Conformational Equilibria in Butane-1,4-diol: A Benchmark of a Prototypical System with Strong Intramolecular H-bonds

Sebastian Kozuch,[†] Steven M. Bachrach,[‡] and Jan M.L. Martin*,[§]

[†]Department of Chemistry and Center for Advanced Scientific Computing and Modeling (CASCaM), University of North Texas, Denton, Texas 76201, United States

[‡]Department of Chemistry, Trinity University, 1 Trinity Place, San Antonio, Texas 78212, United States

[§]Department of Organic Chemistry, Weizmann Institute of Science, 76100 Reḥovot, Israel

S *Supporting Information*

ABSTRACT: Explicitly correlated CCSD(T) valence basis limit relative energies were obtained for the 65 conformers of butane-1,4-diol, a prototypical system with a strong internal hydrogen bond. The performance of a variety of ab initio and DFT methods (with and without empirical dispersion corrections) was assessed in detail. Consideration of all pairwise conformer energies provides a performance gauge for both H-bonds and van der Waals interactions, aside from internal strain of angles and bonds. In the post-HF realm, it was found that SCS(MI)CCSD-F12/cc-pVDZ-F12 can be a cost-effective

alternative to CCSD(T)/CBS, almost without any loss in accuracy. In the DFT arena, the double-hybrid DSD-PBEP86-D3BJ surpasses the accuracy of all other methods (except for SCS(MI)CCSD, but at a small fraction of its cost). Several hybrid functionals provide an acceptable accuracy with the def2-QZVP basis set, especially BMK, M06, LC-ωPBE-D3, and TPSS0-D3. With the more modest 6-311+G(d,p) basis set, the H-bonds are far from basis set completeness and, due to error compensation, the inclusion of a dispersion correction is generally counterproductive. Some functionals that represent "Pauling points" at this level are LC-ωPBE, TPSS0, B1B95, BMK, TPSSh, PBE0, TPSS, and ωB97X.
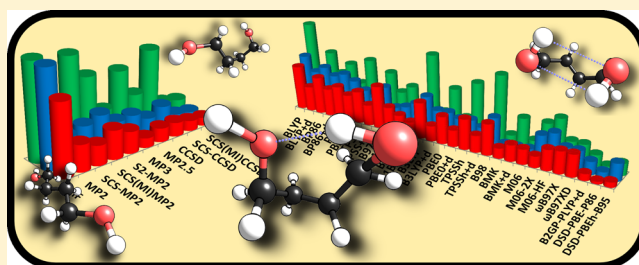
INTRODUCTION

Conformational analysis is a bedrock tool for organic chemists. Molecular structure, chemical reactivity, and spectroscopic features are often rationalized in terms of the conformation of molecules.[1]

Computational quantum chemistry is particularly adept at predicting molecular structure and therefore conformational information. With the recent explosion in computational techniques, both wave function-based methods and, in particular, a myriad of new density functionals, some guidance as to the performance of these new methodologies would be quite valuable for those needing to select an appropriate method for their particular problem.

We have performed just such an examination for alkanes, dealing with rotational isomerization about the carbon−carbon single bond,[2,3] a fundamental component of conformational analysis. A conformational study of melatonin,[4] in addition to accounting for conformations about single and double bonds, included the weak C−H···O and C−H···N interactions.

A logical extension is to explore the method dependency for molecules containing strong hydrogen bonding, such as the O−H···O variety. A system that includes conformations containing an intramolecular hydrogen bond and conformations that lack this hydrogen bond would provide a sensitive test of the ability of a computational method to balance a broad range of effects that account for conformer energetics: steric interactions, dispersion, and hydrogen bonding. An ideal case might

be one where the internal hydrogen bond comes about without too much induced strain in other regions of the molecule. Our choice here is butane-1,4-diol, which along with having open-chain conformations, can form an internal hydrogen bond within a ring-structure that should not be too strained (Scheme 1).

Scheme 1. Open and Ring-Structure Conformers of Butane-1,4-diol
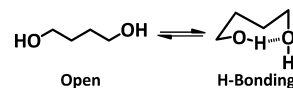
Intramolecular hydrogen bonding of the type exemplified by butane-1,4-diol has broad implication, perhaps most critically in the structure of carbohydrates and other biochemicals. As examples, there can be as many as three internal hydrogen bonds in glycerol,[5] and the pyranose form of glucose can possess up to five internal hydrogen bonds (Figure 1).[6−8] If one is interested in modeling sugars, then being able to appropriately account for internal hydrogen bonding is essential. This ability is of even greater importance when one considers the structure of a sugar
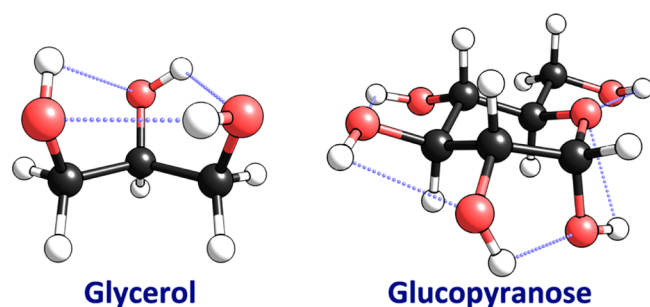
Figure 1. Two molecules with several strong H-bonds.

Figure 2. Some examples of conformers of butane-1,4-diol: the lowest and highest energy **HB** and **nonHB** systems (**B1**, **B7**, **B8**, and **B65**, respectively) and the all trans conformer (**B27**).

in water, where competition between internal and external hydrogen bonding takes place.[9−15]

For weak interactions, CCSD(T)[16,17] may safely be considered a "gold standard", even though some smaller systems have recently been re-examined using post-CCSD(T) methods.[18−20] As for basis set convergence, two prior conformational benchmark studies suggest to us what we may expect. For alkanes, where dispersion predominates, it was shown[2,3] that basis set convergence was quite rapid: using correlation consistent[21,22] basis sets, even conventional CCSD(T)/cc-pVTZ is quite close to the basis set limit, and cc-pVQZ effectively reaches it. For melatonin,[4] which has internal weak hydrogen bonds in some conformers, much slower basis set convergence was observed, with at least aug-cc-pVQZ[23,24] being required to reach results converged to better than 0.2 kcal/mol. However, through explicitly correlated approaches (see refs 25 and 26 for recent reviews), basis set convergence could be dramatically accelerated: using correlation consistent basis sets optimized for explicit correlation (specifically, the cc-pVnZ-F12 series,[27] which are similar in size to aug-cc-pVnZ), we could establish basis set convergence on conformer separations to within 0.02 kcal/mol between cc-pVDZ-F12 and cc-pVTZ-F12 basis sets.

In the present work, we will study the accuracy of several wave function and density function theories (WFT and DFT) on the 65 conformers of butane-1,4-diol. Some conformers display strong internal hydrogen bonds, whereas others are stabilized exclusively by van der Waals forces, which tend to be of a weaker nature compared to the former (Scheme 1 and Figure 2). The conformational landscape of this molecule has been examined by Lopes Jesus and co-workers at the MP2/6-311++G(d,p) level.[28] The lowest free energy open and hydrogen bonded conformers they identified are the same as found in our study.

■ THEORETICAL METHODS

Most wave function ab initio calculations, and particularly all explicitly correlated calculations, were carried out using[29] MOLPRO 2012.1 running on the Faculty of Chemistry cluster at the Weizmann Institute of Science. Most DFT calculations, and a few additional wave function ab initio calculations, were carried out using Gaussian09 Rev. C.01[30] running on the CASCaM (Center for Advanced Scientific Computing and Modeling) cluster at the University of North Texas. Gaussian 09 Rev. D.01 running at Weizmann was employed for some additional DFT calculations.

Our benchmark data were obtained at the CCSD(T)-F12b/cc-pVTZ-F12 level, in conjunction with the appropriate auxiliary basis sets.[31,32] Because strong H-bonds are involved in some conformers, reference data adequately converged in the basis set were deemed indispensable. The CCSD-F12b ansatz[33,34]
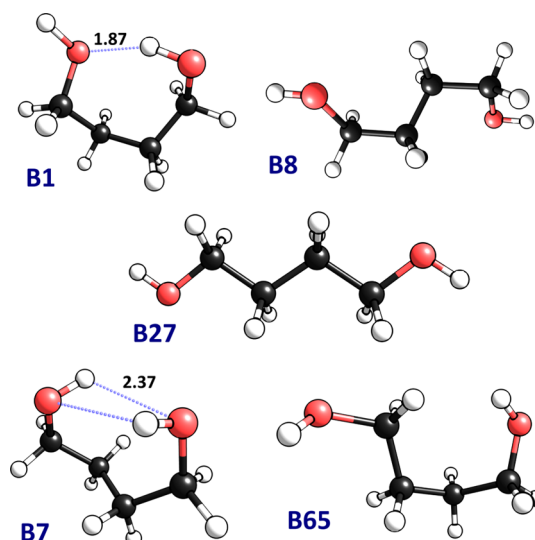
and the 3C(Fix) approximation[35] were used throughout for the F12 calculations. For the (T) term, we employed the Marchetti−Werner approximation,[36,37] which effectively amounts to $E[(T^*)] \approx E[(T)] \times E_{corr}[MP2\text{-}F12]/E_{corr}[MP2]$.

In addition, we considered explicitly correlated calculations using the inexpensive cc-pVDZ-F12 basis set. For the DFT calculations we primarily considered three basis sets: the small 6-31G(d) basis set,[38] the somewhat larger 6-311+G(d,p) basis set,[39] which includes both polarization and diffuse sp functions, and the large def2-QZVPD basis set,[40] in which diffuse functions are added to the already large Karlsruhe def2-QZVP basis.

As lower-level wave function ab initio methods than CCSD(T), we considered MP2, SCS-MP2,[41−43] SCS(MI)MP2,[44] S2-MP2-F12,[45] SCS-CCSD-F12,[46] and SCS(MI)CCSD-F12,[47] all of them obtained as byproducts of the CCSD(T) calculations.

The following DFT exchange-correlation functionals were considered (ordered by the "Jacob's Ladder" of Perdew[48]):

Rung 1: The local density approximation, specifically SVWN5.[49]

Rung 2: Generalized gradient approximations (GGAs). Among the exchange functionals considered are Becke 1988 (B),[50] Perdew−Burke−Ernzerhof (PBE),[51] the modified[52] Perdew−Wang[53,54] functional (mPW), and Handy and Cohen's OptX (O).[55] Among the correlation functionals considered are Perdew86 (P86),[56] Lee−Yang−Parr (LYP),[57] and the correlation part of PBE.[51] Finally, the B97D and B97D3 functional of Grimme,[58] with a heavily parametrized exchange−correlation combo in the Becke−Handy form[59,60] fitted in the presence of an empirical dispersion correction of the D2[58,61] and D3BJ[62] type.

Rung 3: Meta-GGAs (mGGAs). Here we chiefly consider the TPSS exchange and correlation functionals,[63] as well as Becke 1995 (B95) correlation[64] and the M06L heavily parametrized mGGA.[65]

Rung 4: Hybrid (m)GGAs. (a) Among hybrid GGAs we consider B3LYP,[66,67] B3PW91,[66,53] PBE0,[68] O3LYP, X3LYP,[69] and B98.[70] (b) Among hybrid mGGAs we consider B1B95,[64] TPSSh,[63] TPSS0,[71−73] as well as the highly parametrized exchange−correlation combos BMK,[74] M06,[75,76] and M06-2X.[75] (c) We also considered the range-separated hybrid GGAs ωB97X[77] and ωB97X-D[78] (the latter of which was fitted in the presence of a dispersion correction[78] with a D3zero-like damping function[79])

and the range-separated hybrid mGGA M11,[80] as well as the long-range-corrected functionals CAM-B3LYP[81] and LC-ωPBE.[82]

Rung 5: Double hybrids. Here we considered the original B2PLYP,[83] the general-purpose modification B2GP-PLYP,[84] as well as the dispersion-corrected, spin-component-scaled, double hybrids (DSD-DFT) DSD-BLYP,[85] DSD-PBEP86,[86] and DSD-PBEhB95.[87] We note that these latter two come in different parametrizations optimized for different dispersion corrections, of which we considered only D3BJ in this work.

Aside from those functionals that are parametrized around specific dispersion corrections (such as B97D and ωB97XD) we also considered the D3BJ dispersion correction for specific functionals using the DFTD3 program.[88]

Initial geometries were generated by manual conformational scanning at the ωB97XD/6-311+G(d,p) level, followed by reoptimization at the SCS-MP2/cc-pVTZ level. This led to 65 unique conformations. The optimized Cartesian geometries are given in the electronic Supporting Information to the paper: these were used as reference geometries throughout the paper.

■ RESULTS AND DISCUSSION

H-Bonded and Non-H-Bonded Subsets. Butane-1,4-diol has 65 conformers (**B1**−**B65**), which can be divided in two subsets according to the possibility of having internal hydrogen bonds. The group of conformers containing these interactions (denoted **HB** here) includes only seven species (**B1**−**B7**), whereas the 58 others are clearly devoid of internal H-bonds (**nonHB** set, species **B8**−**B65**). In Figure 2 some examples of these conformers are depicted.

Figure 3 shows the marked difference between the **HB** and **nonHB** subsets. Although the two more stable **nonHB**
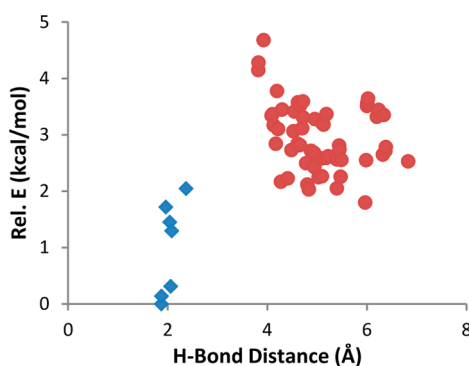

Figure 3. Relative energies (kcal/mol at the CCSD(T)-F12b/cc-pVTZ- level) versus the minimal H-bond distance in the molecule. **HB** systems are in blue, **nonHB** in red.

conformers (**B8** and **B12**) are lower in energy than the highest energy **HB** (**B7**), there is an obvious trend for the **HB** systems to be more stable. An even better discriminant between the subgroups are the shortest HO···H bond distances. All the conformers in the **HB** group have a hydrogen bond in the narrow range 1.87−2.08 Å, except for **B7** (Figure 2) with two equivalent stretched H-bonds of 2.37 Å. All other species have fully dissociated H-bonds, ranging from 3.82 Å (**B63**) to 6.83 Å (**B27**, the "all trans" conformer).

Considering the marked difference between the subsets in their energies, bond distances and evidently the dissimilarity in the internal interactions between the two subsets, we decided to compare the electronic structure methods in three categories: **HB**, **nonHB**, and **mixed**. In each one of these three tests we

compared the 2080 pairwise relative energies between all its members. Therefore, in the **HB** set, having 7 conformers, there are 21 relative energies (according to the $N(N − 1)/2$ number of unique combinations); in the **nonHB** set, there are 1653 such values; and finally in the **mixed** set, there are 406 energies (i.e., the complement of the full set of 2080 pairs minus the **nonHB** and **HB** sets).

Clearly the **nonHB** group does not test for H-bonds, as there are none to assess. This test measures mostly the accuracy of the theoretical method to describe the internal van der Waals forces, and therefore it will probably be the most critical test for the "dispersion corrections" to DFT.

The **HB** set obviously includes H-bonds by definition but is not a good test for them either, as the similarity between the species makes the set prone to error compensation because all the pairs are of similar characteristics. What makes one conformer more unstable than the other when both of them include hydrogen bonds is the required strain on the organic skeleton that permits the O···H interaction. In this way, the **HB** test may be considered, to some extent, a gauge of the method on the quality of strained angles and, probably to a lesser extent, strained bond lengths.

The **mixed** test, on the contrary, relates pairs of conformers where only one partner includes an H-bond; this test is therefore suitable to assess the quality of the theoretical method on internal hydrogen bonds.

It must be pointed out that because hydrogen bonds are much stronger interactions than van der Waals forces, it is expected that the errors in the **mixed** test will be greater in magnitude than in the other tests (we are considering here absolute errors, not relative ones). The average conformational energies are 1.98, 0.99, and 0.64 kcal/mol for the **mixed**, **HB**, and **nonHB** tests, respectively. This indicates that the breaking of H-bonds is, on average, 3 times more expensive than the conformational energies for pure van der Waals changes.

Assessment of Wave Function Methods. The RMSD of the different studied wave function theory methods (WFT) are shown in Figure 4 and Table 1. From these results several points can be deduced:

- *HF*: As expected, Hartree−Fock is of very limited accuracy on systems containing long-range interactions. The **HB** test results are not abysmal, most probably because of error compensation. The RMSD of 2.01 kcal/mol in the **mixed** test is a clear signal of the difficulties of HF to describe H-bonds, illustrating that the quality of the **HB** test is only a red herring.

- *MP2*: This method provides an overall good quality on all the tests. However, as explained before, the **mixed** test is more stringent than the others. It can be concluded that traditional MP2 provides good quality results, in particular for H-bonds.

- *Parametrized MP2*: Neither SCS-MP2 nor SCS(MI)MP2 do a good job with H-bonds, according to the RMSDs of the **mixed** set. Although SCS-MP2 was parametrized for covalent bonding (with same-spin and opposite spin MP2 correlation of $c_s = 1/3$ and $c_o = 5/6$, respectively),[41] performance for general thermochemistry was sacrificed in SCS(MI)MP2[44] ($c_s = 1.29$, $c_o = 0.4$) in an attempt to improve performance for van der Waals interactions. As H-bonds arguably have more in common with the former than with the latter, this may explain the comparatively weak performance of SCS(MI)MP2. Interestingly and
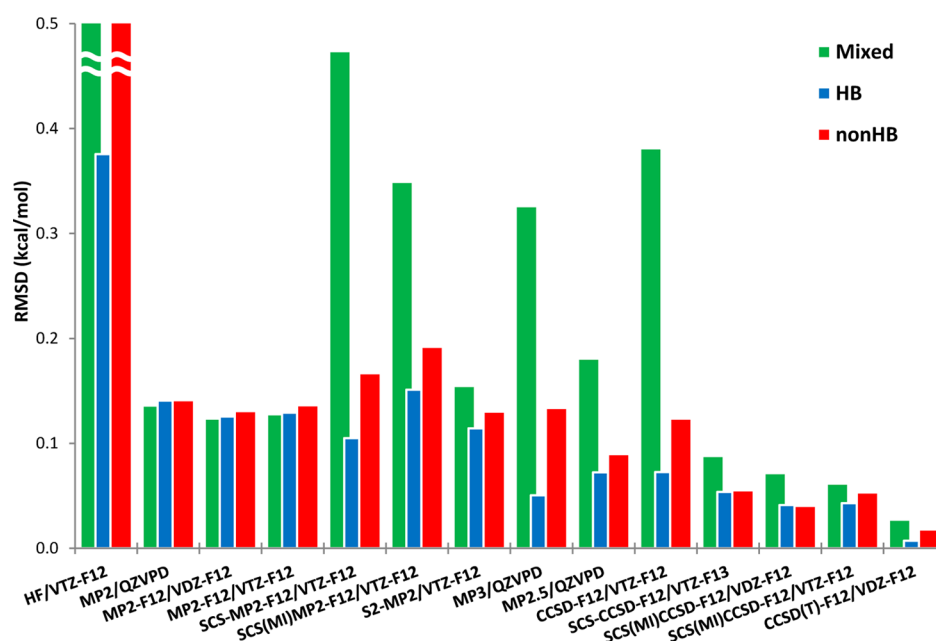
295

dx.doi.org/10.1021/jp410723v | J. Phys. Chem. A 2014, 118, 293−303

Figure 4. RMSD (kcal/mol) for wave function methods.

Table 1. RMSD (kcal/mol) of Wave-Function Methods for the HB, nonHB, and Mixed Tests[a]

method	basis set	HB	nonHB	mixed
HF	VTZ-F12	0.38	0.68	2.01
MP2	QZVPD	0.14	0.14	0.14
MP2-F12	VDZ-F12	0.13	0.13	0.12
MP2-F12	VTZ-F12	0.13	0.14	0.13
SCS-MP2-F12	VTZ-F12	0.10	0.17	0.47
SCS(MI)MP2-F12	VTZ-F12	0.15	0.19	0.35
S2-MP2-F12	VTZ-F12	0.11	0.13	0.15
MP3	QZVPD	0.05	0.13	0.33
MP2.5	QZVPD	0.07	0.09	0.18
CCSD-F12b	VTZ-F12	0.07	0.12	0.38
SCS-CCSD-F12b	VTZ-F12	0.05	0.06	0.09
SCS(MI)CCSD-F12b	VDZ-F12	0.04	0.04	0.07
SCS(MI)CCSD-F12b	VTZ-F12	0.04	0.05	0.06
CCSD(T)-F12b	VDZ-F12	0.01	0.02	0.03

[a]The reference energies are at the CCSD(T)-F12b/cc-pVTZ-F12 level.

unexpectedly, SCS(MI)MP2 does not even improve on the MP2 results on the **nonHB** test, in spite of being designed for van der Waals based systems. Finally, the "nonempirical" S2-MP2[45] ($c_s = 0.75$ and $c_o = 1.15$) yields good performance for all three sets.

- *MP3*: This method provides excellent results for the **HB** test but (despite a significant increase in computational cost) significantly degrades the **mixed** accuracy compared to MP2. The **nonHB** RMSD is virtually the same as in MP2. It can be concluded that MP3 enhances the accuracy of strained systems (with angles distorted from their ideal geometry), but on long-range interactions it is not the way to go.

- *MP2.5*: This is defined as[89,90] the average of MP2 and MP3. Naively, one might expect the RMSDs to be also halfway between the latter two methods. However, because MP2 usually overestimates van der Waals interactions, whereas MP3 overcorrects,[89,2] MP2.5 tends to provide surprisingly good results, as we have also seen in our

previous studies on the pentane surface[2] and melatonin.[4] Presently, we do see an improvement for **nonHB**, whereas for **HB** the RMSD is close to the already very low MP3 value. For the **mixed** test set, we find performance slightly worse than the already fairly good MP2 value. It seems that surpassing MP2 accuracy for H-bonds is only possible with much more rigorous wave function methods, such as CCSD(T).

- *CCSD and derived methods*: The performance of straight CCSD, without spin-component scaling or perturbative triples, disappoints: the improvement for **HB** is outweighed by significant deterioration in **mixed**. In contrast, a spin-component scaling both in the SCS-CCSD[46] version (for general-purpose applications, with $c_o = 1.27$ and $c_s = 1.13$) and in the SCS(MI)CCSD[47] one (optimized for weak interactions, $c_o = 1.11$ and $c_s = 1.28$) yields excellent performance across the board and can be considered the tool of choice where CCSD(T) would become cost-prohibitive.

- *Basis set and F12 method*: For the problem at hand, MP2/def2-QZVPD, MP2-F12b/cc-pVDZ-F12, and MP2-F12b/cc-pVTZ-F12 yield virtually identical results, as do CCSD(T)-F12b/cc-pVDZ-F12 compared to CCSD-(T)-F12b/cc-pVTZ-F12, and SCS(MI)CCSD-F12b with cc-pVDZ-F12 or cc-pVTZ-F12. This, on the one hand, confirms that, for explicitly correlated calculations, even the modest cc-pVDZ-F12 basis set is sufficiently close to the basis set limit for our present purposes, whereas on the other hand, it establishes that def2-QZVPD is sufficiently close to the basis set limit for the conventional calculations. For larger systems where CCSD(T)-F12b calculations are not a practical option, SCS-CCSD-F12b or SCS(MI)CCSD-F12b/cc-pVDZ-F12 may well be the most accurate options available.

Assessment of DFT Methods. For DFT purposes, def2-QZVPD can safely be considered to be near the basis set limit. As can be seen in Figure 5 and Tables 2 and 3, no functional at rung 4 or below can match the accuracy of SCS(MI)CCSD-
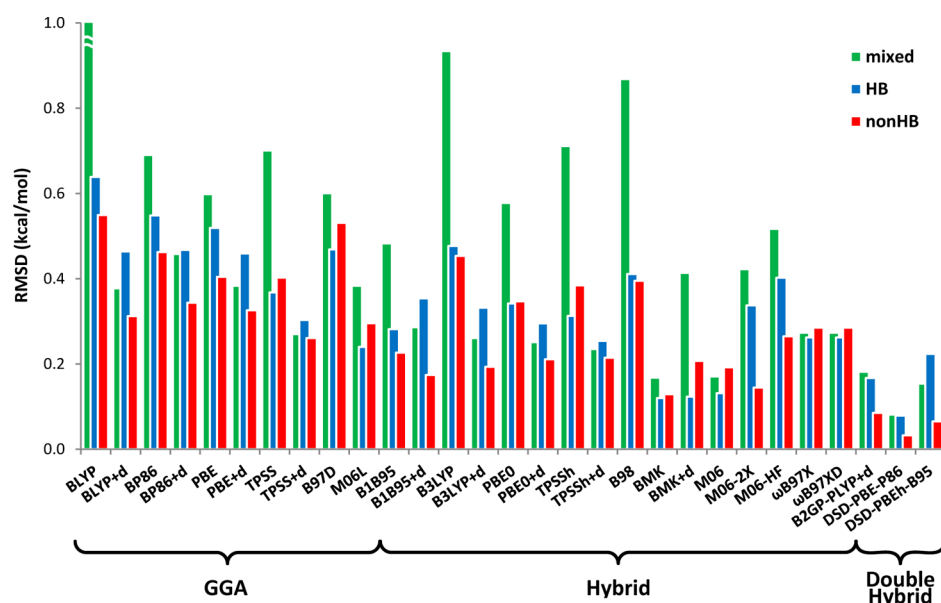
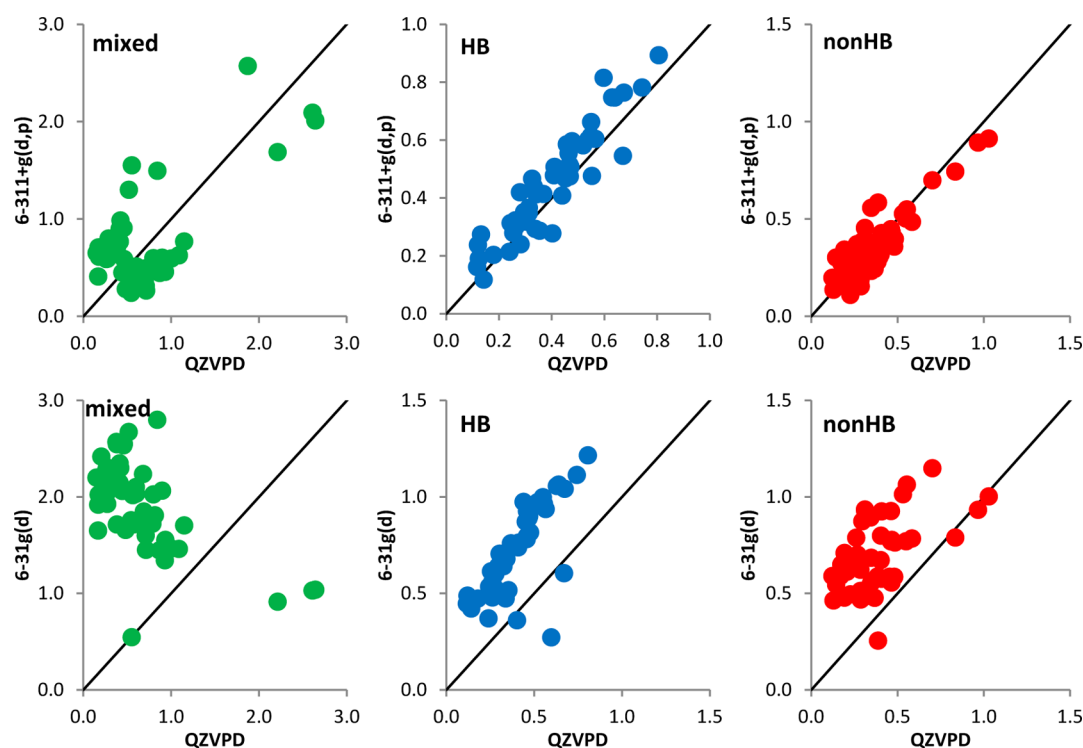**Figure 5.** RMSD (kcal/mol) for selected DFT methods.

Figure 6. Comparison of basis set effect (RMSD in kcal/mol), as a function of the virtually complete basis set def2-QZVPD. Each point corresponds to a different functional (including the "D3" versions). A point over the diagonal line indicates lower accuracy with 6-311+G(d,p) or 6-31G(d).

F12b, but of course their cost scaling with system size is much more amenable to large systems. In the absence of dispersion corrections, two functionals come close to MP2-level accuracy: BMK and M06, although ωB97X also puts in a creditable performance. With a D3BJ correction, the winners are LC-ωPBE-D3 and TPSS0-D3. Clearly, **mixed** is the most sensitive of the three sets to the quality of the functional.

Including an empirical dispersion correction does help with many functionals (see rows 4−7 in Table 4), such as B3LYP, PBE0, TPSS, TPSSh, and the like, but for some functionals such as BMK it does more harm than good.

By and large, hybrids perform better than the underlying (meta)GGAs, but the variation within rung 4 or within the set union of rungs 2 and 3 is too large to allow for easy generalizations. For instance, for the **mixed** test, the average GGA and hybrid DFT RMSDs are 0.83 and 0.54 kcal/mol, but the standard deviation reaches 80% of those average errors (this includes functionals with and without dispersion corrections, see rows 1 and 2 in Table 4).

Double hybrids are clearly more accurate (row 3 in Table 4, average RMSD for the **mixed** set is 0.23 kcal/mol), but the selection of the specific functional still matters a good deal.

Table 2. RMSD (kcal/mol) of DFT Methods for the HB, nonHB, and Mixed Tests, with Three Basis Sets[a]

functional	type[b]	def2-QZVPD			6-311+G(d,p)			6-31G(d)		
		HB	nonHB	mixed	HB	nonHB	mixed	HB	nonHB	mixed
SVWN5	LDA	0.57	0.31	1.87	0.61	0.46	2.57	0.94	0.93	4.30
BLYP	GGA	0.64	0.55	1.15	0.75	0.50	0.77	1.06	0.77	1.71
BP86	GGA	0.55	0.46	0.69	0.61	0.39	0.49	0.96	0.77	1.85
BPBE	GGA	0.56	0.58	1.09	0.61	0.49	0.63	0.96	0.78	1.46
mPWLYP	GGA	0.63	0.47	0.90	0.75	0.43	0.61	1.06	0.78	2.06
mPWPW91	GGA	0.54	0.48	0.82	0.60	0.40	0.49	0.96	0.76	1.81
OLYP	GGA	0.81	0.97	2.61	0.89	0.89	2.09	1.22	0.93	1.03
OPBE	GGA	0.74	1.03	2.64	0.78	0.91	2.01	1.11	1.00	1.04
PBE	GGA	0.52	0.40	0.60	0.58	0.35	0.49	0.97	0.80	2.10
TPSS	mGGA	0.37	0.40	0.70	0.41	0.32	0.35	0.76	0.67	1.73
B97D	GGA+D	0.47	0.53	0.60	0.48	0.53	0.52	0.93	1.01	2.03
B97D3	GGA+D	0.47	0.46	0.56	0.51	0.45	0.50	0.90	0.93	2.02
M06L	mGGA	0.24	0.30	0.38	0.21	0.39	0.71	0.37	0.48	1.71
B1B95	mHybrid	0.28	0.23	0.48	0.24	0.11	0.28	0.52	0.50	1.66
B3PW91	Hybrid	0.41	0.48	0.93	0.48	0.36	0.46	0.74	0.59	1.34
B1LYP	Hybrid	0.46	0.46	1.00	0.59	0.40	0.60	0.78	0.56	1.47
B3LYP	Hybrid	0.48	0.45	0.93	0.60	0.39	0.55	0.82	0.59	1.55
O3LYP	Hybrid	0.67	0.83	2.21	0.76	0.74	1.69	1.04	0.79	0.91
X3LYP	Hybrid	0.46	0.41	0.79	0.58	0.35	0.47	0.79	0.58	1.72
PBE0	Hybrid	0.34	0.35	0.58	0.41	0.23	0.35	0.68	0.56	1.72
TPSSh	mHybrid	0.31	0.38	0.71	0.37	0.28	0.31	0.66	0.59	1.60
TPSS0	mHybrid	0.24	0.37	0.71	0.31	0.24	0.27	0.54	0.48	1.45
B98	Hybrid	0.41	0.40	0.87	0.51	0.31	0.45	0.76	0.58	1.45
BMK	mHybrid	0.12	0.13	0.17	0.24	0.14	0.41	0.49	0.46	1.65
M06	mHybrid	0.13	0.19	0.17	0.27	0.34	0.71	0.47	0.48	1.92
M062X	mHybrid	0.34	0.14	0.42	0.29	0.30	0.99	0.47	0.55	2.30
M06HF	mHybrid	0.40	0.26	0.52	0.28	0.37	1.30	0.36	0.64	2.67
M11	mHybrid	0.67	0.35	0.84	0.55	0.56	1.50	0.60	0.68	2.80
CAM-B3LYP	RSH	0.33	0.31	0.44	0.47	0.27	0.45	0.64	0.52	2.06
LC-ωPBE	RSH	0.12	0.29	0.54	0.16	0.16	0.24	0.45	0.47	1.76
ωB97X	RSH	0.26	0.29	0.27	0.30	0.18	0.59	0.48	0.51	2.05
ωB97XD	RSH+D	0.26	0.29	0.27	0.32	0.24	0.59	0.56	0.62	1.93
Functionals with D3BJ Added a Posteriori										
BLYP-D3	GGA	0.46	0.31	0.38	0.56	0.35	0.64	0.94	0.93	2.57
BP86-D3	GGA	0.47	0.34	0.46	0.51	0.38	0.91	0.89	0.89	2.53
BPBE-D3	GGA	0.45	0.41	0.41	0.47	0.43	0.77	0.87	0.92	2.35
mPWLYP-D3	GGA	0.55	0.30	0.46	0.66	0.32	0.59	1.00	0.87	2.55
OLYP-D3	GGA	0.44	0.55	0.68	0.41	0.55	0.48	0.97	1.06	2.24
OPBE-D3	GGA	0.55	0.70	0.80	0.48	0.70	0.60	0.95	1.15	2.03
PBE-D3	GGA	0.46	0.33	0.38	0.51	0.34	0.77	0.93	0.90	2.55
TPSS-D3	mGGA	0.30	0.26	0.27	0.32	0.29	0.69	0.71	0.79	2.31
B1B95-D3	mHybrid	0.35	0.17	0.29	0.29	0.27	0.80	0.52	0.65	2.19
B3PW91-D3	Hybrid	0.31	0.27	0.28	0.35	0.26	0.66	0.65	0.70	2.10
B3LYP-D3	Hybrid	0.33	0.19	0.26	0.44	0.22	0.59	0.71	0.71	2.28
PBE0-D3	Hybrid	0.30	0.21	0.25	0.35	0.19	0.62	0.64	0.63	2.11
TPSSh-D3	mHybrid	0.25	0.21	0.23	0.28	0.23	0.61	0.61	0.69	2.14
TPSS0-D3	mHybrid	0.18	0.17	0.18	0.20	0.18	0.61	0.47	0.59	2.03
BMK-D3	mHybrid	0.12	0.21	0.41	0.19	0.31	0.90	0.45	0.61	2.15
CAM-B3LYP-D3	RSH	0.28	0.12	0.21	0.42	0.20	0.71	0.60	0.59	2.42
LC-ωPBE-D3	RSH	0.14	0.15	0.15	0.12	0.20	0.65	0.42	0.58	2.20

[a]In the lower part of the table, "-D3" indicates the addition of a D3BJ dispersion correction. The reference energies are at the CCSD(T)-F12b/cc-pVTZ-F12 level. [b]LDA: local density approximation. GGA: generalized gradient approximation. mGGA: meta-GGA. Hybrid: hybrid GGA. mHybrid: hybrid mGGA. RSH: range-separated hybrid. +D: dispersion correction parametrized a priori.

The B2PLYP and B2GP-PLYP double hybrids can both reach MP2-range accuracy with the help of D3BJ; the DSD functionals DSD-BLYP-D3 and DSD-PBEP86-D3 in fact well surpass MP2, with DSD-PBEP86-D3 even edging out MP2.5 and approaching SCS(MI)CCSD (at drastically reduced computational cost).

On a very large and diverse benchmark suite, DSD-PBEhB95-D3 was found to be[87] somewhat superior to DSD-PBEP86-D3, but the latter still appears to have an edge for weak interactions. We recommend it as the method of choice in situations where CCSD-F12 or even MP2.5 would become cost-prohibitive: if a

Table 3. RMSD (kcal/mol) of Double-Hybrid DFT Methods for the HB, nonHB, and Mixed Tests, with def2-QZVPD Basis Sets[a]

	HB	nonHB	mixed
B2PLYP	0.27	0.26	0.55
B2PLYP-D3	0.21	0.09	0.20
B2GP-PLYP	0.21	0.21	0.42
B2GP-PLYP-D3	0.17	0.09	0.18
DSD-BLYP-D3	0.11	0.04	0.08
DSD-PBEPBE-D3	0.07	0.06	0.19
DSD-PBEP86-D3	0.08	0.03	0.08
DSD-PBEhB95-D3	0.22	0.07	0.15

[a]The reference energies are at the CCSD(T)-F12b/cc-pVTZ-F12 level.

Table 4. Average RMSD (kcal/mol) for Subgroups of Functionals with the def2-QZVPD Basis Set (Standard Deviation in Parentheses)

		HB	nonHB	mixed
1	GGA[a]	0.51 (0.13)	0.49 (0.20)	0.83 (0.64)
2	hybrid[b]	0.32 (0.14)	0.30 (0.15)	0.54 (0.42)
3	DH[c]	0.17 (0.07)	0.10 (0.08)	0.23 (0.16)
4	GGA (no d)[d]	0.60 (0.13)	0.61 (0.23)	1.30 (0.79)
5	hybrid (no d)[e]	0.29 (0.11)	0.33 (0.10)	0.61 (0.23)
6	GGA-D3[f]	0.46 (0.07)	0.40 (0.14)	0.48 (0.16)
7	hybrid-D3[g]	0.25 (0.08)	0.19 (0.04)	0.25 (0.07)

[a]BLYP, BP86, BPBE, mPWLYP, mPWPW91, OLYP, OPBE, PBE, TPSS, B97D, B97D3, and M06L, plus the "D3" versions. [b]B1B95, B3PW91, B1LYP, B3LYP, O3LYP, X3LYP, PBE0, TPSSh, TPSS0, B98, BMK, M06, M062X, M06HF, M11, CAM-B3LYP, LC-ωPBE, ωB97X, and ωB97XD, plus the "D3" versions when applicable. [c]B2PLYP, B2GP-PLYP, DSD-BLYP, DSD-PBEPBE, DSD-PBEP86, and DSD-PBEhB95, plus the "D3" versions when applicable. [d]BLYP, BP86, BPBE, mPWLYP, OLYP, OPBE, PBE, and TPSS (GGA without dispersion correction but with "D3" available). [e]B1B95, B3LYP, B3PW91, BMK, CAM-B3LYP, LC-ωPBE, PBE0, TPSSh, and TPSS0 (hybrids without dispersion correction but with "D3" available). [f]All the "D3" GGAs. [g]All the "D3" hybrids.

code that allows for an RI ("resolution of the identity",[91−94] a.k.a. "density fitting") approximation in the MP2 stage is

available, the extra cost of DSD-PBEP86 over ordinary hybrid functionals is quite modest.

It can be argued that def2-QZVPD is too computationally demanding for large systems. Considering that DFT tends to converge relatively rapidly with the size of the basis set, we compared the accuracy of the large quadruple-ζ basis set with the 6-311+G(d,p) Pople basis set as a "medium"-sized alternative, and the popular 6-31G(d) as a "small" choice. A priori, we would expect the latter to provide qualitative results at best, especially for want of diffuse functions and polarization in the hydrogens. But the triple-ζ basis set with the diffuse and polarization functions may be a good compromise between accuracy and speed.

Figure 6 shows a comparison of Pople's basis sets to the def2-QZVPD RMSDs, where each point corresponds to a different functional (including the GGA and hybrid versions, with and without dispersion correction). Dots over the diagonal line indicate functionals with a degraded accuracy with the smaller basis sets. From these graphs and the values of Table 2 it is possible to observe that:

- The small 6-31g(d) is indeed inappropriate for quantitative calculations and, as expected, it can be argued that no method from the tested ones is appropriate for production work. Some specific functionals are more accurate with 6-31g(d) compared to def2-QZVPD (the ones with O exchange), but this is a matter of error compensation. The H-bonds (**mixed** test) is especially sensitive to the size of the basis set.

- The medium size 6-311+g(d,p) does a much better job, with remaining basis set incompleteness error (relative to def2-QZVPD) leading to beneficial error compensation for a number of functions, and degrading the performance of a roughly similar number. Moreover, the points in Figure 6 are closer to the diagonal line compared to the 6-31g(d) graphs. However, in the **mixed** test the larger dispersion of points over and below the line indicates that for H-bonds this "not really triple-ζ"[95] basis set is still small and far from being a complete basis set.

- Including dispersion corrections does not always "improve" results with smaller basis sets. That is, error compensation between internal BSSE (basis set superposition error)

Table 5. Improvement of the RMSD (kcal/mol) with the Inclusion of D3BJ for Different GGA and Hybrid Functionals

		def2-QZVPD			6-311+G(d,p)			6-31G(d)		
		HB	nonHB	mixed	HB	nonHB	mixed	HB	nonHB	mixed
GGA	BLYP	0.17	0.24	0.77	0.19	0.16	0.13	0.13	−0.16	−0.86
	BP86	0.08	0.12	0.23	0.10	0.01	−0.42	0.07	−0.12	−0.69
	BPBE	0.10	0.18	0.67	0.14	0.06	−0.14	0.09	−0.14	−0.89
	mPWLYP	0.08	0.17	0.43	0.09	0.11	0.01	0.06	−0.10	−0.49
	OLYP	0.37	0.41	1.93	0.48	0.34	1.62	0.24	−0.13	−1.21
	OPBE	0.19	0.33	1.84	0.31	0.21	1.41	0.16	−0.15	−0.99
	PBE	0.06	0.08	0.21	0.08	0.00	−0.28	0.05	−0.10	−0.44
	TPSS	0.06	0.14	0.43	0.10	0.03	−0.34	0.05	−0.12	−0.57
hybrid	B1B95	−0.07	0.05	0.20	−0.05	−0.16	−0.52	0.00	−0.15	−0.53
	B3PW91	0.10	0.21	0.65	0.13	0.10	−0.20	0.08	−0.11	−0.75
	B3LYP	0.14	0.26	0.67	0.16	0.17	−0.04	0.11	−0.12	−0.72
	PBE0	0.05	0.14	0.33	0.06	0.05	−0.27	0.04	−0.08	−0.40
	TPSSh	0.06	0.17	0.48	0.09	0.05	−0.30	0.05	−0.10	−0.53
	TPSS0	0.06	0.20	0.54	0.11	0.07	−0.35	0.06	−0.11	−0.57
	BMK	0.00	−0.08	−0.25	0.05	−0.17	−0.49	0.04	−0.15	−0.50
	CAM-B3LYP	0.05	0.18	0.24	0.05	0.07	−0.26	0.04	−0.07	−0.36
	LC-ωPBE	−0.02	0.14	0.39	0.04	−0.05	−0.41	0.03	−0.11	−0.44

and neglect of dispersion may well conspire to create a "Pauling point" (a.k.a., "right answer for the wrong reasons").[96] As can be seen in Table 5, adding "-D3" to 6-311+G(d,p) calculations actually degrades the **mixed** set RMSDs for most functionals, whereas with the (by the authors' standard woefully inadequate) 6-31g(d) basis set even the **non-H** set suffers. One exception to this rule is ωB97XD, which actually yields error statistics very similar to those of ωB97X even with the medium and small basis sets. However, unlike most of the other functionals considered here with D3 corrections, this heavily parametric range-separated hybrid was refitted in the presence of the dispersion correction.

- The best functionals with the 6-311+G(d,p) medium size basis set are (in roughly decreasing order of accuracy) LC-ωPBE, TPSS0, B1B95, BMK, TPSSh, PBE0, TPSS, and ωB97X (all of them without dispersion correction!). For most of them the "D3" versions are still better than the average DFT, but in all cases they are slightly worse than without D3BJ.

CONCLUSIONS

In this work we tested the accuracy of several WFT and DFT methods on butane-1,4-diol, a prototypical system with internal hydrogen bonds. The comparison of the energies of the 65 conformers provided a measure to test both H-bonds and van der Waals interactions, plus internal strain of angles and bonds. The following points can be concluded:

- For this type of problem, basis set convergence of explicitly correlated methods is very rapid, and even cc-pVDZ-F12 yields results that are effectively at the basis set limit. Hydrogen bonds are more susceptible to the size of the basis set compared to van der Waals interactions.
- Pairwise energy separations between hydrogen-bonded and non-hydrogen-bonded conformers appear to be a more sensitive gauge of method performance than energy separations within each class.
- SCS(MI)CCSD-F12b/cc-pVDZ-F12 appears to be an accurate yet cost-effective option in situations where even CCSD(T)-F12b/cc-pVDZ-F12 is cost- or resource-prohibitive.
- Near the Kohn−Sham basis set limit, hybrids typically do have an advantage over (m)GGAs, but there is considerable variation between functionals in each class.
- The overall winner is the DSD-PBEP86-D3 double hybrid, with a computational cost of an MP2 calculation and almost the accuracy of SCS(MI)CCSD.
- Descending to rung 4, the best available choices appear to be LC-ωPBE-D3 and TPSS0-D3. If no empirical dispersion correction is allowed, then BMK and M06 are the winners.
- With smaller basis sets, i.e., 6-311+G(d,p), neglect of dispersion corrections may collude with basis set incompleteness to create a "Pauling point". In this case several functionals provide similar accuracies, including LC-ωPBE, TPSS0, B1B95, BMK, TPSSh, PBE0, TPSS, and ωB97X. This basis set is close to basis set completeness for van der Waals forces, but it is not enough for H-bonds (although this does not necessarily means that the accuracies are degraded).

- An even smaller basis set, 6-31G(d), cannot describe the interactions present in this test and (as expected) is not recommended for any functional.

ASSOCIATED CONTENT

Ⓢ Supporting Information
Optimized SCS-MP2/cc-pVTZ geometries of all conformers as Cartesian coordinates in XMol.xyz format; total energies for the different wave function and DFT methods. Full refs 29 and 30. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
*J. M. L. Martin: e-mail, gershom@weizmann.ac.il; phone, +972 8 9342533.

Author Contributions
The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes
The authors declare no competing financial interest.

REFERENCES

(1) Barton, D. H. R. The Principles of Conformational Analysis. In *Nobel Lectures, Chemistry 1963−1970*; Elsevier: Amsterdam, 1972.

(2) Martin, J. M. L. What Can We Learn about Dispersion from the Conformer Surface of n-Pentane? *J. Phys. Chem. A* **2013**, *117*, 3118−3132.

(3) See also Gruzman, D.; Karton, A.; Martin, J. M. L. Performance of *Ab Initio* and Density Functional Methods for Conformational Equilibria of C$_n$H$_{2n+2}$ Alkane Isomers (n = 4−8). *J. Phys. Chem. A* **2009**, *113*, 11974−11983.

(4) Fogueri, U. R.; Kozuch, S.; Karton, A.; Martin, J. M. L. The Melatonin Conformer Space: Benchmark and Assessment of Wave Function and DFT Methods for a Paradigmatic Biological and Pharmacological Molecule. *J. Phys. Chem. A* **2013**, *117*, 2269−2277.

(5) Callam, C. S.; Singer, S. J.; Lowary, T. L.; Hadad, C. M. Computational Analysis of the Potential Energy Surfaces of Glycerol in the Gas and Aqueous Phases: Effects of Level of Theory, Basis Set, and Solvation on Strongly Intramolecularly Hydrogen-Bonded Systems. *J. Am. Chem. Soc.* **2001**, *123*, 11743−11754.

(6) Ma, B.; Schaefer, H. F.; Allinger, N. L. Theoretical Studies of the Potential Energy Surfaces and Compositions of the d-Aldo- and d-Ketohexoses. *J. Am. Chem. Soc.* **1998**, *120*, 3411−3422.

(7) Barrows, S. E.; Dulles, F. J.; Cramer, C. J.; French, A. D.; Truhlar, D. G. Relative Stability of Alternative Chair Forms and Hydroxymethyl Conformations of β-d-Glucopyranose. *Carbohydr. Res.* **1998**, *276*, 219−251.

(8) Lii, J. H.; Ma, B.; Allinger, N. L. Importance of Selecting Proper Basis Set in Quantum Mechanical Studies of Potential Energy Surfaces of Carbohydrates. *J. Comput. Chem.* **1999**, *20*, 1593−1603.

(9) Cramer, C. J.; Truhlar, D. G. Quantum Chemical Conformational Analysis of 1,2-Ethanediol: Correlation and Solvation Effects on the

Tendency to Form Internal Hydrogen Bonds in the Gas Phase and in Aqueous Solution. *J. Am. Chem. Soc.* **1994**, *116*, 3892−3900.

(10) Wladkowski, B. D.; Chenoweth, S. A.; Jones, K. E.; Brown, J. W. Exocyclic Hydroxymethyl Rotational Conformers of β- and α-d-Glucopyranose in the Gas Phase and Aqueous Solution. *J. Phys. Chem. A* **1998**, *102*, 5086−5092.

(11) Kirschner, K. N.; Woods, R. J. Solvent Interactions Determine Carbohydrate Conformation. *Proc. Natl. Acad. Sci. U. S. A.* **2001**, *98*, 10541−10545.

(12) Hommel, E. L.; Merle, J. K.; Ma, G.; Hadad, C. M.; Allen, H. C. Spectroscopic and Computational Studies of Aqueous Ethylene Glycol Solution Surfaces. *J. Phys. Chem. B* **2005**, *109*, 811−818.

(13) Momany, F. A.; Appell, M.; Willett, J. L.; Bosma, W. B. B3LYP/6-311++G** Geometry-Optimization study of Pentahydrates of α- and β-d-Glucopyranose. *Carbohydr. Res.* **2005**, *340*, 1638−1655.

(14) Dashnau, J. L.; Sharp, K. A.; Vanderkooi, J. M. Carbohydrate Intramolecular Hydrogen Bonding Cooperativity and Its Effect on Water Structure. *J. Phys. Chem. B.* **2005**, *109*, 24152−24159.

(15) Wang, D.; Ámundadóttir, M. L.; van Gunsteren, W. F.; Hünenberger, P. H. Intramolecular Hydrogen-Bonding in Aqueous Carbohydrates as a Cause or Consequence of Conformational Preferences: A Molecular Dynamics Study of Cellobiose Stereoisomers. *Eur. Biophys. J.* **2013**, *42*, 521−537.

(16) Raghavachari, K.; Trucks, G. W.; Pople, J. A.; Head-Gordon, M. A Fifth-Order Perturbation Comparison of Electron Correlation Theories. *Chem. Phys. Lett.* **1989**, *157*, 479−483.

(17) Watts, J. D.; Gauss, J.; Bartlett, R. J. Coupled-Cluster Methods With Noniterative Triple Excitations for Restricted Open-Shell Hartree−Fock and Other General Single Determinant Reference Functions. Energies and Analytical Gradients. *J. Chem. Phys.* **1993**, *98*, 8718−8733.

(18) Boese, A. D. Assessment of Coupled Cluster Theory and more Approximate Methods for Hydrogen Bonded Systems. *J. Chem. Theor. Comput.* **2013**, *9*, 4403−4413.

(19) Řezáč, J.; Hobza, P. Describing Noncovalent Interactions beyond the Common Approximations: How Accurate Is the "Gold Standard," CCSD(T) at the Complete Basis Set Limit? *J. Chem. Theory Comput.* **2013**, *9*, 2151−2155.

(20) Šimová, L.; Řezáč, J.; Hobza, P. Convergence of the Interaction Energies in Noncovalent Complexes in the Coupled-Cluster Methods Up to Full Configuration Interaction. *J. Chem. Theory Comput.* **2013**, *9*, 3420−3428.

(21) Dunning, T. H. Gaussian Basis Sets for Use In Correlated Molecular Calculations. I. The Atoms Boron Through Neon and Hydrogen. *J. Chem. Phys.* **1989**, *90*, 1007−1023.

(22) For a review see: Dunning, T. H.; Peterson, K. A.; Woon, D. E.; Basis Sets: Correlation Consistent Sets. In *Encyclopedia of Computational Chemistry (5 volumes)*; Schleyer, P. v. R., Eds.; Wiley: Chichester, U.K., 1998; Vol. *1*, pp 88−115. DOI: 10.1002/0470845015.cca053.

(23) Kendall, R. A.; Dunning, T. H.; Harrison, R. J. Electron Affinities of the First-Row Atoms Revisited. Systematic Basis Sets and Wave Functions. *J. Chem. Phys.* **1992**, *96*, 6796−6806.

(24) Woon, D. E.; Dunning, T. H. Gaussian Basis Sets for Use in Correlated Molecular Calculations. IV. Calculation of Static Electrical Response Properties. *J. Chem. Phys.* **1994**, *100*, 2975−2988.

(25) Kong, L.; Bischoff, F.; Valeev, E. Explicitly Correlated R12/F12 Methods for Electronic Structure. *Chem. Rev.* **2012**, *112*, 75−107.

(26) Hättig, C.; Klopper, W.; Köhn, A.; Tew, D. P. Explicitly Correlated Electrons in Molecules. *Chem. Rev.* **2012**, *112*, 4−74.

(27) Peterson, K. A.; Adler, T. B.; Werner, H.-J. Systematically Convergent Basis Sets for Explicitly Correlated Wavefunctions: The Atoms H, He, B−Ne, and Al−Ar. *J. Chem. Phys.* **2008**, *128*, 084102.

(28) Lopes Jesus, A. J.; Rosado, M. T. S.; Reva, I.; Fausto, R.; Eusébio, M. E. S.; Redinha, J. S. Structure of Isolated 1,4-Butanediol: Combination of MP2 Calculations, NBO Analysis, and Matrix-Isolation Infrared Spectroscopy. *J. Phys. Chem. A* **2008**, *112*, 4669−4678.

(29) MOLPRO is a package of *ab initio* programs written by Werner, H.-J.; Knowles, P. J.; Knizia, G.; Manby, F. R.; Schütz, M.; Celani, P.; Korona, T.; Lindh, R.; Mitrushenkov, A.; Rauhut, G.; et al., *MOLPRO* 2012.1; Department of Chemistry, University of Cardiff: Wales, U.K., 2012. For the current version, see http://www.molpro.net.

(30) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; et al. *Gaussian 09*, Revision C1; Gaussian, Inc.: Wallingford, CT, 2009. For the current version, see http://www.gaussian.com.

(31) Yousaf, K. E.; Peterson, K. A. Optimized Auxiliary Basis Sets for Explicitly Correlated Methods. *J. Chem. Phys.* **2008**, *129*, 184108.

(32) Yousaf, K. E.; Peterson, K. A. Optimized Complementary Auxiliary Basis Sets for Explicitly Correlated Methods: aug-cc-pVnZ Orbital Basis Sets. *Chem. Phys. Lett.* **2009**, *476*, 303−307.

(33) Adler, T. B.; Knizia, G.; Werner, H.-J. A Simple and Efficient CCSD(T)-F12 Approximation. *J. Chem. Phys.* **2007**, *127*, 221106.

(34) Knizia, G.; Adler, T. B.; Werner, H.-J. Simplified CCSD(T)-F12 Methods: Theory and Benchmarks. *J. Chem. Phys.* **2009**, *130*, 054104.

(35) Ten-no, S. Initiation of Explicitly Correlated Slater-Type Geminal Theory. *Chem. Phys. Lett.* **2004**, *398*, 56−61.

(36) Marchetti, O.; Werner, H. J. Accurate Calculations of Intermolecular Interaction Energies Using Explicitly Correlated Wave Functions. *Phys. Chem. Chem. Phys.* **2008**, *10*, 3400−3409.

(37) Marchetti, O.; Werner, H. J. Accurate Calculations of Intermolecular Interaction Energies Using Explicitly Correlated Coupled Cluster Wave Functions and a Dispersion-Weighted MP2 Method. *J. Phys. Chem. A* **2009**, *113*, 11580−11585 specifically eq. (8) there.

(38) Hariharan, P. C.; Pople, J. A. The Influence of Polarization Functions on Molecular Orbital Hydrogenation Energies. *Theor. Chem. Acc.* **1973**, *28*, 213−22.

(39) Raghavachari, K.; Binkley, J. S.; Seeger, R.; Pople, J. A. Self-Consistent Molecular Orbital Methods. XX. A Basis Set for Correlated Wave Functions. *J. Chem. Phys.* **1980**, *72*, 650−654.

(40) Rappoport, D.; Furche, F. Property-Optimized Gaussian Basis Sets for Molecular Response Calculations. *J. Chem. Phys.* **2010**, *133*, 134105.

(41) Grimme, S. Improved Second-Order Møller−Plesset Perturbation Theory by Separate Scaling of Parallel- and Antiparallel-Spin Pair Correlation Energies. *J. Chem. Phys.* **2003**, *118*, 9095−9102.

(42) For a physical interpretation of the SCS-MP2 method in terms of Feenberg scaling, see: Szabados, A. Theoretical Interpretation of Grimme's Spin-Component-Scaled Second Order Møller-Plesset Theory. *J. Chem. Phys.* **2006**, *125*, 214105.

(43) For a review, see: Grimme, S.; Goerigk, L.; Fink, R. F. Spin-Component-Scaled Electron Correlation Methods. *WIREs Comput. Mol. Sci.* **2012**, *2*, 886−906.

(44) DiStasio, R. A.; Head-Gordon, M. Optimized Spin-Component Scaled Second-Order Møller-Plesset Perturbation Theory for Intermolecular Interaction Energies. *Mol. Phys.* **2007**, *105*, 1073−1083.

(45) Fink, R. F. Spin-Component-Scaled Møller−Plesset (SCS-MP) Perturbation Theory: A Generalization of the MP Approach with Improved Properties. *J. Chem. Phys.* **2010**, *133*, 174113.

(46) Takatani, T.; Hohenstein, E. G.; Sherrill, C. D. Improvement of the Coupled-Cluster Singles and Doubles Method via Scaling Same- and Opposite-Spin Components of the Double Excitation Correlation Energy. *J. Chem. Phys.* **2008**, *128*, 124111.

(47) Pitoňák, M.; Rezac, J.; Hobza, P. Spin-Component Scaled Coupled-Clusters Singles and Doubles Optimized Towards Calculation of Noncovalent Interactions. *Phys. Chem. Chem. Phys.* **2010**, *12*, 9611.

(48) Perdew, J. P.; Schmidt, K. Jacob's Ladder of Density Functional Approximations for the Exchange-Correlation Energy. *AIP Conf. Proc.* **2001**, *577*, 1−20.

(49) Vosko, S. H.; Wilk, L.; Nusair, M. Accurate Spin-Dependent Electron Liquid Correlation Energies for Local Spin Density Calculations: A Critical Analysis. *Can. J. Phys.* **1980**, *58*, 1200−1211.

(50) Becke, A. D. Density-Functional Exchange-Energy Approximation with Correct Asymptotic Behavior. *Phys. Rev. A* **1988**, *38*, 3098−3100.

(51) Perdew, J. P.; Burke, K.; Ernzerhof, M. Generalized Gradient Approximation Made Simple. *Phys. Rev. Lett.* **1996**, *77*, 3865−3868. Erratum. *Phys. Rev. Lett.* **1997**, *78*, 1396.

(52) Adamo, C.; Barone, V. Exchange Functionals with Improved Long-Range Behavior and Adiabatic Connection Methods Without Adjustable Parameters: The mPW and mPW1PW Models. *J. Chem. Phys.* **1998**, *108*, 664−675.

(53) Perdew, J. P. In *Electronic Structure of Solids '91: Proceedings of the 75. WE-Heraeus-Seminar and 21st Annual International Symposium on Electronic Structure of Solids*; Ziesche, P., Eschrig, H., Eds.; Akademie Verlag: Berlin, 1991; p 11.

(54) Perdew, J. P.; Chevary, J. A.; Vosko, S. H.; Jackson, K. A.; Pederson, M. R.; Singh, D. J.; Fiolhais, C. Atoms, Molecules, Solids, and Surfaces: Applications of the Generalized Gradient Approximation for Exchange and Correlation. *Phys. Rev. B* **1992**, *46*, 6671−6687. Perdew, J. P.; Chevary, J. A.; Vosko, S. H.; Jackson, K. A.; Pederson, M. R.; Singh, D. J.; Fiolhais, C. Erratum. *Phys. Rev. B* **1993**, *48*, 4978−6687.

(55) Handy, N. C.; Cohen, A. J. Left-Right Correlation Energy. *Mol. Phys.* **2001**, *99*, 403−412.

(56) Perdew, J. P. Density-Functional Approximation for the Correlation Energy of the Inhomogeneous Electron Gas. *Phys. Rev. B* **1986**, *33*, 8822−8824.

(57) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti Correlation-Energy Formula into a Functional of the Electron Density. *Phys. Rev. B* **1988**, *37*, 785−789.

(58) Grimme, S. Semiempirical GGA-Type Density Functional Constructed with a Long-Range Dispersion Correction. *J. Comput. Chem.* **2006**, *27*, 1787−1799.

(59) Becke, A. D. Density-Functional Thermochemistry, V. Systematic Optimization of Exchange-Correlation Functionals. *J. Chem. Phys.* **1997**, *107*, 8554−8560.

(60) Hamprecht, F. A.; Cohen, A. J.; Tozer, D. J.; Handy, N. C. Development and Assessment of New Exchange-Correlation Functionals. *J. Chem. Phys.* **1998**, *109*, 6264−6271.

(61) Grimme, S. Accurate Description of van der Waals Complexes By Density Functional Theory Including Empirical Corrections. *J. Comput. Chem.* **2004**, *25*, 1463−1473.

(62) Grimme, S.; Ehrlich, S.; Goerigk, L. Effect of the Damping Function in Dispersion Corrected Density Functional Theory. *J. Comput. Chem.* **2011**, *32*, 1456−1465.

(63) Tao, J.; Perdew, J. P.; Staroverov, V. N.; Scuseria, G. E. Climbing the Density Functional Ladder: Nonempirical Meta−Generalized Gradient Approximation Designed for Molecules and Solids. *Phys. Rev. Lett.* **2003**, *91*, 146401.

(64) Becke, A. D. Density-Functional Thermochemistry. IV. A New Dynamical Correlation Functional and Implications for Exact-Exchange Mixing. *J. Chem. Phys.* **1996**, *104*, 1040−1046.

(65) Zhao, Y.; Truhlar, D. G. A New Local Density Functional for Main-Group Thermochemistry, Transition Metal Bonding, Thermochemical Kinetics, and Noncovalent Interactions. *J. Chem. Phys.* **2006**, *125*, 194101.

(66) Becke, A. D. Density-Functional Thermochemistry. III. The Role of Exact Exchange. *J. Chem. Phys.* **1993**, *98*, 5648−5652. This paper defines the B3 hybrid exchange functional.

(67) The first published reference to the "B3LYP" combination appears to be: Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. *Ab Initio* Calculation of Vibrational Absorption and Circular Dichroism Spectra Using Density Functional Force Fields. *J. Phys. Chem.* **1994**, *98*, 11623−11627.

(68) Adamo, C.; Barone, V. Toward Reliable Density Functional Methods Without Adjustable Parameters: The PBE0 Model. *J. Chem. Phys.* **1999**, *110*, 6158−6169.

(69) Xu, X.; Goddard, W. A. The X3LYP Extended Density Functional for Accurate Descriptions of Nonbond Interactions, Spin States, and Thermochemical Properties. *Proc. Natl. Acad. Sci.* **2004**, *101*, 2673−2677.

(70) Schmider, H. L.; Becke, A. D. Optimized Density Functionals From the Extended G2 Test Set. *J. Chem. Phys.* **1998**, *108*, 9624−9631.

(71) Grimme, S. Accurate Calculation of the Heats of Formation for Large Main Group Compounds with Spin-Component Scaled MP2 Methods. *J. Phys. Chem. A* **2005**, *109*, 3067−3077.

(72) Quintal, M. M.; Karton, A.; Iron, M. A.; Boese, A. D.; Martin, J. M. L. Benchmark Study of DFT Functionals for Late-Transition-Metal Reactions. *J. Phys. Chem. A* **2006**, *110*, 709−716.

(73) The TPSS0 functional, which uses TPSS correlation with a 25:75 mixture of Hartree−Fock like and TPSS exchange (rather than the 10:90 mixture in TPSSh) appears to have been introduced independently in the two previous references, as TPSS0 and TPSS25TPSS, respectively.

(74) Boese, A. D.; Martin, J. M. L. Development of Density Functionals for Thermochemical Kinetics. *J. Chem. Phys.* **2004**, *121*, 3405−3416.

(75) Zhao, Y.; Truhlar, D. G. The M06 Suite of Density Functionals for Main Group Thermochemistry, Thermochemical Kinetics, Non-covalent Interactions, Excited States, and Transition Elements: Two New Functionals and Systematic Testing of Four M06-Class Functionals and 12 Other Functionals. *Theor. Chem. Acc.* **2008**, *120*, 215−241.

(76) Zhao, Y.; Truhlar, D. G. Density Functionals with Broad Applicability in Chemistry. *Acc. Chem. Res.* **2008**, *41*, 157−167.

(77) Chai, J.-D.; Head-Gordon, M. Systematic Optimization Of Long-Range Corrected Hybrid Density Functionals. *J. Chem. Phys.* **2008**, *128*, 084106.

(78) Chai, J.-D.; Head-Gordon, M. Long-Range Corrected Hybrid Density Functionals with Damped Atom−Atom Dispersion Corrections. *Phys. Chem. Chem. Phys.* **2008**, *10*, 6615−6620.

(79) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. A Consistent and Accurate *Ab Initio* Parametrization of Density Functional Dispersion Correction (DFT-D) for the 94 Elements H-Pu. *J. Chem. Phys.* **2010**, *132*, 154104.

(80) Peverati, R.; Truhlar, D. G. Improving the Accuracy of Hybrid Meta-GGA Density Functionals by Range Separation. *J. Phys. Chem. Lett.* **2011**, *2*, 2810−2817.

(81) Yanai, T.; Tew, D. P.; Handy, N. C. A New Hybrid Exchange−Correlation Functional Using the Coulomb-Attenuating Method (CAM-B3LYP). *Chem. Phys. Lett.* **2004**, *393*, 51−57.

(82) Vydrov, O. A.; Scuseria, G. E. Assessment of a Long-Range Corrected Hybrid Functional. *J. Chem. Phys.* **2006**, *125*, 234109.

(83) Grimme, S. Semiempirical Hybrid Density Functional with Perturbative Second-Order Correlation. *J. Chem. Phys.* **2006**, *124*, 034108.

(84) Karton, A.; Tarnopolsky, A.; Lamère, J. F.; Schatz, G. C.; Martin, J. M. L. Highly Accurate First-Principles Benchmark Data Sets for the Parametrization and Validation of Density Functional and Other Approximate Methods. Derivation of a Robust, Generally Applicable, Double-Hybrid Functional for Thermochemistry and Thermochemical Kinetics. *J. Phys. Chem. A* **2008**, *112*, 12868−12886.

(85) Kozuch, S.; Gruzman, D.; Martin, J. M. L. DSD-BLYP: A General Purpose Double Hybrid Density Functional Including Spin Component Scaling and Dispersion Correction. *J. Phys. Chem. C* **2010**, *114*, 20801−20808.

(86) Kozuch, S.; Martin, J. M. L. DSD-PBEP86: In Search of the Best Double-Hybrid DFT with Spin-Component Scaled MP2 and Dispersion Corrections. *Phys. Chem. Chem. Phys.* **2011**, *13*, 20104−20107.

(87) Kozuch, S.; Martin, J. M. L. Spin-Component-Scaled Double Hybrids: An Extensive Search for the Best Fifth-Rung Functionals Blending DFT and Perturbation Theory. *J. Comput. Chem.* **2013**, *34*, 2327−2344.

(88) Grimme, S.; Antony, J.; Ehrlich, S.; Krieg, H. *DFT-D3 - A Dispersion Correction for Density Functionals, Hartree-Fock and Semi-Empirical Quantum Chemical Methods*; Mulliken Institute for Theoretical Chemistry, University of Bonn, Germany, 2012. For current version see: http://www.thch.uni-bonn.de/tc/index.php?section=downloads&subsection=DFT-D3.

(89) Pitoňák, M.; Neogrády, P.; Černý, J.; Grimme, S.; Hobza, P. Scaled MP3 Non-Covalent Interaction Energies Agree Closely with

Accurate CCSD(T) Benchmark Data. *ChemPhysChem* **2009**, *10*, 282–289.

(90) Sedlak, R.; Riley, K. E.; Řezáč, J.; Pitoňák, M.; Hobza, P. MP2.5 and MP2.X: Approaching CCSD(T) Quality Description of Non-covalent Interaction at the Cost of a Single CCSD Iteration. *ChemPhysChem* **2013**, *14*, 698–707.

(91) Vahtras, O.; Almlöf, J.; Feyereisen, M. W. Integral Approximations for LCAO-SCF Calculations. *Chem. Phys. Lett.* **1993**, *213*, 514–518.

(92) Kendall, R. A.; Früchtl, H. A. The Impact of the Resolution of the Identity Approximate Integral Method on Modern *Ab Initio* Algorithm Development. *Theor. Chem. Acc.* **1997**, *97*, 158–163 and references therein.

(93) Bernholdt, D. E. Scalability of Correlated Electronic Structure Calculations on Parallel Computers: A Case Study of the RI-MP2 Method. *Parallel Comput.* **2000**, *26*, 945–963 and references therein.

(94) Weigend, F.; Häser, M. RI-MP2: First Derivatives and Global Consistency. *Theor. Chem. Acta* **1997**, *97*, 331–340.

(95) Grev, R. S.; Schaefer, H. F. 6-311G Is Not of Valence Triple-Zeta Quality. *J. Chem. Phys.* **1989**, *91*, 7305–7306.

(96) Löwdin, P.-O. Twenty-Five Years of Sanibel Symposia: A Brief Historic and Scientific Survey. *Int. J. Quantum Chem.* **1985**, *28*, 19–37.