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The Melatonin Conformer Space: Benchmark and Assessment of Wave Function and DFT Methods for a Paradigmatic Biological and Pharmacological Molecule

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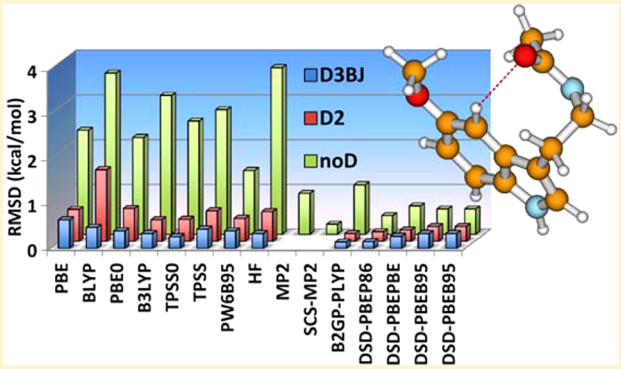
Supporting Information

ABSTRACT: Reference quality conformational energies have been obtained for the 52 unique conformers of melatonin by means of explicitly correlated ab initio methods as well as the ccCA composite method. These data have then been used to evaluate more approximate methods, including a variety of density functionals both on their own and paired with various empirical dispersion corrections. Owing to the presence of internal contacts of the C−H···O and C−H···N variety, basis set convergence is much slower than for alkane conformers, for example, and basis sets of aug-cc-pVQZ or def2-QZVP quality seem to be required to obtain firm estimates of the basis set limit. Not just HF, but also many DFT functionals, will transpose the two lowest conformers unless empirical dispersion corrections are added. Somewhat surprisingly, many DFT functionals reproduce the reference data to fairly high accuracy when combined with the D3BJ empirical dispersion correction or the "nonlocal" Vydrov−Van Voorhis dispersion model. The two best performers including dispersion corrections are the double hybrids DSD-PBEP86-D3BJ and B2GP-PLYP-D; if no such correction is permitted, then M06-2X puts in the best performance. Of lower-cost ab initio-like models, MP2.5 yields the best performance, followed by SCS-MP2.



INTRODUCTION

Conformational equilibria would naïvely seem to be a very easy target for quantum mechanical calculations. In fact, it has been known for some time[1] that density functional methods, in particular, perform well below their usual par for conformer equilibria even in alkane chains. In a recent benchmark study on the conformers of the n-alkanes,[2] we highlighted the great importance of dispersion in conformer equilibria: Schleyer[3] may have been the first to hint at this.

As DFT (at least up to the fourth rung of Jacob's Ladder[4]) involves short-range correlation functionals, it tends to perform very poorly for dispersion unless empirical dispersion corrections (see ref 5 for a review) are added.

In molecules with strong internal hydrogen bonds (such as, for instance, certain carbohydrates[6]), these strongly affect the gas-phase structure (and thus, presumably, may do the same to conformational equilibria). Because electrostatic and charge-transfer terms dominate strong hydrogen bonds (with dispersion being of subsidiary importance[7]), one might expect such systems to be relatively tolerant of poor dispersion descriptions.

Weak internal hydrogen bonds[8] of the C−H···X type are a murkier situation, in that no clear primacy of electrostatic or dispersion terms can be assumed. In the present paper, we consider a biologically important molecule (melatonin, a.k.a., *N*-acetyl-5-methoxytryptamine, IUPAC name *N*-[2-(5-methoxy-1*H*-indol-3-yl)ethyl]acetamide) where $C_{aromatic}H\cdots X$ contacts play a significant role in the conformer equilibrium (Figure 1). This interaction has aspects of both a weak hydrogen bond and of a quadrupole−dipole aromatic−amide interaction.[9]

The presence of the melatonin hormone, a metabolite of the essential dietary amino acid tryptophan, in living organisms can be traced back to ancient photosynthetic prokaryotes.[10] Having been called "Nature's most versatile biological signal",[11] it has a bewildering array of biochemical functions (and potential therapeutic applications): The two most important ones are as "a broad-spectrum cellular antioxidant and free radical scavenger"[12] and (this is the one best known to frequent air

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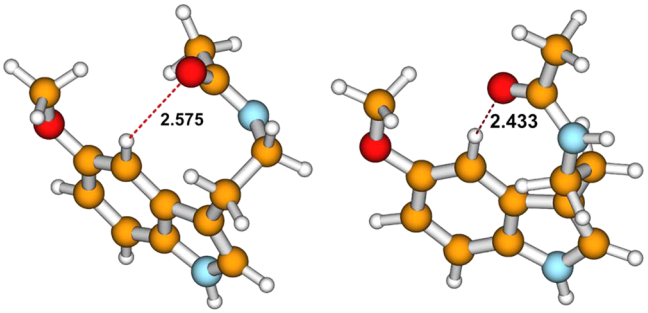

Figure 1. Lowest two conformers of melatonin, aa with conformation $x^{-}g^{+}x^{+}tp$ and ac with conformation $x^{+}tx^{+}tp$. Note the $C_{AR}H\cdots OC$ contacts. The first four letters of the conformational label count away from the ring along the side chain; the fifth refers to the methoxy group. *p* = parallel, *g* = gauche, *x* = cross/perpendicular, *t* = trans, ± are used to indicate the relative "sign" of the angle.

travelers and shift workers) as a regulator of circadian rhythm in animals, including *Homo sapiens*.[13] It has even shown some promise as an ancillary treatment for Alzheimer's disease.[14]

Tasi and co-workers[15] first carried out an exhaustive search of the conformer space of this molecule at the HF/6-31G* level. In a subsequent study, Lovas and co-workers[16] considered the effect of electron correlation at the MP2/6-31G* level and found that not only is the energetic profile qualitatively different at the HF and MP2 levels, but several local minima found at the HF/6-31G* level disappear at the MP2/6-31G* level, while several new ones appear. Most strikingly, the global minimum structure changes from conformation $x^{+}tx^{+}tp$ (the right-hand structure in Figure 1) to $x^{-}g^{+}x^{+}tp$ (the left-hand structure there). Needless to say, second-order perturbation theory and a double-ζ plus polarization basis set fall quite short of the *n*-particle space and 1-particle basis set limits, respectively. In our previous study on alkane conformers,[2] we showed that convergence on both axes is considerably slower than one might expect: here, one faces the additional complication of internal hydrogen bonds. Excessively small basis sets are known to exaggerate hydrogen bond energies due to intramolecular basis set superposition error (see, for example, ref 17 and Table 6 of ref 6 for the example of water dimer).

In the present work, we shall establish benchmark values for the conformer energy spectrum of melatonin and assess the performance of various ab initio and DFT methods for the same application. These findings are of interest not just for the sake of melatonin, but using the latter molecule as a proxy for what can be expected for the conformer manifolds of many biologically and pharmacologically important molecules.

METHODS

Most of the density functional calculations were carried out using either an in-house modified version of Gaussian 09 rev. C01 or ORCA 2.9,[18,19] while a few were carried out using MOLPRO 2010.1.[20] All of the wave function ab initio calculations at levels beyond (SCS)MP2, as well as all explicitly correlated calculations, were performed using MOLPRO 2010.1. Hardware used was either the Dell C910 cluster at CASCaM at the University of North Texas (for the lion's share of calculations) or the IBM iDataplex cluster at the Faculty of Chemistry at the Weizmann Institute of Science (for the remainder). Our largest machines, which were custom-built for us in Texas, had 256 GB of memory and over 6 TB of local scratch space per unit.

The following wave function-based electron correlation methods were considered: HF, MP2, MP3, MP4, CCSD(T),[21] SCS-MP2,[22] SCS(MI)MP2,[23] SCS-MP3,[24] SCS-CCSD,[25] SCS-(MI)CCSD,[26] and MP2.5.[27]

The following DFT functionals were considered: on the second rung of the "Jacob's Ladder",[4] BLYP[28] and PBE;[29] on the third rung, TPSS[30] and M06L;[31] on the fourth rung, B3LYP,[32,28] PBE0,[29,33] M06,[34] M06-2X,[35] PW6B95,[36] TPSSh,[30] and TPSS0;[37] and on the fifth rung, the double hybrid[38] B2GP-PLYP[39] and the spin-component scaled DSD-BLYP,[40] DSD-PBEP86,[41] DSD-PBE,[42] and DSD-PBEhB95[42] double-hybrids.

The following three variants of the empirical dispersion correction were considered, each representing one step on the "stairway to Heaven" of dispersion treatments proposed by Klimeš and Michaelides:[43]

- Grimme's 2006 version,[44] denoted by the suffix "-D" in earlier paper and by the suffix "-D2" in the present work (to distinguish it from later versions).
  The length-scaling factor sR is set to a fixed value of 1.1, which leaves D2 with only a single parameter s_6 for every level of theory. It is obtained by linear least-squares minimization of the error over a set of well-known weak interaction energies, generally the S22 benchmark set of Hobza and co-workers.[45]
- Grimme's 2010 version,[46] which includes r^{-8} terms as well as connectivity-dependent atomic parameters, but sets $s_6 = 1.0$ (to ensure proper asymptotic behavior) and has two parameters: the overall r^{-8} admixture coefficient s_8 and the length scaling s_R. Unlike "-D2", published parameters for DFT-D3 cover the elements H–Pu, including the transition metals. In a minor modification,[47] the cutoff function was replaced by one inspired by Becke and Johnson,[48] hence the notation D3BJ.
- In addition to these "static" corrections (which use no wave function or density information, only the nuclear positions, which of necessity limits their flexibility in adapting to changing chemical environments), the Vydrov–van Voorhis (VV10)[49] "nonlocal" correction was considered, which does not rely on atomic dispersion parameters at all but instead employs a local response model that extracts all required information (except for a single short-range damping parameter) from the molecular electron density. These calculations were carried out using the implementation in ORCA 2.9.[18]

The following basis sets were considered: (a) correlation consistent basis sets, both in their regular[50] cc-pVnZ and (diffuse function-)augmented[51] aug-cc-pVnZ variants; (b) the Weigend–Ahlrichs def2 basis sets;[52] (c) the Pople family 6-31G* and 6-311G** basis sets;[53,54] (d) Jensen's polarization-consistent basis sets;[55] (e) for the explicitly correlated calculations, the cc-pVnZ-F12 basis sets[56] and accompanying auxiliary basis sets.[57]

Initial geometries were harvested from the MP2/6-31G* structures in the Supporting Information of Lovas et al.[16] For reasons of convenience, we have labeled these 102 structures aa, ab,..., dx, in the order they appear in Supporting Information. Fifty two of them are unique (the others are stereoisomers) and were taken as starting points first for MP2/

Table 1. Best Conformational Energies (kcal/mol) for Melatonin, as Well as Conformational Labels and Group Assignment[a]

label	conf	grp	best	ccCA	label	conf	grp	best	ccCA
aa	$x^-g^+x^+tp$	1	0.000	0.000	ca	$x^+g^+x^+pt$	9	5.042	5.015
ac	$x^+t\ x^+tp$	2	0.593	0.498	cc	$x^+t\ x^+pp$	11	4.661	4.576
ae	$x^+g^-x^-tt$	1	1.873	1.847	ce	$t\ g^+t\ tx^-$	10	5.651	5.643
ag	$x^-g^-x^-tp$	3	1.402	1.366	cg	$x^-g^+x^-pt$	12	5.680	5.656
ai	$x^-g^+x^-tp$	4	2.071	2.089	ci	$x^+t\ x^-pp$	13	5.187	5.113
ak	$x^-g^+x^+pp$	5	2.362	2.345	ck	$x^+g^+x^+px^+$	9	6.528	6.586
am	$x^-x^+x^-pp$	6	2.678	2.647	cm	$x^+g^+x^+px^-$	9	6.542	6.601
ao	$x^+g^-x^+tt$	4	2.802	2.818	co	$x^+g^-x^-pt$	5	6.076	6.049
aq	$x^-g^-x^-tt$	3	2.483	2.444	cq	$t\ g^-t\ pp$	14	5.671	5.599
as	$x^-g^-x^+pp$	7	2.879	2.866	cs	$x^+t\ x^+pt$	11	5.845	5.761
au	$x^+g^-x^+tx^+$	4	4.134	4.213	cu	$x^-g^+x^-px^-$	12	7.589	7.647
aw	$x^+g^-x^+tx^-$	4	4.325	4.403	cw	$x^+t\ x^-pt$	13	6.207	6.127
ay	$x^-g^-x^-tx^-$	3	3.867	3.911	cy	$t\ t\ x^-pp$	15	5.960	5.869
ba	$x^+t\ x^-tp$	8	2.548	2.448	da	$x^+t\ x^+px^+$	11	7.309	7.312
bc	$x^-g^-x^-tx^+$	3	4.008	4.051	dc	$x^+t\ x^+px^-$	11	7.384	7.386
be	$x^-g^+x^+px^+$	5	5.172	5.234	de	$t\ g^-t\ pt$	14	6.733	6.652
bg	$x^-x^+x^-px^+$	6	5.111	5.158	dg	$x^+t\ x^-px^+$	13	7.672	7.676
bi	$x^+t\ x^+tt$	2	3.468	3.359	di	$x^+t\ x^-px^-$	13	7.724	7.730
bk	$x^-g^-x^+pt$	7	3.839	3.824	dk	$t\ t\ t\ pp$	16	6.548	6.445
bm	$x^+g^+x^+pp$	9	4.081	4.060	dl	$t\ g^+t\ px^+$	14	8.174	8.183
bo	$x^+t\ x^-tt$	8	3.412	3.304	dn	$t\ g^-t\ px^+$	14	8.249	8.258
bq	$x^-g^-x^+px^-$	7	5.316	5.380	dp	$t\ t\ x^-pt$	15	7.136	7.036
bs	$x^-g^-x^+px^+$	7	5.359	5.422	dr	$t\ t\ x^-px^+$	15	8.584	8.579
bu	$x^-t\ x^+tx^-$	8	4.806	4.785	dt	$t\ t\ x^-px^-$	15	8.594	8.589
bw	$t\ g^-t\ tt$	10	4.215	4.118	dv	$t\ t\ t\ pt$	16	7.668	7.556
by	$x^+t\ x^-tx^-$	8	4.877	4.857	dw	$t\ t\ t\ px^-$	16	9.141	9.125

[a]Our best data are CCSD(T)/cc-pVTZ(p on H)−MP2/cc-pVTZ(p on H)+MP2-F12/cc-pVTZ-F12.

6-311G** optimizations and then (see below) subjected to final optimization at the SCS-MP2/cc-pVTZ level.

To ascertain that all conformers are local minima at this level, it would have been highly desirable to carry out SCS-MP2/cc-pVTZ frequency calculations for all 52 structures. However, this proved to be beyond the available computational resources. We were, however, able to carry out SCS-MP2/6-31G* and SCS-MP2/6-311G** geometry optimizations and frequency calculations for all 52 structures and found each to be a unique local minimum at both levels. While it cannot be entirely ruled out that the situation might be different with the cc-pVTZ basis sets, we deem this highly improbable.

The conformations can be characterized, as in ref 16, by five torsional angles, or the corresponding conformational labels for them, e.g., $x^-g^+x^+tp$ and x^+tx^+tp. (In this notation, p = parallel/eclipsed, g = gauche, x = cross/perpendicular, t = trans, and + and − are used to indicate the relative sign of torsion angles. The first four labels refer to the backbone angles along the ethylacetamide group (counting outward from the indole ring), while the fifth refers to the 5-methoxy group. If the fifth label is ignored, the conformers can be classified in 16 groups (see Table 1).

RESULTS AND DISCUSSION

Initial Basis Set Convergence Study. Following some initial exploratory calculations, we chose the DSD-PBEP86-D3BJ level for a basis set convergence study. Initially, we employed the MP2/6-311G**-optimized geometries.

The largest conventional basis set we were able to apply was aug-cc-pVQZ; however, the RMS difference over the 52 conformer energies with the aug-cc-pVTZ basis set was still 0.186 kcal/mol, which we did not consider to be an acceptable degree of basis set convergence.

To better establish a basis set limit, we additionally carried out explicitly correlated DSD-PBEP86-F12/cc-pVTZ-F12 calculations using the approach detailed in ref 58. The same calculations, but with the smaller cc-pVDZ-F12 basis set, yield conformer energies within just 0.060 kcal/mol RMSD of the cc-pVTZ-F12 results; given the much more rapid basis set convergence of explicitly correlated calculations relative to orbital-based ones, we felt justified in taking the cc-pVTZ-F12 data as our reference. RMSDs from that for different basis sets are given in Table 2.

Table 2. RMSD (kcal/mol) from DSD-PBEP86-F12/cc-pVTZ-F12 conformer Energies at the DSD-PBEP86 Level with Different Basis as Well as at the DSD-PBEP86-F12/cc-pVDZ-F12 Explicitly Correlated Level

cc-pVDZ	cc-pVTZ	aug-cc-pVTZ	cc-pVQZ	aug-cc-pVQZ
0.709	0.357	0.170	0.064	0.029
AV{T,Q}Z	def2-SVP	def2-TZVP	def2-TZVPP	def2-QZVP
0.134	1.068	0.258	0.224	0.022
6-31G*	6-311G**	pc-1	pc-2	VDZ-F12
0.694	0.885	1.300	0.254	0.060

It is immediately apparent that the 6-31G* basis set used by Lovas et al. is some distance from the basis set limit, where it should be kept in mind that this is still a double-hybrid DFT functional, for which basis set convergence is expected to be slower than for a "conventional" DFT method but faster than for a wave function ab initio method like MP2. But none of the small basis sets fare well here: in fact, 6-311G**, def2-SVP, and

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pc-1 have even worse RMSDs of 0.885, 1.068, and 1.300 kcal/mol, respectively, and neither does cc-pVDZ (0.709 kcal/mol) fare well.

Fully polarized triple-ζ basis sets do better, with 0.254 kcal/mol for pc-2 and 0.258 kcal/mol for def2-TZVP, the latter of which is only slightly further improved to 0.224 kcal/mol with the def2-TZVPP basis set. While cc-pVTZ is somewhat disappointing at 0.357 kcal/mol, addition of diffuse functions cuts the error in half.

To approach the basis set limit conformer energies with orbital basis sets, we still have to go to quadruple-ζ sets, where both def2-QZVP and aug-cc-pVQZ put in outstanding performances at 0.022 and 0.029 kcal/mol, respectively. We see some degradation in unaugmented cc-pVQZ, with an RMSD of 0.064 kcal/mol, which is not surprising, as the cc-pVnZ basis sets were optimized for wave function ab initio correlation, which typically results in tighter (less diffuse) exponents than basis sets optimized for SCF or DFT calculations.

Of the basis sets that yield the best performance, def2-QZVP is the smallest one and also appears to be used by numerous groups (e.g., Grimme[59]) as a kind-of "de facto basis set limit" in DFT evaluations. We have therefore chosen this basis set for evaluating DFT methods in our final assessment.

Reference Data and Assessment of More Approximate Methods. Seeking a compromise between accuracy and computational cost, and desiring to use something at least ab initio-related, we settled for SCS-MP2/cc-pVTZ as the level of theory for reference geometry optimizations. Two of the structures, labeled be and bm, required special care to avoid collapse of the optimization onto other conformers (ak and bk, respectively). The final structures, in Cartesian coordinates, can be found in Supporting Information.

Large basis set CCSD(T) data would be the most desirable energy reference. However, from Table 2, it would seem that no orbital basis set smaller than aug-cc-pVQZ would be adequate (especially because basis set convergence for a wave function method will be still slower than for a double hybrid functional), while the largest orbital basis set in which we were able to obtain actual CCSD(T) data for all 52 conformers turned out to be cc-pVTZ(p on H). CCSD(T)-F12/cc-pVTZ-F12 would be highly desirable, but such calculations turned out to be beyond the limitations of the hardware available to us. MP2/cc-pVTZ-F12 was quite feasible, however, and the combination of large basis set (SCS-)MP2 energetics combined with a "CCSD(T) − MP2" correction in a comparatively small basis set was found in the past to be a quite effective technique for problems involving weak interactions; witness, for example, the S22 reference data set of Hobza and co-workers[45] as well as very recent studies on halogen-bonded complexes[60] and on the tetrapeptide conformers.[61]

One of the reviewers inquired about the effect of straight MP2 instead of SCS-MP2 on the geometry and the energetics. As a gauge, we reoptimized the two lowest conformers at the MP2/cc-pVTZ level starting from SCS-MP2/cc-pVTZ geometries. Superimpositions of the initial and final geometry can be seen in Supporting Information: suffice to say that, while covalent bond distances are not greatly affected, the internal hydrogen bond distances change appreciably, from 2.680 Å (aa) and 2.524 Å (ac) at the SCS-MP2/cc-pVTZ level to 2.524 and 2.412 Å, respectively, at the MP2/cc-pVTZ level. The effect on the relative energetics, however, is 1 order of magnitude weaker than the difference between MP2 and SCS-MP2 values, with the SCS-MP2/cc-pVTZ ΔE only changing from 1.02 to 0.95 kcal/mol, and its MP2/cc-pVTZ counterpart only from 1.70 to 1.76 kcal/mol.

Table 3 lists RMSDs at the MP2 level compared to MP2-F12/cc-pVTZ-F12. First of all, the lightning-fast basis set convergence of MP2-F12/cc-pVnZ-F12 calculations is illustrated nicely by the RMSD of just 0.019 kcal/mol obtained with the cc-pVDZ-F12 basis set. We can thus be confident that the cc-pVTZ-F12 numbers are indeed fair measures of the basis set limit.

Table 3. RMSD (kcal/mol) from MP2-F12/cc-pVTZ-F12 Conformer Energies at the MP2 Level with Different Orbital Basis Sets, as Well as at the MP2-F12/cc-pVDZ-F12 Explicitly Correlated Level[a]

	cc-pVDZ	cc-pVTZ	aug-cc-pVTZ	cc-pVQZ	aug-cc-pVQZ
lowest 13	0.416	0.240	0.349	0.091	0.117
whole set	0.512	0.418	0.548	0.138	0.189
	V{T,Q}Z	AV{T,Q}Z	def2-SVP	def2-TZVP	def2-TZVPP
lowest 13	0.036	0.068	0.516	0.270	0.248
whole set	0.077	0.081	0.805	0.395	0.368
	def2-QZVP	6-31G*	6-311G**	VTZ(p on H)	VDZ-F12
lowest 13	0.100	0.441	0.468	0.234	0.014
whole set	0.139	0.502	0.721	0.365	0.019

[a]V{T,Q}Z denotes extrapolation from cc-pVTZ and cc-pVQZ results.

Second, turning to orbital-based calculations, the only options for getting within even 0.1 kcal/mol require at least cc-pVQZ or def2-QZVP basis sets. If one needs to compromise between accuracy and cost, cc-pVTZ and def2-TZVPP yield about similar performance (especially for the lower 13 conformers): the choice of cc-pVTZ for the final SCS-MP2 geometry optimizations would then seem to be justified. Presumably due to error compensation, 6-31G* accidentally does better than 6-311G**, albeit not quite acceptably for our purpose. Reducing the polarization complement for hydrogen in cc-pVTZ to a single p function, while leaving the heavy-atom basis sets unchanged, clearly does not degrade the conformer energies obtained. This is just as well, cc-pVTZ(p on H) being the largest basis set for which we were able to obtain CCSD(T) energetics.

In this case, basis set extrapolation works rather better than for the double hybrid functionals: witness the RMSD of 0.077 kcal/mol (and just 0.036 for the lowest 13 conformers!) obtained extrapolating from cc-pVTZ and cc-pVQZ with the familiar L^{-3} principal expansion formula.[62]

Our reference data were thus obtained as

$$E[\mathrm{ref}] = E[\mathrm{MP2\text{-}F12/cc\text{-}pVTZ\text{-}F12}] - E[\mathrm{MP2/cc\text{-}VTZ(p\ on\ H)}] + E[\mathrm{CCSD(T)/cc\text{-}pVTZ(p\ on\ H)}] \quad (1)$$

The relevant total energies can be found in Supporting Information; the conformer energies are listed above in Table 1.

As a "sanity check" on our data, we also applied a slightly modified form of the ccCA (correlation consistent composite approach) of Wilson and co-workers.[63] The ccCA-PS3 protocol[64] was applied more or less to the letter except for two details: (a) the level of theory for the reference geometry

(where we used the same SCS-MP2/cc-pVTZ geometries as for the other levels); (b) the cc-pVTZ step was, of course, performed in a slightly reduced basis set. The ccCA data are listed in Table 1 while a component breakdown can be found in Supporting Information: we will only note a few salient points here. The scalar relativistic contribution to the conformer energies was found to be negligible at 0.006 kcal/mol RMSD; the core−valence contributions are somewhat more significant at 0.026 kcal/mol RMSD but still negligible on the accuracy scale of interest to us. (We note that this step relies on an error compensation between basis set incompleteness and inadequacy of MP2.[65,66]) The post-MP2 correction is found to contribute a frighteningly large RMSD = 0.76 kcal/mol, while basis set extrapolation beyond MP2/A'VQZ accounts for another 0.158 kcal/mol RMSD.

For comparison, the RMSD between MP2-F12/cc-pV{D,T}-Z-F12 is only 0.019 kcal/mol. Yet, on balance the ccCA approach acquits itself remarkably well, with RMSD = 0.064 kcal/mol compared to our reference data. The fact that we obtain such similar data by two different approaches to reaching the basis set limit bolsters our trust in our reference data.

For the DFT functionals, we considered three different dispersion corrections: (a) Grimme's original 2006 correction (D2); (b) the updated correction with Becke-Johnson damping (D3BJ); (c) the Vydrov−Van Voorhis post-DFT dispersion functional, which is free of atomic parameters (NL).

RMSD statistics for the lowest 12 conformers are given in Table 4, while statistics for the entire set can be found in Table 5.

It is easily seen that the performance of SCF is outright dismal, especially for the higher-up conformers. Perhaps the standout defect for the lower conformers, already noted by Lovas and co-workers, is that SCF predicts conformer ac, rather than aa, to be the global minimum: in contrast, our best estimate for the aa−ac difference is 0.59 kcal/mol (ccCA: 0.50 kcal/mol). A surprising number of DFT functionals, in the absence of dispersion corrections, exhibit the same defect, such as BLYP, B3LYP, PBE, PBE0, TPSS, TPSS0, PW6B95, ... and even (by a small amount) the B2GP-PLYP double hybrid. MP2 gets this at least qualitatively correct, but the aa−ac difference is clearly quite sensitive to the level of theory, being 1.305 kcal/mol at the MP2-F12/cc-pVTZ-F12 level.

Overall performance statistics for most "traditional" DFT functionals without dispersion correction are not much better than that of HF. The Truhlar M06 functionals acquit themselves well (especially M06-2X), as do the no-dispersion-corrections variants of the spin-component scaled double hybrids (DSD-PBE-noD, DSD-PBEP86-noD, and DSD-PBEB95-noD).

While the MP2 RMSD is about 4 times smaller than the corresponding HF value in both tables, HF with dispersion corrections quite astonishingly outperforms MP2. Also, the MP2 RMSD for the whole set is twice as large as for the lowest 12 conformers, suggesting that the method has a more difficult time coping with the higher (more crowded?) conformers. SCS-MP2 exhibits neither defect, with a respectable RMSD = 0.22 kcal/mol over the whole set, at no additional cost over MP2.

Adding dispersion corrections dramatically improves performance for the traditional DFT functionals, D3BJ more than D2. In most cases, the RMSDs of D3BJ and the parameter-free NL are comparable, or give D3BJ a slight edge. The performance of TPSS0/D3BJ is especially noteworthy.

Table 4. RMSD (kcal/mol) for the 12 Lowest Conformer Energies (13 lowest conformers) of Melatonin Using the def2-QZVP Basis Set and Various DFT Functionals with and without Empirical Dispersion Corrections (reference data are approximate CCSD(T)-F12/cc-pVTZ-F12 (see text))

	no D	D2	D3BJ	NL
PBE	1.30	0.64	0.49	0.44
BLYP	1.85	0.86	0.44	0.30
PBE0	1.15	0.46	0.28	0.29
B3LYP	1.56	0.46	0.25	0.44
TPSS0	1.33	0.44	0.20	0.23
TPSS	1.52	0.63	0.33	0.40
PW6B95	0.75	0.41	0.26	0.26
M06L	0.46	0.46		
M06	0.24	0.42		
M06-2X	0.27	0.27		
B2GP-PLYP	0.60	0.18	0.12	
PWPB95			0.19	
DSD-BLYP			0.18	
DSD-PBEP86	0.27	0.18	0.15	
DSD-PBEPBE	0.38	0.23	0.21	
DSD-PBEB95	0.28	0.28	0.26	
HF	1.72	0.34	0.28	0.47
SCS-MP2	0.24			
MP2	0.47			
ccCA-PS3	0.053			

For the B2GP-PLYP double hybrid, both D2 and D3BJ are very helpful and lead to among the lowest RMSD values in Table 5 (0.17 and 0.14 kcal/mol, respectively). For the spin-component-scaled double hybrids, parameters within the functional also shift (in particular, the same-spin "MP2" coefficient), and hence the improvements are more modest; yet with the D2 and especially with the D3BJ correction, the results are quite respectable. DSD-PBEP86-D3BJ and B2GP-PLYP-D3BJ are basically tied for first place, at 0.15 and 0.14 kcal/mol RMSD. Nevertheless, while the double hybrids clearly still have an edge over conventional DFT functionals, this edge is much reduced once dispersion corrections are applied. With

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Table 5. RMSD (kcal/mol) for the Conformer Energies of All 52 Conformers of Melatonin Using the def2-QZVP Basis Set and Various DFT Functionals with and without Empirical Dispersion Corrections (reference data are approximate CCSD(T)-F12/cc-pVTZ-F12 (see text))

	no D	D2	D3BJ	NL
PBE	2.32	0.71	0.64	0.56
BLYP	3.60	1.60	0.47	0.35
PBE0	2.16	0.73	0.39	0.37
B3LYP	3.10	0.48	0.33	0.56
TPSS0	2.53	0.49	0.26	0.30
TPSS	2.78	0.68	0.43	0.52
PW6B95	1.42	0.51	0.39	0.43
M06L	0.90	0.90		
M06	0.52	0.57		
M06-2X	0.29	0.29		
B2GP-LYP	1.10	0.17	0.14	
PWPB95			0.30	
DSD-BLYP			0.26	
DSD-PBEP86	0.41	0.21	0.15	
DSD-PBEPBE	0.63	0.25	0.27	
DSD-PBEB95	0.56	0.33	0.33	
HF	3.72	0.66	0.33	0.54
SCS-MP2	0.22[a]			
MP2	0.91[a]			
ccCA-PS3	0.064			

[a]SCS-MP2-F12/cc-pVTZ-F12: RMSD = 0.28 kcal/mol. [b]MP2-F12/cc-pVTZ-F12: RMSD = 0.78 kcal/mol.

the D3BJ correction in place, and considering the lower conformers, a hierarchy hybrid > meta-GGA > GGA appears to hold; considering then the entire set, things become less clear, except that double hybrids trump them all.

We have addressed basis set convergence as well as performance of DFT functionals. What about convergence of the correlation method? While we were obviously unable to assess this at the basis set limit, Table 6 lists some statistics for the cc-pVTZ(p on H) basis set, with CCSD(T) obviously being the reference

We note that (T) are apparently quite important, as the RMSD for CCSD, 0.647 kcal/mol, is not greatly improved over MP2's. A certain degree of oscillation can be seen along the MP series: for instance, the aa−ac separation energy, which is 1.061 kcal/mol at the CCSD(T) level with this basis set, goes from 1.773 at the MP2 level to 0.397 at the MP3 level to 0.673 at the MP4(SDQ) level to 0.571 at the CCSD level. This virtually begs for application of MP2.5 (i.e., the average of MP2 and MP3, which would yield 1.085 kcal/mol for this property), and indeed, over the whole sample, the RMSD of MP2.5 is just 0.092 kcal/mol, compared to SCS-MP3 at 0.585 kcal/mol. In fact, it reaches the same quality as SCS-CCSD (0.090 kcal/mol) at a fraction of the computational cost. A fully ad-hoc optimized SCS-MP3 would do little better than MP2.5, at 0.065 kcal/mol.

SCS(MI)MP2, a variant[23] of SCS-MP2 optimized for weak interactions, offers a slight improvement at the cost of sacrificing performance for equilibrium thermochemistry. Likewise, SCS(MI)CCSD offers some improvement over the already excellent SCS-CCSD, but without such deterioration in general thermochemistry. The underlying method (CCSD) is both more expensive and more flexible than MP2, and therefore an ad hoc parametrization for one property will be less warped for other properties.[67]

A final note is perhaps due on basis set convergence. We showed above that def2-QZVP is close enough to the basis set limit for double hybrids, and one would a fortiori expect the same for ordinary hybrid functionals. In Table 7 we consider the basis set convergence for PBE0.

As can be seen there, all three quadruple-ζ basis sets, namely cc-pVQZ, pc-3, and def2-QZVP yield results very close to each other, especially pc-3 and def2-QZVP. Unlike for the double hybrids, however, it is possible here to obtain results of similar quality with the triple-ζ pc-2 basis set; it should be remembered that the pc-n series is explicitly optimized for DFT applications. Def2-TZVPP performs only slightly worse, while cc-pVTZ represents a marked degradation. Again, this should not come as a surprise, because cc-pVTZ is optimized for wave function correlated calculations, for which the requirements are quite different from DFT. Finally, none of the double-ζ basis sets perform acceptably.

General Observations. In our studies on conformer equilibria in alkanes,[2] we found that basis set convergence to 0.1 kcal/mol or better was already reached with cc-pVTZ or comparable basis sets, and that basis sets of that quality are entirely adequate for assessing the performance of any method. In contrast, in the present system, the intramolecular weak hydrogen bonds cause quite slow basis set convergence as well, and basis set incompleteness issues can easily mask the accuracy ordering of density functionals and/or empirical dispersion corrections unless one is willing to go to basis sets that ensure convergence. In fact, the present researchers were led up the garden path themselves during an earlier (thankfully unpublished) incarnation of the present work.

Some remarks are due concerning computational cost. Using ORCA 2.9 running in parallel on eight 2.67 GHz Intel Nehalem cores, and the def2-QZVP basis set with corresponding auxiliary basis sets,[68] elapsed times ratios for representative GGA, hybrid GGA, hybrid meta-GGA, and double-hybrid functionals are 1:3.75:4:4.75:5 for PBE:PBE0:TPSS0:MP2:DSD-PBEP86. Different functionals on the same rung of Jacob's Ladder have comparable CPU times. For comparison, RI-MP2-F12/cc-pVTZ-F12 requires 64 times as

Table 6. RMSD (kcal/mol) from CCSD(T)/cc-pVTZ(p on H) for Different Wavefunction Methods in the Same Basis Set

HF	MP2	SCS-MP2	SCS(MI)MP2	MP3	MP4(SDQ)
3.716	0.770	0.236	0.183	0.856	0.513
SCS-MP3	CCSD	SCS-CCSD	SCS(MI)CCSD	ad hoc SCS-MP3[a]	MP2.5
0.589	0.650	0.090	0.065	0.065	0.092

[a]Parameters: c_{2SS} = 1.081, c_{2AB} = 1.092, c3 = 0.712.

Table 7. RMSD (kcal/mol) from PBE0/def2-QZVP for Various Basis Sets

RMSD	6-31G*	6-311G**	pc-1	pc-2	pc-3	cc-pVDZ
lowest 13	0.641	0.489	0.664	0.033	0.018	0.582
whole set	1.086	1.044	1.466	0.080	0.036	0.973
RMSD	cc-pVTZ	cc-pVQZ	def2-SVP	def2-TZVP	def2-TZVPP	def2-QZVP
lowest 13	0.193	0.056	0.698	0.156	0.090	0.000
whole set	0.340	0.090	1.280	0.428	0.132	0.000

much CPU time as RI-PBE/def2-QZVP, and CCSD(T)/cc-pVTZ(1p on H) requires 678 times as much.

CONCLUSIONS

Reference quality conformational energies have been obtained for the 52 unique conformers of melatonin by means of explicitly correlated ab initio methods as well as the ccCA composite method. These data have then been used to evaluate more approximate methods, including a variety of density functionals both on their own and paired with various empirical dispersion corrections.

Owing to the presence of internal contacts of the C−H···O and C−H···N variety, basis set convergence is much slower than for, for example, alkane conformers, and basis sets of aug-cc-pVQZ or def2-QZVP quality seem to be required to obtain firm estimates of the basis set limit.

Not just HF but also many DFT functionals will transpose the two lowest conformers unless empirical dispersion corrections are added. Somewhat surprisingly, many DFT functionals reproduce the reference data to fairly high accuracy when combined with the D3BJ empirical dispersion correction or the "nonlocal" Vydrov−Van Voorhis dispersion model. The two best performers including dispersion corrections are the double hybrids DSD-PBEP86-D3BJ and B2GP-PLYP-D; if no such correction permitted, then M06-2X puts in the best performance. Of lower-cost ab initio-like models, MP2.5 yields the best performance, followed by SCS-MP2. We believe the present findings to be useful for the computational modeling of flexible biomolecules and (pro)drugs.

ASSOCIATED CONTENT

Supporting Information

Cartesian coordinates (in Xmol/Jmol .xyz format) for the SCS-MP2-cc-pVTZ geometries of the 52 conformers; figure of superimposed SCS-MP2/cc-pVTZ and MP2/cc-pVTZ structures of the lowest conformer; total energies and component breakdown for the benchmark data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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■ NOTE ADDED IN PROOF

As an addendum to Tables 4 and 5, we have considered the error statistics of the range-separated hybrids ωB97X,[69] which has no dispersion correction, and ωB97X-D,[70] which has one with a damping function similar to ref 46. For the bottom 13 conformers, RMSD values are 0.434 and 0.333 kcal/mol, respectively; over the entire set, we obtain 0.811 and 0.312 kcal/mol, respectively. This latter result places ωB97X-D among the best non-double-hybrid functionals in Table 5.