M05-2X functional has almost the same performance as MP2 for the C2–O bond lengths. TPSSh performs much better than the B3LYP functional, but it still gives a MUE about 0.04 Å. For the C1–O (Cn–O) bond lengths, M05-2X gives the lowest MUE (0.004 Å), followed by MP2 (0.008 Å). In Table 2, we also tabulated a quantity called mean MUE (MMUE)

$$\text{MMUE} = 1/2 \text{MUE}(\text{C2-O}) + 1/2 \text{MUE}[\text{C1-O}(\text{Cn-O})] \quad (2)$$

If we use MMUE as a criterion to judge the performance of the tested methods for the calculation of the bond lengths in these protonated epoxides, M05-2X outperforms MP2 by a small margin, although M05-2X gives a larger maximum error (0.025 Å) than MP2 (0.009 Å). Note that M05-2X is a more affordable method than MP2.

Much progress has been made in the past decade in the design of functionals with improved performance for many areas where B3LYP fails.<sup>40,51–54</sup> As pointed out by Carlier et al., it is not prudent for organic chemists to rely on the popular B3LYP

**TABLE 2. Bond Lengths (Å) for Twelve Protonated Epoxides<sup>a,b</sup>**

molecule	CCSD	Deviation from CCSD Bond Length			
	C2–O	MP2	B3LYP	TPSSh	M05-2X
1-H <sup>+</sup>	1.517	0.004	0.012	0.010	–0.006
cis-3-H <sup>+</sup>	1.551	0.005	0.040	0.032	0.000
trans-3-H <sup>+</sup>	1.556	0.005	0.046	0.036	0.002
5-H <sup>+</sup>	1.599	–0.001	0.191	0.075	0.008
cis-7-H <sup>+</sup>	1.584	0.004	0.077	0.047	0.005
trans-7-H <sup>+</sup>	1.58	0.006	0.069	0.043	0.004
cis-8-H <sup>+</sup>	1.543	0.007	0.023	0.020	–0.001
trans-8-H <sup>+</sup>	1.545	0.008	0.024	0.021	0.000
9-H <sup>+</sup>	1.547	0.007	0.026	0.022	0.000
10-H <sup>+</sup>	1.567	0.009	0.030	0.027	0.002
11-H <sup>+</sup>	1.594	0.000	0.073	0.058	0.025
12-H <sup>+</sup>	1.569	0.001	0.061	0.056	0.017
MSE		0.005	0.056	0.037	0.005
MUE		0.005	0.056	0.037	0.006
C1–O (Cn–O)					
1-H <sup>+</sup>	1.517	0.005	0.012	0.010	–0.006
cis-3-H <sup>+</sup>	1.512	0.007	0.003	0.006	–0.007
trans-3-H <sup>+</sup>	1.511	0.007	0.001	0.005	–0.007
5-H <sup>+</sup>	1.504	0.010	–0.024	–0.004	–0.008
cis-7-H <sup>+</sup>	1.532	0.011	0.000	0.008	–0.004
trans-7-H <sup>+</sup>	1.535	0.011	0.004	0.013	–0.002
cis-8-H <sup>+</sup>	1.543	0.007	0.023	0.020	–0.001
trans-8-H <sup>+</sup>	1.545	0.008	0.025	0.021	0.000
9-H <sup>+</sup>	1.54	0.008	0.021	0.019	–0.002
10-H <sup>+</sup>	1.567	0.009	0.030	0.027	0.002
11-H <sup>+</sup>	1.51	0.004	0.003	0.008	–0.002
12-H <sup>+</sup>	1.505	0.003	0.005	0.009	–0.001
MSE		0.008	0.009	0.012	–0.003
MUE		0.008	0.013	0.013	0.004
overall	MMUE	0.006	0.034	0.025	0.005

<sup>a</sup> The 6-311++G(d,p) basis set is employed for all calculations in this table. The results for B3LYP, MP2, and CCSD are taken from Carlier et al.<sup>25</sup> <sup>b</sup> MUE denotes mean unsigned error, which is same as mean absolute deviation.

functional. However, B3LYP is often applied<sup>23,24,55</sup> rather than more accurate newly developed and improved functionals.

The functionals that perform well for the difficult structure 5-H<sup>+</sup> also perform well for a variety of other properties, including (i) reaction barrier heights,<sup>35,36,40,44,56</sup> (ii) noncovalent interactions,<sup>37,40,51,52,57,58</sup> (iii) metal–metal<sup>59</sup> and metal–ligand<sup>60</sup> binding of coordinatively unsaturated transition metals,<sup>37,40,46</sup> (iv) alkyl bond dissociation energies,<sup>37,40,46</sup> and (v) thermochemistry.<sup>35,37,40,46</sup> For example, M05 is excellent for i, ii, iii, and v; MPW1B95 is very good for i, ii, and v; and M05-2X is excellent for i, ii, iv, and v. The good performance of M05-2X is attributable to improved functional dependence on spin density, its gradient, spin kinetic energy density, and Hartree–Fock exchange and to consistent optimization of exchange and correlation functionals against a broad set of carefully selected data combined with the strategy of constraint satisfaction.<sup>40</sup> It

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is encouraging that this functional, optimized as a general-purpose main-group functional, performs well for this troublesome case. The good performance of M05 is also encouraging because M05, unlike all the other hybrid functionals in ref 25 or Table 1, also performs excellently for coordinatively unsaturated transition metal compounds.<sup>45</sup> The reasons for its success are the same as for M05-2X.

Summarizing the results in Tables 1 and 2, one can see that M05-2X is a density functional that has comparable performance to the MP2 method for the study of the protonated epoxides and other cyclic ethers. It is less expensive than MP2, especially for large systems where MP2 is prohibitively expensive, for

example, in the study of the enzyme-catalyzed epoxide ring-opening reactions.<sup>9</sup>

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**Supporting Information Available:** Optimized geometries (M05-2X/6-311++G(d,p)), electronic and zero-point vibrational energies. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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