Accurate Conformational Energy Differences of Carbohydrates: A Complete Basis Set Extrapolation

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S *Supporting Information*

ABSTRACT: Correlated ab initio wave function calculations have been performed, using nonrelativistic frozen core MP2 complete basis set extrapolation model chemistry. The calculations have been made for three test sets of gas-phase saccharide conformations to provide reference values for their relative energies. The remaining correlation effects are estimated from frozen core coupled-cluster singles and doubles $[CCSD(T)]$ calculations. The test sets consist of 15 conformers of α- and β-D-allopyranose, 15 of 3,6-anhydro-4-O-methyl-D-galactitol, and four of β-D-glucopyranose. For each set, conformational energies varied by about 7 kcal/mol. These benchmark quality relative conformational energies are used to re-evaluate the performance of the best density functional methods for conformational analyses of saccharides. Our results show that the B3PW91 and PBE0 relative energies are systematically better than the B3LYP and M05-2X results. Overall, the functionals based on the exact constraints perform better for the relative energies of monosaccharide conformers than the empirically fitted functionals.

1. INTRODUCTION

This paper is a continuation of our recent study about the performance of various model chemistries on carbohydrate conformations.[1] We use three test sets that sample the lowest 6−7 kcal/mol energy range of conformation space. The AnGol15 test set contains 15 conformers of 3,6-anhydro-4-O-methyl-D-galactitol (cf. Figure 1). The GLC4 test set contains two low energy $^4C_1$ chair and two higher energy $^1C_4$ chair forms of β-D-glucopyranose. The ALL15 test set contains 13 $^4C_1$ structures (8 α- and 5 β-anomers, with *gg*, *gt*, and *tg* hydroxymethyl rotamers) and 2 $^1C_4$ conformers of α- and β-D-allopyranose.

In our previous paper[1] we tested nonempirical functionals, such as the local spin density approximation (LSDA), generalized gradient approximation GGA (e.g., Perdew−Burke−Ernzerhof, PBE)[2], and meta-GGA (e.g., Tao−Perdew−Staroverov−Scuseria, TPSS).[3] We also tested semiempirical global hybrid functionals like PBE0,[4,5] B3LYP,[6] and B3PW91[7,8] and a many-fit-parameter empirical hybrid functional, M05-2X.[9,10] Our results showed a good performance of M05-2X methods for the ALL15 and AnGol15 test sets. However, for the GLC4 test set, the PBE and several other functionals performed better than the M05-2X functional.[1]

Because the best density functionals might reach a considerable accuracy, the uncertainties in the reference relative energies for the conformational space of carbohydrates make the evaluation and ranking of the approximate methods uncertain. Monosaccharides are relatively large molecules (containing almost 100 electrons). Thus obtaining accurate relative energies requires a very large computational effort that uses a correlated wave function.

Calculations using the canonical MP2 method ($O(N)^5$ scaling of computer time with the size N) are such an effort. The slow convergence of the relative energies with the cardinal number of

the basis set also worsens the problem. An earlier canonical MP2 study[11] found that for alanine octapeptides, the basis set errors exceeded 4 kcal/mol when the augmented triple-ζ basis set was used.

The pseudospectral local MP2 (LMP2) approximation[12,13] of the canonical MP2 is considerably faster than MP2 and approaches linear scaling for large systems. Another possible advantage is that the LMP2 results are less affected by the basis set size. Even augmented double-ζ basis sets yielded reasonably accurate relative energies for peptides if the domain selection is based on the natural population analysis and natural localized molecular orbitals.[11,14] It was observed that this method yields more stable domains with respect to the basis set and geometry of peptides than the conventional method (for details see ref 11). However, LMP2 neglects dispersion-relevant double excitation terms, and a consistent domain selection is critically important for good relative energies of different conformers. We have found[1] that the LMP2/cc-pVTZ(−f) and MP2/aug-cc-pVTZ model chemistries give somewhat similar relative energies for the conformers in the GLC4 and ALL15 test sets. However, the agreement between LMP2 and MP2 results was considerably worse for larger basis sets and for the AnGol15 test set, possibly due to problems with the applied LMP2 domain selection method. In this paper we check whether this divergence between the LMP2 and MP2 methods persists at the basis set limit.

Finally, as the MP2 method misses a large part of the correlation energy, the more expensive CCSD(T) calculations ($O(N)^7$ scaling of computer time with the size N) might be necessary for improved relative energies. Recently Goerigk and
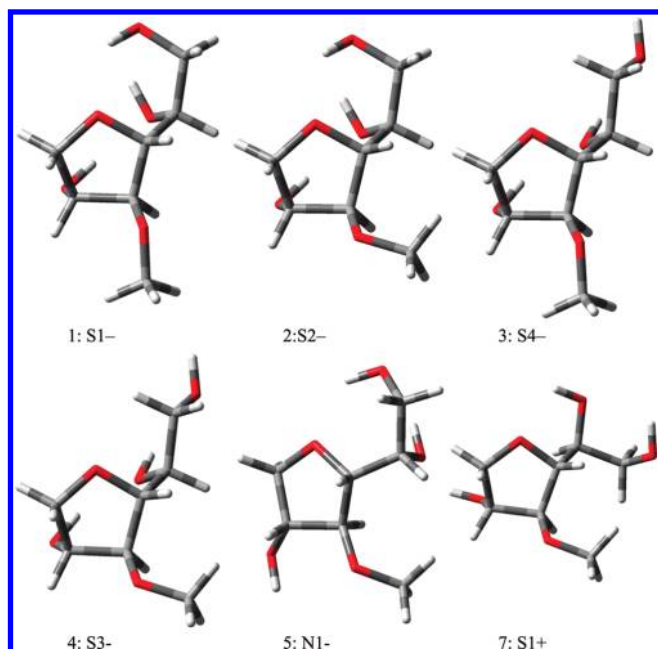
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Figure 1. The five lowest energy and the seventh S1+ conformers of the AnGol15 conformational space.

Grimme[15] performed high-level calculations for the AnGol15 and the GLC4 test sets (called the SCONF subset of the GMTKN24 test set). The MP2/complete basis set (CBS) limit was estimated from aug-cc-pVDZ and TZ energies. The differences between CCSD(T) and MP2 correlation energies for the AnGol15 test set were estimated with the cc-pVDZ basis set. The reference values for the GLC4 set were provided by one of us in a private communication (MP2/CBS with aug-cc-pVTZ and aug-cc-pVQZ; difference between CCSD(T)/cc-pVTZ and MP2/cc-pVTZ).[15]

In the current study we go further and perform calculations up to the MP2/cc-pV5Z model chemistry using the optimized B3LYP/6-31+G(d,p) geometries. For more accurate estimation of the relative energies we also include CCSD(T) results for the GLC4 test set. This allows the accuracy of our earlier reference data to be checked and we can replace the less accurate reference values.

We observed in our earlier study that our assessment of the performance of a given density functional theory (DFT) approximation might depend critically on the choice of the reference conformer (see Section 4.1). In this study we shall show how the choice of the reference conformer influences the accuracy of the CBS extrapolation. We shall select the conformer pairs for which the CBS extrapolation is particularly accurate, and we shall use these accurately known relative energies for the evaluation of the functionals. Given the new reference data, we re-evaluate the best DFT functionals.

2. METHODS

2.1. Complete Basis Set Extrapolation. We have performed frozen core MP2 calculations with cc-pVXZ ($X = 3-5$) and aug-cc-pVXZ ($X = 3-4$) correlation-consistent basis sets denoted as VXZ and AVXZ, respectively, in the remainder of the article, where X is the cardinal number of the correlation-consistent basis set. As these basis sets are expensive, we also tested a simplified AV3Z basis set. The aV3Z($-$df) basis set contains no diffuse and d functions for

H atoms and no f functions for C and O atoms. All calculations were performed with MOLPRO.[16]

The HF and the MP2 correlation complete basis set extrapolations were done separately. For a given conformer the MP2 total energy is composed from the HF and the MP2 correlation energy correction:

$$E_{MP2}(i) = E_{HF}(i) + E_{MP2corr}(i) \qquad (1)$$

For two-point extrapolations we use the following simple formula:

$$E_m[X-1, X] = E_m[X] + C_m[X-1, X](E_m[X] - E_m[X-1]) \qquad (2)$$

where $C_m[X-1, X]$ is the extrapolation coefficient for correlation-consistent basis sets, and m is the method, HF or MP2 correction for correlation. Note that different forms exist for two-point extrapolation, but all these formulas give the same $C_m[X-1, X]$ coefficient after fitting to the same reference data.

2.2. Extrapolation of the HF Energy. We do not discuss the various (inverse power law, exponential) forms of the fit equations here; more details are in ref 17. For the AV[3,4]Z extrapolation, the following $C_{HF}[X-1, X]$ coefficient can be derived from the $A + B/X^\alpha$ form:

$$C_{HF}[3, 4] = \frac{1}{\left(\dfrac{4}{3}\right)^\alpha - 1} = 0.274,$$

$$\text{rmsd} = 0.13 \text{kcal/mol} \qquad (3)$$

where $\alpha = 5.34$ is an effective decay exponent obtained by minimizing the root-mean-square deviation (rmsd) from the numerical HF $E_m[\infty]$ for the test set proposed by Jensen.[18]

Karton and Martin[17] have found that the $A + B/X^5$ extrapolation used in W1 theory gives reasonable results for AV[3,4]Z extrapolation. (Note that the fitted $\alpha = 5.34$ parameter in eq 3 is close to 5). But the $A + B/X^5$ extrapolation gives poor results for AV[4, 5]Z and AV[5, 6]Z extrapolation. Those results are worse than the simple AV5Z and AV6Z results, respectively.

For the more accurate AV[4,5]Z extrapolation, a different optimized coefficient was found:[17]

$$C_{HF}[4, 5] = \frac{1}{\left(\dfrac{5}{4}\right)^{8.74} - 1} = 0.166,$$

$$\text{rmsd} = 0.08 \text{kcal/mol} \qquad (4)$$

It was also observed[17] that the conventional three-point geometric extrapolation with the AV[3,4,5]Z basis sets gives inferior results compared to the simple AV5Z results.

The aug-cc-pV($n + d$)Z basis sets[19] contain an extra high-exponent d function for second-row atoms, in order to recover "inner polarization" effects.[20] For the aug-cc-pV($n + d$)Z basis sets ($n \geq 4$), a very similar $C_{HF}[4, 5]$ was found:[17]

$$C_{HF}[4, 5+d] = \frac{1}{\dfrac{5e^{9(\sqrt{5} - 2)}}{6} - 1} = 0.167 \qquad (5)$$

The optimized coefficients in eqs 3−5 might show some transferability, as comparison of eqs 4 and 5 shows some basis set independence. But in general such coefficients should be reoptimized for different test and basis sets, leading to various empirical coefficients.

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2.3. Extrapolation of the Correlation Energy. For frozen core MP2 or coupled cluster (CC) correlation energy, it was assumed that the basis set convergence follows an X^{-3} law with respect to the cardinal number X of the correlation-consistent basis sets.[21] The two-point CBS MP2 correction for correlation can be derived from the form $A + B/X$:[3]

$$C_{MP2corr}[3, 4] = \frac{1}{\left(\frac{4}{3}\right)^3 - 1} \approx 0.730 \quad \text{and}$$

$$C_{MP2corr}[4, 5] = \frac{1}{\left(\frac{5}{4}\right)^3 - 1} \approx 1.049 \quad (6)$$

Notice that L^{-3} and L^{-5} laws were found for the unlike- and the like-spin pairs for MP2 correlation energy, where L is the largest angular momentum in the basis set.[22] Even in these cases the basis set convergence follows an X^{-3} law. However, for the He—He interatomic potential, separate extrapolation of singlet and triplet pairs improves the results.[23] Notice also that the extrapolation formula in eq 2 is a linear combination of two energies. Consequently optimized geometries and transition structures can be obtained readily from linear combinations of gradients and Hessians.[24,25] The higher level correlation is estimated from the difference of MP2 and CCSD(T) relative energies calculated with a moderately large AV3Z(−df) basis set. This simplification is necessary as the CCSD(T)/AV3Z calculations are prohibitively expensive for monosaccharides. It is assumed that this procedure gives reasonable CCSD(T)/ CBS relative energy estimations.

3. RELATIVE ENERGIES

The relative energies are defined as the difference between the energy of the ith conformer and the energy of an r reference conformer $(i \neq r)$ using the given model chemistry:

$$\Delta E_{model}(i, r) = E_{model}(i) - E_{model}(r) \quad (7)$$

Note that this way the large total energy terms translate into much smaller reference relative energy terms.

The relative energy difference for the ith conformer between two model chemistries, modelA and modelB, is:

$$\Delta\Delta E_{modelA-modelB}(i, r) = \Delta E_{modelA}(i, r) - \Delta E_{modelB}(i, r) \quad (8)$$

where the difference between the two models can be in the basis set or in the treatment of electron correlation. For the present paper the relative energy difference between correlated (MP2 or CCSD(T)) and HF methods is particularly important and denoted as $\Delta E_{MP2corr}(i, r)$. To obtain MP2/ CBS relative energies, we sum CBS estimations of the HF and MP2corr:

$$\Delta E_{MP2/CBS}(i, r) = \Delta E_{MP2corr/CBS}(i, r) + \Delta E_{HF/CBS}(i, r) \quad (9)$$

The model chemistry and reference conformer dependent mean deviation (MD) is defined as

$$MD_{model\ A\text{-}model\ B}(r) = \frac{1}{n-1} \sum_{i=1}^{n} \Delta\Delta E_{model\ A\text{-}model\ B}(i, r) \quad (10)$$

and the model and reference conformer dependent mean absolute deviation (MAD) is defined as:

$$MAD_{model\ A\text{-}model\ B}(r) = \frac{1}{n-1} \sum_{i=1}^{n} |\Delta\Delta E_{model\ A\text{-}model\ B}(i, r)| \quad (11)$$

Within a given test set of conformers, the mean deviation and the mean deviation between the two compared models depend on the choice of the reference conformer. This makes the evaluation and comparison of model chemistries noninvariant under the choice of the reference conformer. The range of the relative difference (RRD) = max $\Delta\Delta E$ − min $\Delta\Delta E$ can be used as an invariant measure of the model chemistry dependent but reference conformer independent relative energies, where max $\Delta\Delta E$ is the most positive and min $\Delta\Delta E$ is the most negative relative energy difference.

For specific groups of conformers, accurate relative energies can be obtained at a considerably reduced cost, if one or more of the following conditions are fulfilled:

(1) The basis set dependence of the relative HF energy is less than 0.1 kcal/mol: $|\Delta E_{HF/V4Z}(i, r) - \Delta E_{HF/V3Z}(i, r)| < 0.1$ kcal/mol.
(2) The relative correlation energy is small: $|\Delta E_{MP2corr/V3Z}(i, r)| < 0.05$ kcal/mol.
(3) The basis set dependence of the relative correlation energy is less than 0.1 kcal/mol: $|\Delta E_{MP2corr/V4Z}(i, r) - \Delta E_{MP2corr/V3Z}(i, r)| < 0.1$ kcal/mol.

The consequence of fulfilling conditions 1 and 2 is that the MP2/CBS relative energies can be estimated from HF/V3Z results with a small error. This is the basis of the earlier observations that HF relative energies are surprisingly good for several test sets. But this good performance is occasional and based on special structural similarity, as we shall show in this paper. Fulfillment of condition 3 alone makes the MP2/V3Z results a good estimation of the MP2/CBS relative energies.

4. RESULTS AND DISCUSSION

4.1. 3,6-Anhydro-4-O-methyl-D-galactitol Conformers. The schematic representations of the torsion angles in the 3,6-anhydro-4-O-methyl-D-galactitol (AnGol) and the full conformational space can be found in refs 1 and 26. AnGol has a flexible five-membered ring and six exocyclic torsion angles. The two main stable conformations of the five-membered ring were denoted as North (N) (Cremer—Pople puckering[27] parameter $\phi \approx 250-320°$) and South (S) ($\phi \approx 120°$). The 15 conformers numbered from 1 to 15 were designated as S1−, S2−, S4−, S3−, N1−, N2−, S1+, S2+, N3−, N1+, S4+, S3+, N3+, N2+, and N4+, respectively in refs 1 and 26. The positions of the exocyclic torsions of six conformers are shown in Figure 1. These torsions are explained in detail in the Supporting Information. This conformational space differs from the typical monosaccharide conformational space of allopyranose or glucopyranose, as also shown in the Supporting Information.

Traditionally the most stable conformer is selected as reference. Figure 2 shows the dependence of the HF relative energies on the cardinal number X of the VXZ basis sets if S1− is the reference conformer (the relevant total energies are shown in the Supporting Information). Condition 1 is fulfilled for the relative HF energies of the first two conformers, S1− and S2−, and the
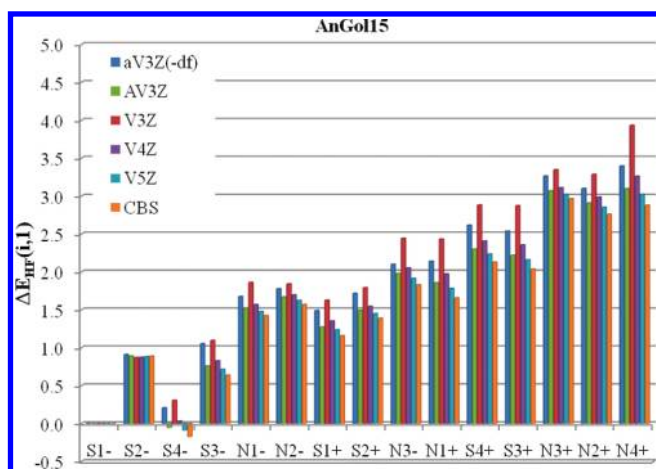
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Figure 2. The HF relative energies, $\Delta E_{HF}(i, 1)$ (kcal/mol) of the members of the AnGol15 test set, calculated with basis sets with cardinal numbers from 3 to 5, compared to the most stable S1— conformer (no. 1).

Figure 3. The HF relative energy differences, $\Delta\Delta E_{HF}(i, 1)$ (kcal/mol), between the elements of the AnGol15 test set, compared to the most stable S1— conformer (no. 1). $E(VXZ) - E(VX + 1Z)$ means the difference between the relative energies for cardinal number of X.

Figure 4. The HF relative energy differences, $\Delta\Delta E_{HF}(i, 3)$ (kcal/mol), between the elements of the AnGol15 test set, compared to the S4— conformer (no. 3).

Figure 5. The MP2 relative correlation energies, $\Delta E_{MP2corr}(i, 1)$ (kcal/mol), of the elements of the AnGol15 test set, calculated with basis sets with cardinal numbers from 3 to 5, compared to the most stable S1— conformer (no. 1).
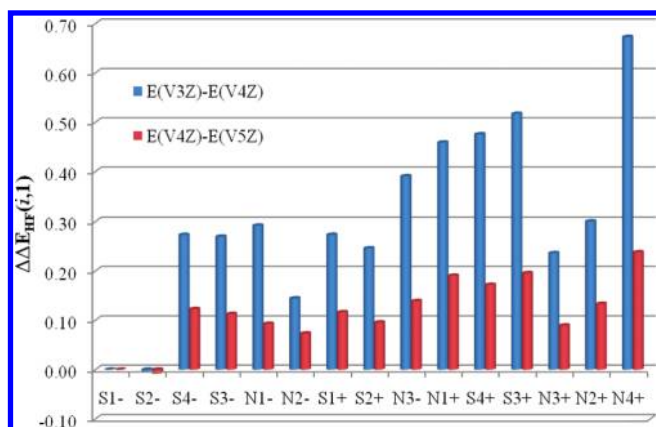
HF/V3Z result is practically converged. The figure also shows that this is not true for the other 13 conformers.

Figure 3 shows how the HF relative energy differences, $\Delta\Delta E_{HF}(i, 1)$ (kcal/mol) change with increase of the cardinal number of the basis set by one, if the S1— conformer is the reference. This figure shows how small is the basis set dependence of the HF relative energies for S1— and S2— conformers. However, this is not true for the other conformers; the largest difference can be observed for N4+ conformer. The figure also shows how much better the V4Z basis set is than the V3Z (RRD = 0.22 vs 0.68 kcal/mol, respectively).

Figure 4 shows how the basis set convergence changes if we choose the third (S4—) conformer as reference. The relative HF energies of S4—, S3—, and S1+ conformers converge parallel with the increase of the basis set, and the relative HF energies N1—, S2+, N3+, and N2+ conformers behave very similarly within 0.1 kcal/mol. The sets {S1—, S2—} and { S4—, S3—, S1+, N1—, S2+, N3+, N2+} fulfill criterion 1. Thus even the relative energies calculated with V3Z basis set are practically converged. A similar observation can be made for the {N1+, S4+, S3+} set.
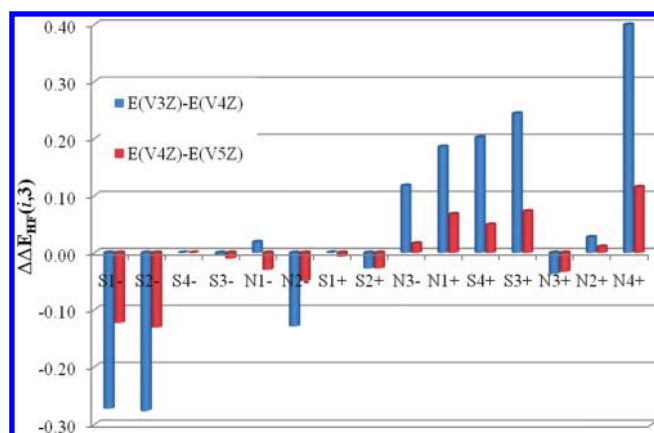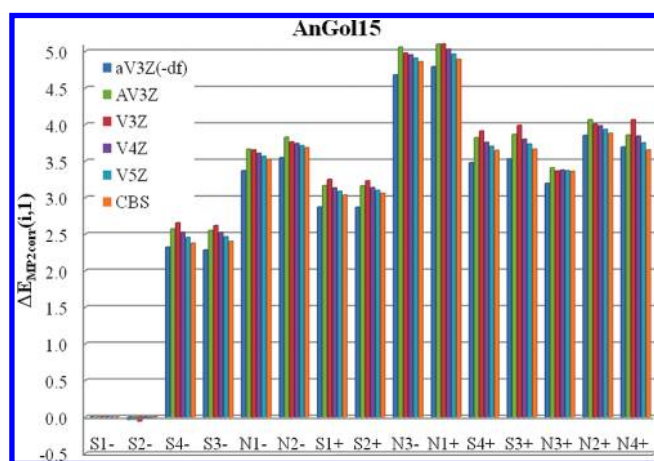
Figure 5 shows the AVXZ and VXZ (X = 3—5) basis set dependence of the relative MP2 correlation energies compared to the lowest energy S1— conformer. Comparison of the Figures 2 and 5 shows the important contribution of the MP2 correlation energy to the relative energies. The HF/V5Z relative energy differences span a range of 3 kcal/mol, while the MP2corr/V5Z energy differences span almost 5 kcal/mol. Another, somewhat surprising observation is that the HF relative energies converge in bigger steps than that of the MP2corr relative energies. Consequently for several conformers the larger part of the error of MP2/V3Z relative energy comes from the HF error. So the convergence of the HF relative energies is particularly important for these conformers. This again depends on the choice of the reference conformer (cf. Figures 3, 4, 6, and 7). The results show that there is almost no difference between the MP2 relative correlation energies of S1— and S2— conformers (conditions 1 and 2 are fulfilled). This makes the $\Delta E_{MP2/CBS}(2, 1) \approx \Delta E_{HF/V3Z}(2, 1)$. Thus for these two conformers the inexpensive HF/V3Z relative energy (0.87 kcal/mol) is close to the very expensive MP2/CBS[4, 5] relative energy (0.88 kcal/mol). Notice that the CCSD-(T)/CBS relative energy is 0.83 kcal/mol,[15] thus $\Delta E_{CCSD(T)/CBS}(2,1) \approx \Delta E_{HF/V3Z}(2, 1)$, with the negligible error of 0.05 kcal/mol.

Figure 6. The MP2 correlation relative energy differences, $\Delta\Delta E_{\text{MP2corr}}(i, 1)$ (kcal/mol), between the elements of the AnGol15 test set, compared to the most stable S1− conformer (no. 1). $E(VXZ) - E(VX + 1Z)$ means the difference between the relative energies for cardinal number of X.
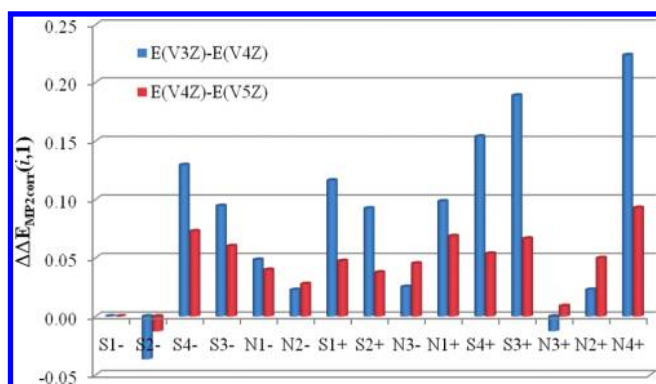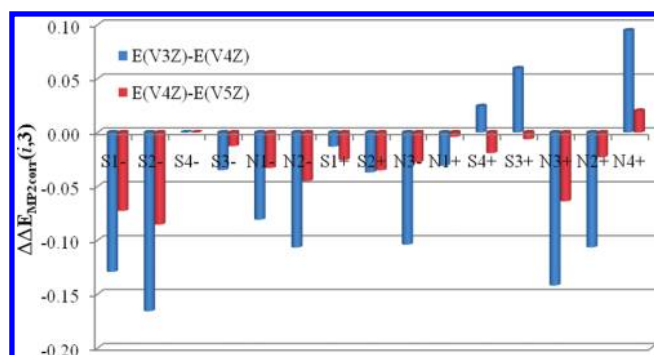

Figure 7. The MP2 correlation relative energy differences, $\Delta\Delta E_{\text{MP2corr}}(i, 3)$ (kcal/mol), between the elements of the AnGol15 test set, compared to the S4− conformer (no. 3). $E(VXZ) - E(VX + 1Z)$ means the difference between the relative energies for cardinal number of X.

Figure 6 shows that the relative MP2 correlation energy is practically basis set independent for S1− and N3+ (1 and 13) conformers. Thus condition 3 is fulfilled, and this makes the $\Delta E_{\text{MP2corr/CBS}}(13, 1) = \Delta E_{\text{MP2corr/V3Z}}(13, 1) = 3.36$ kcal/mol. As condition 1 is not valid, we have to calculate the HF/CBS energy: $\Delta E_{\text{MP2/CBS}}(13, 1) \approx \Delta E_{\text{MP2corr/V3Z}}(13, 1) + \Delta E_{\text{HF/CBS}}(13, 1)$. Figure 6 also shows that condition 3 is also valid for N1−, N2−, N3−, and N2+ (5, 6, 9, and 14) conformers and $|\Delta E_{\text{MP2corr/CBS}}(i, 1) - \Delta E_{\text{MP2corr/V3Z}}(i, 1)| < 0.13$ kcal/mol for these conformers. This condition makes the MP2corr/CBS extrapolation quite reliable.

Figure 7 shows that the relative MP2 correlation energies of the S4−, S3−, S1+, S2+, N1+, and S4+ (3, 4, 7, 8, 10, and 11) conformations also fulfill condition 3, making MP2corr/CBS extrapolation very accurate within this subset.

Table 1 summarizes the MP2 and CCSD(T) results and statistics for the relative energies compared to S1− conformer. We use CCSD(T)/CBS results[15] as reference. The MP2/CBS[3, 4, 5] uses the conventional three point geometric extrapolation formula for HF basis set limit. The MP2/CBS[4, 5] uses the HF limits obtained from eq 4. Both extrapolations use the two point MP2corr/CBS[4, 5] (cf. eq 6). The MP2/CBS[4, 5] results are closer to the MP2/V5Z and CCSD(T)/CBS results. We have also performed an MP2/CBS[A3, A4] extrapolation using eqs 3 and 6. This extrapolation uses AV3Z and AV4Z basis sets, and it gives particularly good agreement with the MP2/V5Z results. The economical 6-311+G-(d,p) basis set used in earlier studies[26] gives the largest basis set error. The simplified aV3Z(−df) basis set shows a particularly good performance due to the compensation of the HF and MP2 errors (cf. Figures 2 and 5); however, such an error compensation is unreliable as we shall show in Section 4.3. The diffuse functions added to the triple-ζ basis sets of the oxygen atoms are essential for the correct description of the electron densities around the oxygen atoms (lone pairs) and the O−H···O interactions. However, on the hydrogen atoms the diffuse functions have a negligible effect on the relative energies.

The results show that for the AnGol15 test set, the LMP2 and MP2 results diverge at the basis set limit (cf. Table S3 in the Supporting Information). This is in agreement with our previous observation of a considerable difference between the MP2 and LMP2/AV3Z relative energies for these conformers.[1] Similar problems were noticed with the LMP2 implementation in the JAGUAR program.[28]

Finally we summarize the most accurately known relative energies in Table 2 for various reference conformers. Analysis of the results shows the excellent performance of the smallest aV3Z(−df) basis set for these conformer pairs and the almost perfect agreement between MP2/V5Z, CBS[A3, A4], and CBS-[4, 5] results (MAD = 0.03 kcal/mol). The MP2 and CCSD(T) results also agree well statistically (MAD = 0.1 kcal/mol). The largest CCSD(T) correction (about 0.2 kcal/mol) to the MP2 can be found for the relative energies of {13, 1}, {10, 3} and {13, 14} conformer pairs.

4.2. β-D-glucopyranose Conformers.

The GLC4 test set is composed of two low-energy $^4C_1$ conformers (1 and 2) and two $^1C_4$ conformers (3 and 4) of β-D-glucopyranose, as shown in Figure 8. These four conformers were used for testing KS-DFT functionals before.[29,30] In our previous work,[1] we used the MP2/aV3Z(−df)//B3LYP/6-31+G(d,p) model chemistry as a reference (cf. Table 3).

The GLC4 test set is an interesting example for a situation in which the less stable $^1C_4$ conformer has stronger stabilizing electron correlation effects than the most stable $^4C_1$ conformer. This situation is very different from that of observed for the AnGol15 test set in which the electron correlation effects mostly destabilize the higher energy conformers (cf. Figure 5). If one unites the AnGol15 and GLC4 test sets, the opposite errors from incorrect treatment of the electron correlation might cancel, and the results might improve statistically but not in reality. We treat the two test sets separately.

It was observed earlier that the double-ζ polarized (DZP) basis set gives surprisingly good HF relative energies for $^1C_4$ and $^4C_1$ conformers of β-D-glucopyranose[29,30] and very poor MP2 relative energies. From our results it is clear that the origin of these good HF/DZP results is a large, 6−7 kcal/mol basis set error that erroneously stabilizes the $^1C_4$ conformers. The opposite exchange−correlation effects might systematically compensate each other[29,30] and help the semilocal DFT approximations to give reasonable results.

In Table 3 we show our highest level CCSD(T)/CBS estimations of the relative energies. These were calculated from MP2/CBS[4, 5] and CCSD(T) correction to the MP2/V3Z(−df) relative energies. This correction stabilizes the $^1C_4$ conformers by about 0.2−0.3 kcal/mol compared to the reference conformer. The results in Table 3 show again the surprisingly good performance of the least expensive MP2/aV3Z(−df) model chemistry (MAD = 0.2 kcal/

Table 1. Relative Energies of AnGol Conformers (kcal/mol), Compared to S1− Conformer Calculated with MP2, and CCSD(T) Methods, Various Basis Sets, and CBS Extrapolations[a]

		MP2						CCSD(T)
no.	conformer	6-311+G(d,p)[b]	aV3Z(−df)[b]	AV3Z[c]	V5Z[c]	CBS[3, 4, 5][d]	CBS[4, 5][e]	CBS[f]
1	S1−	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	S2−	1.05	0.87	0.85	0.87	0.87	0.88	0.83
3	S4−	2.11	2.53	2.52	2.36	2.19	2.27	2.60
4	S3−	3.07	3.34	3.31	3.18	3.03	3.10	3.37
5	N1−	5.15	5.05	5.18	5.04	4.96	4.98	4.87
6	N2−	5.51	5.32	5.50	5.34	5.23	5.29	5.18
7	S1+	4.23	4.36	4.44	4.32	4.19	4.25	4.47
8	S2+	4.54	4.59	4.66	4.55	4.45	4.49	4.68
9	N3−	6.91	6.78	7.04	6.82	6.70	6.75	6.69
10	N1+	6.90	6.93	7.00	6.75	6.54	6.64	6.75
11	S4+	6.05	6.09	6.12	5.94	5.78	5.85	6.08
12	S3+	5.99	6.07	6.09	5.89	5.71	5.79	6.05
13	N3+	6.78	6.46	6.48	6.39	6.33	6.37	6.17
14	N2+	7.05	6.95	6.98	6.79	6.63	6.71	6.75
15	N4+	7.10	7.09	6.96	6.77	6.55	6.64	6.71
MD		0.09	0.09	0.14	−0.01	−0.15	−0.08	
MAD		0.25	0.13	0.16	0.13	0.19	0.16	

[a] Mean deviation, MD, and mean absolute deviation, MAD, compared to CCSD(T)/CBS; see eqs 9 and 10. [b] Ref 1. [c] This work. [d] This work: HF/CBS[3, 4, 5] + MP2/CBS[4, 5]. [e] This work: HF/CBS[4, 5] + MP2/CBS[4, 5]. [f] Ref 15.

mol). This confirms that our earlier reference[1] is relatively good, but it cannot distinguish between KS-DFT functionals with small errors. Our results show that the more expensive MP2/V3Z and AV3Z models perform worse (MAD = 1.28 and 0.27 kcal/mol, respectively). These results support our earlier observations about the particular importance of the diffuse functions on the oxygen atoms (cf. O−H···O interactions) and their unimportance for the hydrogen atoms. The CBS[A3, A4] limit results agree particularly well again with the almost converged V5Z results. The conventional three-point geometric extrapolation formula for HF combined with a two-point MP2corr/CBS[4, 5] extrapolation, annotated as CBS-[3, 4, 5] in Table 3, shows again worse agreement with the MP2/V5Z and CCSD(T)/CBS results than the CBS[4, 5] extrapolation. There is a slight disagreement between our results and the previous CCSD(T)/CBS[15] estimation of the relative energies (MAD = 0.07 kcal/mol) because here we used the MP2/CBS [4, 5] estimation that was not available earlier.

4.3. D-Allopyranose Conformers. For the ALL15 test set[1] we selected 15 optimized B3LYP/6-31+G(d,p) conformers out of 102 recently published α- and β-D-allopyranose conformers.[31] The test set includes 13 $^4C_1$ conformers (8 α- and 5 β-anomers, with gg, gt, and tg hydroxymethyl rotamers), one α- and one β-$^1C_4$ conformer. The first, low-energy reference conformer is the $^4C_1$ α-D-allopyranose denoted as conformer 1 in Figure 9. Ref 1 gives a detailed description of the ring conformations, the anomers, and the exocyclic torsional angles. This test set is particularly suitable for demonstrating the importance of electron correlation for anomeric effects and ring conformations.

In our previous paper[1] we chose the MP2/aV3Z(−df) relative energies as reference for the ALL15 test set. The results in Table 4 show a reasonable performance of the MP2/aV3Z(−df) model chemistry (MAD = 0.2 kcal/mol, RRD = 0.8 kcal/mol). The error compensation of the aV3Z(−df) basis set is less

efficient for the ALL15 conformers than it was for the AnGol15 conformers. Because of this, our earlier reference[1] is not suitable to correctly judge the performance of the functionals with small 0.2−0.5 kcal/mol deviations. The MP2/AV3Z relative energies are better (MAD = 0.1 and RRD = 0.4 kcal/mol), and the MP2/V5Z relative energies are very well converged. Consequently the MP2/CBS[4, 5] relative energies are reliable within 0.1 kcal/mol.

Conditions 1 and 2 are valid for the subset of {1, 8, 15}; thus even the HF/V4Z model chemistry gives converged relative energies. For the subsets of the conformers {1, 4, 5, 7, 8, 10, 14, 15} and {2, 6, 9, 11, 12} the condition 3 is valid. For these subsets even the MP2/AV3Z relative energies are well converged (cf. Table 4).

According to the HF/CBS results the most stable conformer is 3 (β-$^4C_1$) (cf. Figure 9) and $\Delta E_{HF/CBS}(3, 1) = -2.63$ kcal/mol. The HF method erroneously stabilizes the β anomers by about 2.8−3.3 kcal/mol (cf. conformers 2, 3, and 6 in Table 4; the HF energies can be found in the Supporting Information). The MP2 electron correlation effects stabilize the α anomers and make conformer 1 (α-$^4C_1$) the most stable (cf. Table 4). This is another example of the stabilizing correlation effects (cf. the GLC4 test set).

5. EVALUATION OF THE DENSITY FUNCTIONAL RESULTS

The most stable conformers of the AnGol15, GLC4, and ALL15 conformational space are special in the gas phase. In these conformers the O−H···O interactions show stabilizing cooperative effects. Overestimation of these stabilizing effects makes the first conformer too stable compared to the other conformers and leads to too-large relative energies. Underestimation of these stabilization effects leads to too-small relative energies and thus negative deviations from the accurate relative energies. The GLC4 test set is an interesting counter example: the less

Table 2. Well Converged Relative Energies (kcal/mol) of Selected AnGol Conformers (Conformer *i*), Compared to Various Reference Conformers Calculated with MP2, and CCSD(T) Methods and Various Basis Sets and CBS Extrapolations[a]

conformers		MP2				CCSD(T)
i	reference	aV3Z(−df)[b]	V5Z[b]	CBS[A3, A4][c]	CBS[4, 5][d]	CBS[e]
2	1	0.87	0.87	0.88	0.88	0.83
5	1	5.05	5.04	5.03	4.98	4.87
6	1	5.32	5.34	5.35	5.29	5.18
9	1	6.78	6.82	6.82	6.75	6.69
13	1	6.46	6.39	6.38	6.37	6.17
14	1	6.95	6.79	6.81	6.71	6.75
5	2	4.17	4.17	4.16	4.11	4.04
6	2	4.45	4.46	4.47	4.42	4.34
9	2	5.91	5.95	5.95	5.87	5.86
13	2	5.59	5.52	5.51	5.49	5.34
14	2	6.08	5.91	5.94	5.83	5.92
4	3	0.81	0.81	0.83	0.83	0.77
7	3	1.83	1.96	2.02	1.99	1.87
8	3	2.05	2.19	2.26	2.23	2.08
10	3	4.40	4.38	4.40	4.38	4.15
11	3	3.56	3.57	3.62	3.59	3.48
7	4	1.02	1.14	1.20	1.16	1.11
8	4	1.25	1.37	1.44	1.40	1.31
10	4	3.59	3.57	3.57	3.55	3.38
11	4	2.76	2.76	2.80	2.76	2.72
6	5	0.28	0.30	0.32	0.31	0.31
9	5	1.74	1.78	1.79	1.77	1.82
13	5	1.42	1.35	1.35	1.38	1.30
14	5	1.91	1.74	1.78	1.73	1.88
9	6	1.46	1.49	1.47	1.46	1.51
13	6	1.14	1.05	1.03	1.07	0.99
14	6	1.63	1.45	1.46	1.42	1.58
8	7	0.22	0.23	0.24	0.24	0.20
10	7	2.57	2.42	2.38	2.39	2.27
11	7	1.73	1.62	1.60	1.60	1.61
10	8	2.35	2.20	2.14	2.15	2.07
11	8	1.51	1.39	1.36	1.36	1.41
13	9	−0.32	−0.43	−0.44	−0.38	−0.52
14	9	0.17	−0.04	−0.01	−0.04	0.06
11	10	−0.84	−0.81	−0.78	−0.79	−0.67
14	13	0.49	0.40	0.43	0.34	0.58
MD		0.09	0.05	0.06	0.04	
MAD		0.12	0.10	0.10	0.10	

[a] Mean deviation, MD, and mean absolute deviation, MAD, compared to CCSD(T)/CBS; see eqs 9 and 10. [b] This work. [c] This work: HF/CBS[A3, A4] + MP2/CBS[A3, A4], where A means augmented basis set. [d] This work: HF/CBS[4, 5] + MP2/CBS[4, 5]. [e] Ref 15.
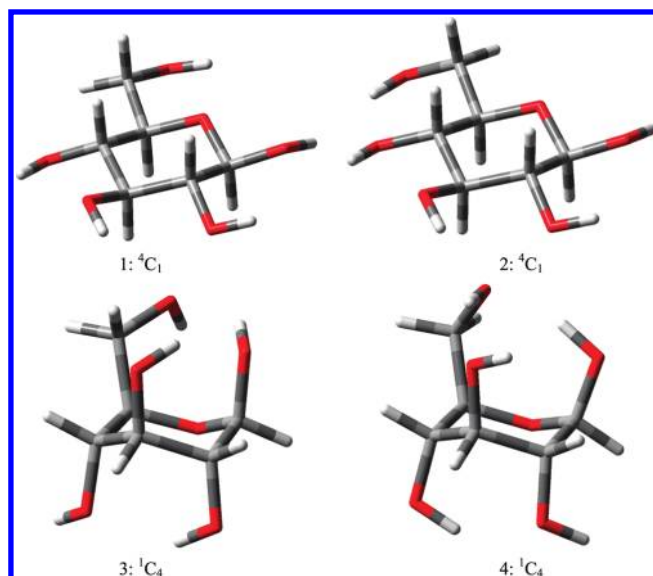

**Figure 8.** The four conformers of the GLC4 test set.

LSDA, but the relative conformational energies might remain statistically too large (mean deviation is smaller but positive) for the AnGol15 and ALL15 test sets.[1] For such (meta-)GGA functionals an empirical dispersion correction does not improve the results. Global mixing of the (meta-) GGAs with exact exchange might further improve the results by reducing overestimation of the relative energies, thus shifting the mean deviation close to zero. A sufficiently large exact exchange fraction might even lead to underestimation of the stabilizing correlation effects. Such errors of the global hybrid functionals can be efficiently corrected by a simple and quick empirical dispersion correction, as will be discussed later in this section.

To illustrate these tendencies, Figure 10 shows the AnGol15 $\Delta\Delta E_{\mathrm{modelA-modelB}}(i, 1)$ relative energy differences for modelA = M05-2X, B3LYP, B3PW91, estimated CCSD(T)/CBS, PBE, and TPSS and for modelB = MP2/CBS[4, 5]. All the DFT results are from ref 1, and the estimated CCSD(T)/CBS results are from ref 15. In the DFT calculations the 6-311+G(d,p) basis set and the B3LYP/6-31+G(d,p) geometries were used. PBE and TPSS give excellent relative energies for the N1−, N2−, and N3− conformers but overestimate the relative energies of the S4−, S3−, S1+, and S2+ conformers. Interestingly the CCSD-(T)/CBS, PBE, TPSS show qualitatively similar deviations from the MP2/CBS relative energies (cf. Figure 10). The opposite error occurs for B3LYP relative energies leading to serious underestimation of the relative energies of the N1−, N2−, and N3− conformers (cf. Figure 10). The mean absolute deviations and the ranges of the relative differences are similar for B3LYP, PBE, and TPSS (MAD = 0.5 kcal/mol, RRD = 1.5 kcal/mol). Notice that PBE and TPSS perform better than B3LYP if compared to CCSD(T)/CBS. The B3PW91 results are the best (MAD = 0.4 kcal/mol), but they show the same error pattern as the other three functionals (cf. the large RRD = 1.6 kcal/mol). The only functional that shows a different error pattern is the M05-2X (MAD = 0.4 kcal/mol, RRD = 1.0 kcal/mol). We have observed that different implementation of the M05-2X functional leads to worse results, and thus further study is required. The order of the functionals if compared to the CCSD(T)/CBS results is from best to worse: B3PW91, PBE = M05-2X, and

stable $^1C_4$ conformer has stronger stabilizing electron correlation effects than the most stable $^4C_1$ conformer.

Our previous study showed[1] that LSDA strongly overestimates and the HF method strongly underestimates these stabilization effects. The GGAs and meta-GGAs improve on the

Table 3. Relative Energies of GLC4 β-D-Glucose Conformers (kcal/mol), Compared to The Most Stable $^4C_1$ Conformer Calculated with MP2, and CCSD(T) Methods, Various Basis Sets, and CBS Extrapolations[a]

no.	ring conformation	MP2								CCSD(T)	
		aV3Z(−df)[b]	V3Z[c]	AV3Z[c]	V5Z[c]	CBS[3, 4][c]	CBS[A3, A4][c]	CBS[3, 4, 5][d]	CBS[4, 5][e]	CBS[f]	CBS[c]
1	$^4C_1$	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	$^4C_1$	0.38	0.06	0.28	0.28	0.30	0.26	0.31	0.30	0.27	0.30
3	$^1C_4$	5.76	4.30	5.68	6.14	6.25	6.12	6.40	6.33	5.92	6.01
4	$^1C_4$	5.10	3.47	4.90	5.34	5.43	5.35	5.65	5.57	5.29	5.38
MD		−0.14	−1.28	−0.27	0.03	0.10	0.02	0.23	0.17	−0.07	
MAD		0.20	1.28	0.27	0.06	0.10	0.06	0.23	0.17	0.07	

[a] Mean deviation, MD, and mean absolute deviation, MAD, compared to CCSD(T)/CBS; see eqs 9 and 10. [b] Ref 1. [c] This work. [d] This work: HF/CBS[3, 4, 5] + MP2/CBS[4, 5]. [e] This work: HF/CBS[4, 5] + MP2/CBS[4, 5]. [f] Ref 15.
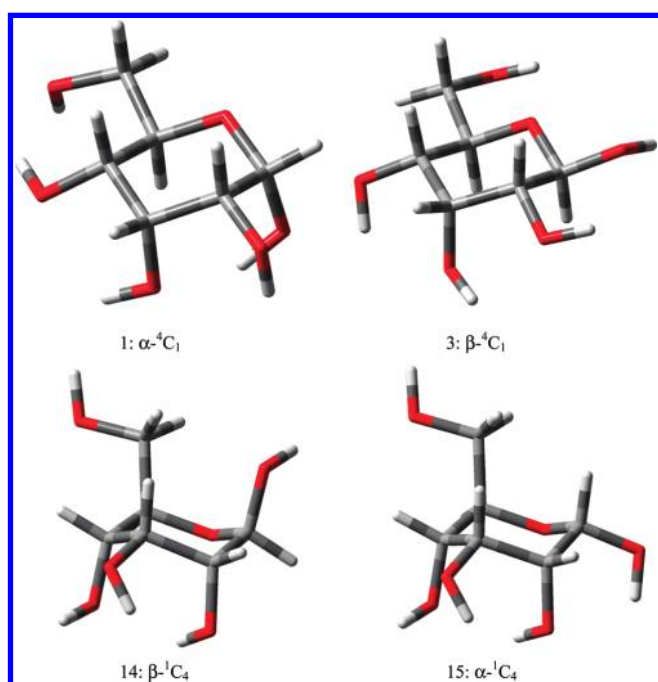
Figure 9. Four selected conformers of the ALL15 test set (conformers 1, 3, 14, and 15) representing the α and β anomers of $^4C_1$ and $^1C_4$ hexapyranose rings.

TPSS = B3LYP (MAD = 0.3, 0.4, 0.4, 0.6, and 0.6 kcal/mol, respectively).

We have also compared the DFT results to the particularly accurate relative energies shown in the Table 2. For these conformer pairs the PBE results show the best agreement with the reference (MAD = 0.3 kcal/mol), closely followed by TPSS and M05-2X results. The B3LYP results agree the worst (MAD = 0.6 kcal/mol).

For the three relative energies of the GLC4 test set, the global hybrid PBE0 and B3PW91 functionals perform equally well (MAD = 0.3 kcal/mol), while B3LYP is somewhat worse (MAD = 0.5 kcal/mol). Notice that the large overbinding basis error in the HF/DZP results helps to obtain reasonable results. The M05-2X performs the worst (MAD = 0.8 kcal/mol). In all calculations the 6-311+G(d,p) basis set and the optimized B3LYP/6-31G(d) geometries were used.[1]

Table 4. Relative Energies of ALL15 conformers (kcal/mol), Compared to The Most Stable α-$^4C_1$ Conformer Calculated with MP2 Method, and Various Basis Sets and CBS Extrapolations[a]

no.	conformer	MP2					
		aV3Z(−df)	AV3Z	V5Z	CBS[A3, A4]	CBS[3, 4, 5]	CBS[4, 5]
1	α-$^4C_1$	0.00	0.00	0.00	0.00	0.00	0.00
2	β-$^4C_1$	0.56	0.65	0.51	0.43	0.43	0.46
3	β-$^4C_1$	0.84	0.88	0.72	0.63	0.60	0.64
4	α-$^4C_1$	0.48	0.59	0.62	0.52	0.58	0.59
5	α-$^4C_1$	0.30	0.47	0.51	0.42	0.50	0.50
6	β-$^4C_1$	1.11	1.10	0.96	0.94	0.88	0.91
7	α-$^4C_1$	0.44	0.55	0.55	0.46	0.53	0.53
8	α-$^4C_1$	1.55	1.62	1.67	1.56	1.70	1.68
9	α-$^4C_1$	2.01	1.95	1.89	1.80	1.88	1.89
10	α-$^4C_1$	2.28	2.47	2.54	2.49	2.53	2.54
11	β-$^4C_1$	3.12	2.93	2.78	2.74	2.66	2.70
12	α-$^4C_1$	2.62	2.78	2.82	2.71	2.71	2.75
13	β-$^4C_1$	4.30	4.36	4.24	4.14	4.08	4.14
14	β-$^1C_4$	4.28	4.51	4.65	4.59	4.64	4.64
15	α-$^1C_4$	4.93	5.02	5.09	5.01	5.04	5.06
MD		−0.01	0.06	0.04	−0.04	−0.02	
MAD		0.18	0.11	0.04	0.05	0.02	

[a] Mean deviation, MD, and mean absolute deviation, MAD, compared to CCSD(T)/CBS; see eqs 9 and 10.

Analysis of the earlier results for the SCONF test set[15] (AnGol15 + GLC4) shows that in agreement with our results, the PBE and TPSS perform considerably better than the B3LYP functional. Our new results show that B3PW91 and the PBE0 functionals perform even better than PBE. A posteriori empirical dispersion correction (DFT-D)[32] of the already too large PBE and TPSS relative energies deteriorates the results.[15] The B3LYP relative energies that underestimate the intramolecular stabilization effects might be improved by the DFT-D correction (MAD = 0.3 kcal/mol). The considerably more expensive B2PLYP double hybrid[33,34] does not perform well without the D correction (MAD = 0.6 kcal/mol). However, the B2PLYP-D results show the best agreement with the reference (MAD = 0.2 kcal/mol).[15] One major drawback of B2PLYP is its $O(N)^5$ scaling of computer time with the size N. As this approach uses not only the occupied orbitals but also the unoccupied orbitals, it goes beyond the fourth-rung hyper-GGA approximations, and it can be called a fifth-rung DFT approximation.[35] Observe also that in
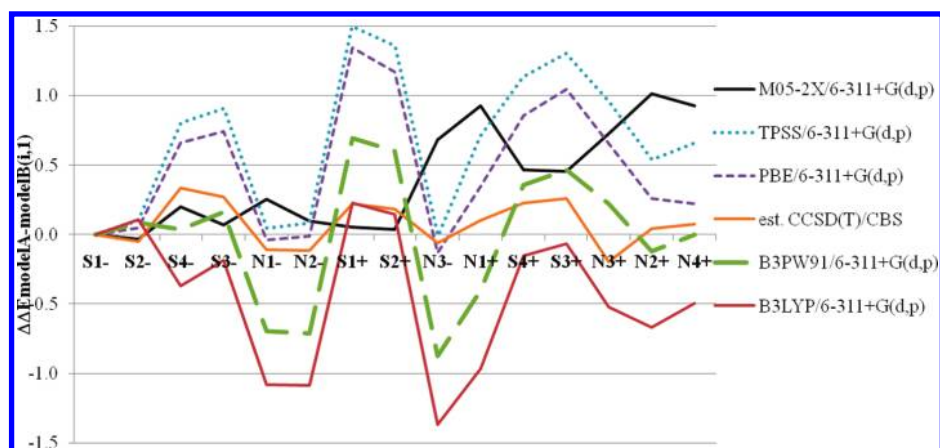
Figure 10. The AnGol15 $\Delta\Delta E_{\text{modelA-modelB}}(i, 1)$ relative energy differences (kcal/mol) for modelA = M05-2X/6-311+G(d,p), B3LYP/6-311+G(d,p), B3PW91/6-311+G(d,p), estimated CCSD(T)/CBS, PBE/6-311+G(d,p), and TPSS/6-311+G(d,p) and for modelB = MP2/CBS[4, 5]. All the DFT results are from ref 1 and the estimated CCSD(T)/CBS results are from ref 15. All calculations use the B3LYP/6-31+G(d,p) geometries.

contrast with standard DFT functionals, B2PLYP diverges for bulk metals.

For the ALL15 test set in all the DFT and HF calculations we use the 6-311+G(d,p) basis set and the optimized B3LYP/6-31G(d,p) geometries.[1] The two worst performers are the LSDA and the HF methods. While LSDA systematically overestimates the conformational energy differences (MD = 1.8 and MAD = 1.8 kcal/mol), the HF shows the opposite error (MD = −1.4 and MAD = 1.4 kcal/mol). TPSS, PBE, and M05-2X show improvements compared to the LSDA but conserve some of the LSDA overestimation error (MD = 0.3−0.5 kcal/mol, MAD < 0.6 kcal/mol). The 25% of global mixing of exact exchange decreases the overestimation, and the PBE0 results are improved (MD = 0.2 kcal/mol, RRD = 0.6 kcal/mol). This is a very promising result compared to the other functionals. The remaining small positive deviations might be further reduced by a recently proposed 32% mixing of the exact exchange.[36] The best performance is shown by the B3PW91 functional (MAD = 0.16 kcal/mol). The B3LYP functional performs only slightly worse (MAD = 0.2 kcal/mol), but the range of the relative difference is large (RRD = 0.9 kcal/mol). This shows that the B3LYP results will not improve if a different reference conformer is chosen, while the global hybrid of PBE results can be improved further.

Our results show that the nonempirical functionals constructed on the basis of constraint satisfaction, such as PBE and TPSS, perform quite well, and they might outperform the empirical B3LYP or M05-2X functionals. The original B3PW91 functional gives consistently better results than B3LYP. The relative energies given by the best DFT methods are quite close to the reference values with mean absolute deviations around 0.1−0.2 kcal/mol. Thus for correct evaluation of such functionals, accurate reference values are necessary. We plan to test PBEh$_a$,[36] PBEsol,[37] revTPSS,[38] M06-2X,[39] and M08-HX[40] functionals in the near future. The benefits of the a posteriori dispersion correction[32,41] will also be studied.

6. CONCLUSIONS

We have performed a series canonical MP2 complete basis set extrapolations using correlation consistent basis sets up to the cardinal number 5 for the AnGol15, GLC4, and ALL15 monosaccharide test sets. Accurate MP2/CBS[4, 5] reference energies

were obtained, and CCSD(T) corrections were also considered for the relative energies of the Angol15 and GLC4 test sets. Good agreement was observed with the earlier CCSD(T)/CBS results,[15] and our results are converged for relative energies within 0.1 kcal/mol. This accuracy is necessary for the correct evaluation of DFT methods, as these methods might reach 0.1−0.2 kcal/mol average accuracy. The accuracy of the MP2/aV3Z(−df) results (0.2−0.5 kcal/mol) is generally not enough for correct evaluations. We have observed that the less expensive local MP2 methods do not give consistent results with the 0.03 domain selection criterion for the AnGol15 test set. Further LMP2 studies are necessary to resolve this problem.

Detailed analysis of the convergence of the HF and the MP2 correlation energies with respect to the cardinal number of the basis set revealed that for several conformer pairs little computational effort yields well-converged relative energies. We introduced three criteria that monitor the convergence of the relative energies with respect to the cardinal number. By applying two of these criteria we were able to select conformer pairs for which even HF/V3Z relative energies are well converged. Fulfillment of the third criterion makes the MP2/V4Z energy well-converged.

The most stable conformers of the AnGol15, GLC4, and ALL15 conformational space are stabilized by the cooperative intramolecular O−H···O interactions and other (e.g., anomeric) electron correlation effects. The HF method misses these effects, seriously underestimating the stability of these conformers compared to the other conformers having weaker stabilizing correlation effects. This leads to too-small relative energies and negative mean deviation from the reference values. Our previous studies showed that LSDA strongly overestimates these stabilization effects, leading to too-large relative energies that show positive mean deviation.[1]

The GGAs and meta-GGAs improve on LSDA, but the relative conformational energies might remain statistically too large (mean deviation is smaller but positive).[1] For such GGA functionals an empirical dispersion correction does not improve the results. Global mixing of the GGAs with the exact exchange might further improve the results by reducing overestimation of the relative energies, thus shifting mean deviation close to zero. A sufficiently large exact exchange fraction might even lead to underestimation of the correlation effects. Such global hybrid

functionals can be efficiently corrected by simple and quick empirical dispersion correction.

For the AnGol15 test set, the ordering of the functionals compared to the CCSD(T)/CBS results is, from best to worse: B3PW91, PBE = M05-2X, and TPSS = B3LYP (MAD = 0.3, 0.4, 0.4, 0.6, and 0.6 kcal/mol, respectively).

For the GLC4 test set, the B3PW91 and PBE0 functionals perform equally well (MAD = 0.3 kcal/mol), while B3LYP is somewhat worse (MAD = 0.5 kcal/mol). The M05-2X performs the worst (MAD = 0.8 kcal/mol).

For the ALL15 test set, the B3PW91 performs the best (MAD = 0.16 kcal/mol), followed by PBE0 and a slightly worse B3LYP (MAD = 0.2 kcal/mol). The M05-2X performs somewhat worse (MAD = 0.5 kcal/mol). These results suggest that a new PBE hybrid with 32% weight of the exact exchange might perform better and might be efficiently corrected in the DFT-D or dD10 framework.

These new CCSD(T) and MP2/CBS reference energies modify our previous conclusions.[1] The overall best performer is B3PW91, closely followed by PBE0. Due to the errors in the MP2/aV3Z(−df) energies used as reference in our previous study the good performance of B3PW91 was not this clear, and the performance of the M05-2X was judged considerably better than here. In agreement with our earlier conclusion the B3LYP functional is not the best choice, but the B3LYP-D performs considerably better. In other areas of molecular chemistry the M05-2X and B3LYP perform better than here. The monosaccharide test sets do not sample strong steric interactions or significant dispersion attractions; however, they sample elaborate systems of intramolecular interactions. The correct description of these conformation spaces is required from good model chemistry for biomolecules. The reference energies published here are suitable to evaluate the performance of future KS-DFT and -D or -dD10 corrected functionals with a sufficient accuracy.

■ ASSOCIATED CONTENT

ⓢ Supporting Information.   The schematic representation of the conformational spaces; the HF, MP2 and LMP2 energies for the AnGol15 and ALL15 test sets. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

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