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Molecular Conformations and Relative Stabilities Can Be as Demanding of the Electronic Structure Method as Intermolecular Calculations

Tanja van Mourik,*,† Panagiotis G. Karamertzanis,† and Sarah L. Price†

Department of Chemistry, University College London, 20 Gordon Street, London WC1H 0AJ

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We have performed a variety of high-level electronic structure calculations on two moderately sized organic molecules and found considerable sensitivity of the intramolecular potential energy surface to the method employed. The gas-phase structure of tyrosine−glycine varies qualitatively between B3LYP and MP2 optimizations, producing different close contacts between the tyrosine ring and the glycine moiety. The relative energies of the 2-(acetylamino)benzamide conformations found in its two polymorphs can vary by over 20 kJ mol^{-1} between MP2 and B3LYP calculations, using the same basis set. It is shown by a novel analysis that the intramolecular equivalent of basis set superposition error competes with the errors in the intramolecular dispersion in causing this sensitivity.

1. Introduction

Most computational chemistry textbooks imply that the calculation of conformational energy differences and the determination of "gas-phase" structures of organic molecules is relatively routine by applying readily available electronic structure methods combined with moderately sized basis sets.[1,2] However, while computing the molecular structure of gas-phase peptide molecules, and evaluating the relative stability of different crystal structures of one particular molecule, we found examples where various routine electronic structure calculations give results that are at variance with each other. Exploring the relative conformational energies and optimized structures by both MP2 (second-order Møller−Plesset perturbation theory) and DFT (density functional theory) showed considerable variation between the results obtained with different correlated methods. In addition to reporting this variation, we rationalize its occurrence by utilizing concepts borrowed from the theory of intermolecular forces and the electronic structure modeling of weakly bound intermolecular complexes.

DFT is currently one of the most popular electronic structure methods. In particular, the combination of the B3LYP[3] density functional and the 6-31G(d) basis set is pervasive in molecular modeling of (bio-)organic molecules. Despite its greater computational efficiency as compared to correlated wave function methods, it is found that the accuracy of DFT often rivals that of more expensive electronic structure methods.[4,5] It has been shown that DFT methods reproduce the electric moments and polarizabilities of molecules accurately,[6] and hence satisfactorily account for the electrostatic interactions, as shown by the accurate prediction of hydrogen-bonding energies and equilibrium structures.[7] However, over the last years several papers have appeared in the literature that highlight the deficiency of commonly used density functionals (such as B3LYP) for the calculation of intermolecular dispersion interactions[5,6,8−21] (although a number of newly developed functionals have recently been reported to give reasonable results for weak intermolecular interactions[22−24]). Although DFT will account for some dispersion-like interactions near the equilibrium configuration for van der Waals complexes,[25,26] in molecules of considerable size there will be conformations for which functional groups are further away, and hence attracted by the classical C_6/R^6 London dispersion, which is not included in commonly used functionals. In such cases, a method that properly accounts for dispersion needs to be used instead. MP2 is a popular choice, as it is one of the most computationally efficient correlated ab initio methods available. Thus, a qualitative difference between results obtained with MP2 and DFT could indicate that the DFT functional used is not adequate for the molecular system at hand. For example, this had been observed for the indole−water complex: B3LYP calculations yielded two different π-bonded minima with the water bonded to either the pyrrole or the phenyl ring,[27] whereas MP2 yielded only one π-bonded minimum, in which the water molecule interacts with both rings simultaneously.[17,28] The MP2 intermolecular binding energies are in excellent agreement with experiment, providing support for the validity of the MP2 results.

As B3LYP generally severely underestimates dispersion,[12] one may assume that MP2 gives the more accurate results for intermolecular binding energies and structures. However, basis set superposition errors (BSSE),[29] where the basis functions on one molecule are used to improve the electronic structure of the other molecule, can be large in MP2 calculations, particularly when using small to moderately sized basis sets. For intermolecular complexes (like indole−water[28]), the intermolecular BSSE effects on geometry and interaction energy can effectively be accounted for by using the counterpoise[30] procedure. However, there is no straightforward way to correct for intramolecular BSSE. For molecules in conformations where functional groups are close in space, such as in intramolecular

† E-mail: T.v.M., t.vanmourik@ucl.ac.uk; P.G.K., p.karamertzanis@ucl.ac.uk; S.L.P., s.l.price@ucl.ac.uk.

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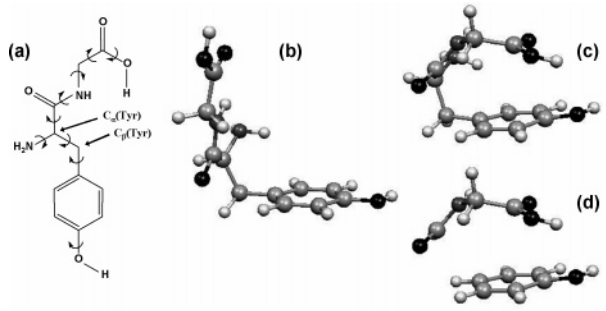

Figure 1. (a) Tyr−Gly molecule ([(2-amino-3-(4-hydroxyphenyl)propionyl)amino]acetic acid). (b) B3LYP/6-31+G(d) optimized "book" structure of the conformer considered in this work (conformer 6 in ref 31). (c) Resulting structure when (b) is re-optimized at the MP2/6-31+G(d) level of theory ("book/OHO(Tyr)"). (d) (*N*-formylglycine)-phenol complex where the phenol and *N*-formylglycine monomers adopt the same conformations and relative spatial arrangement as in the MP2-optimized Tyr−Gly conformer. Here, the $C_\beta(Tyr)H_2$ and $NH_2C_\alpha(Tyr)H$ groups were replaced by hydrogen atoms. The positions of these two hydrogen atoms were optimized for the isolated fragments (phenol and *N*-formylglycine), at the MP2/6-31+G(d) level of theory, employing the NWChem program package.[32]

hydrogen bonds, there is clearly the possibility of BSSE as well as genuine through-space dispersion interactions. Because dispersion and BSSE have very different distance dependence, the relative effects of BSSE and inaccuracies in the modeling of dispersion will be very different in alternative conformations where the functional groups are more distant. In the current study we explore the balance between inaccuracies in the description of dispersion (a true physical effect) and intramolecular BSSE (an artificial attraction) in two such molecules, the tyrosine−glycine (Tyr−Gly) dipeptide and 2-(acetylamino)benzamide, in more detail.

2. Illustrative Example: Differences in Optimized Conformations for Tyr−Gly

In the case of the Tyr−Gly dipeptide (Figure 1a), DFT and MP2 give remarkably different structures for some of the Tyr−Gly minima.[31] The sixth most stable minimum on the B3LYP/6-31+G(d) surface resembles a partly open book (Figure 1b). However, when this structure is optimized at the MP2 level with the same basis set, it results in a conformer (Figure 1c) that is much more folded and exhibits an OH···O interaction between the C-terminal OH group and the tyrosine hydroxyl oxygen. Conversely, when the MP2/6-31+G(d) optimized book/OHO(Tyr) structure (Figure 1c) is optimized at the B3LYP level, the original book minimum (Figure 1b) is obtained. Hence there are major qualitative differences in the MP2 and B3LYP conformational energy surfaces.

It is difficult to quantify these differences from the 13 kJ mol^{-1} energy lowering during the MP2 optimization starting from the B3LYP minimum (and conversely, the 33 kJ mol^{-1} energy lowering during the B3LYP optimization starting from the MP2 minimum), as a significant proportion of these energy lowerings comes from the small differences in the optimal bond lengths between the two methods. If the starting point is a conformation partially optimized at the MP2 level with the torsion angles that specify the geometry of the flexible peptide backbone (Figure 1a) fixed at the book structure, then the full optimization at the MP2 level leads to the book/OHO(Tyr) structure with an energy lowering of 9 kJ mol^{-1}. This value may be an underestimate of the true energy lowering, as constraining even more degrees of freedom to the book structure values would further destabilize the starting geometry. In contrast, similar calculations show that the book structure is more stable than the book/OHO(Tyr) structure by 19 kJ mol^{-1} on the B3LYP surface.

TABLE 1: Counterpoise-Corrected and Uncorrected Interaction Energies (ΔE^{CP} and ΔE^{noCP}) and BSSE Values for the (*N*-Formylglycine)phenol Complex[a]

method	ΔE^{CP},[b] kJ mol^{-1}	ΔE^{noCP}, kJ mol^{-1}	BSSE, kJ mol^{-1}
Modeling Book: B3LYP/6-31+G(d) Optimized Minimum of Tyr−Gly			
HF/6-31+G(d)	12.1	10.4	−1.7
B3LYP/6-31+G(d)	8.6	7.0	−1.7
MP2/6-31+G(d)	3.0	−6.4	−9.4
B3LYP/6-311++G(2d,2p)	7.7	6.8	−1.0
MP2/6-311++G(2d,2p)	−2.2	−7.4	−5.2
Modeling Book/OHO(Tyr): MP2/6-31+G(d) Optimized Minimum of Tyr−Gly			
HF/6-31+G(d)	28.5	22.4	−6.1
B3LYP/6-31+G(d)	19.3	13.9	−5.3
MP2/6-31+G(d)	−7.0	−35.1	−28.8
B3LYP/6-311++G(2d,2p)	18.9	15.3	−3.6
MP2/6-311++G(2d,2p)	−18.1	−34.5	−16.4

[a] As the geometry optimizations of the Tyr−Gly conformers do not include corrections for intramolecular BSSE, the uncorrected interaction energies (ΔE^{noCP}) correspond to the stability difference of the MP2- and B3LYP-optimized structures. [b] "Vertical" counterpoise-corrected interaction energy; i.e., the monomer deformation energies are not taken into account.

The close contact between the aromatic ring and the glycine residue in the MP2-optimized structure could be caused by BSSE or genuine energy contributions, such as dispersion, as both are expected to be much larger in the MP2 calculations. To estimate the intramolecular BSSE, the Tyr−Gly structures were modeled by intermolecular complexes of *N*-formylglycine and phenol, with conformations and relative spatial arrangements identical to the MP2- and B3LYP-optimized Tyr−Gly minima (the former is shown in Figure 1d). The counterpoise-corrected (*N*-formylglycine)phenol interaction energies were computed using Gaussian 03[33] (Table 1). As generally observed,[5] the BSSE is much smaller for HF and B3LYP than for MP2. Even with the large 6-311++G(2d,2p) basis set, the BSSE is still substantial in the MP2 calculations, and more importantly, the effect is not the same for the two conformations; i.e., BSSE significantly alters the intermolecular potential energy surface even with this large basis set.

The interaction between phenol and *N*-formylglycine in the complex derived from the MP2-optimized book/OHO(Tyr) structure is very favorable at the MP2 level. This attraction is much reduced in the less folded B3LYP-optimized book structure. B3LYP predicts a repulsive interaction in both complexes, though the repulsion is smaller in the book structure. It is therefore likely that the increased foldedness of the Tyr−Gly conformer after MP2 geometry optimization is caused by the larger attraction (at the MP2 level) between the phenyl ring and the glycine residue in the more folded configuration. A significant part of this attraction appears to be caused by BSSE: before applying the counterpoise correction, the book/OHO(Tyr) conformer is more stable than the book conformer by ∼28 kJ mol^{-1} (at the MP2/6-31+G(d) level); counterpoise correction reduces this to 10 kJ mol^{-1}. Thus, counterpoise correction does not invert the relative stability of the two complexes, which implies that dispersion also plays a significant role in the stabilization of the book/OHO(Tyr) conformer. B3LYP predicts that the book/OHO(Tyr) structure is less stable than the book structure by ∼10 kJ mol^{-1}, which suggests that the B3LYP underestimate of dispersion is of the order of 20

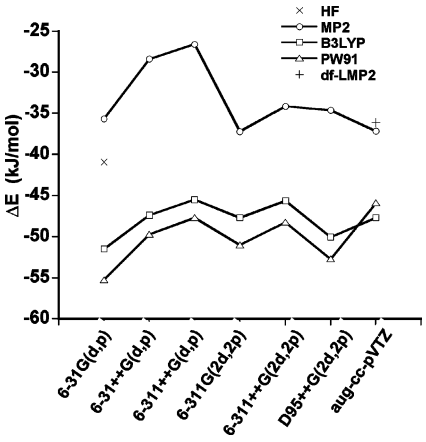

Figure 2. Relative stability of the conformers of 2-(acetylamino)benzamide found in the α and β polymorphs as a function of electronic structure theory. The structures were optimized with each method/basis set combination, with the torsion angles $\phi = \tau$(C3−C4−N5−C6), $\psi = \tau$(N1−C2−C3−C4), $\omega_1 = \tau$(H11−N1−C2−O), and $\omega_2 = \tau$(H12−N1−C2−O) constrained to their experimental values (α-form:[36] 169.6, −152.8, −166.1, and −8.3°, respectively; β-form:[36] −60.2, −51.3, 173.0, and 1.4°, respectively). For all cc-pVTZ calculations only single-point relative energies at the MP2/6-311++G(2d,2p) optimized structures are reported.

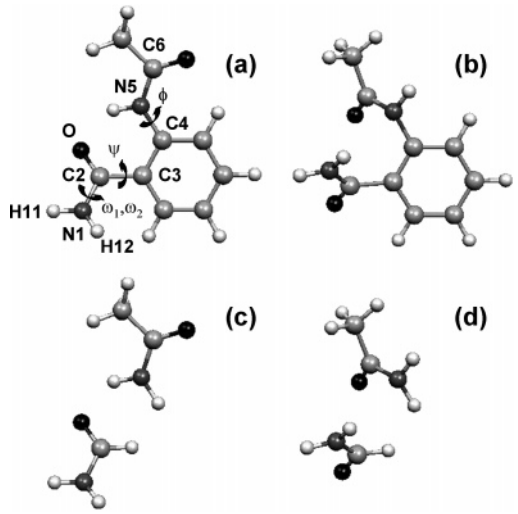

Figure 3. α (a) and β (b) conformers of 2-(acetylamino)benzamide, optimized at the MP2/6-31G(d,p) level of theory, with the ϕ, ψ, ω_1 and ω_2 torsions constrained to their experimental values (see Figure 2). (c) and (d) formamide−acetamide complex structures derived from the α- and β-conformers of the 2-(acetylamino)benzamide structures displayed in (a) and (b) used in estimating the importance of BSSE. The phenyl ring was removed and the phenyl carbon atoms in contact with the formamide and acetamide fragments were replaced with hydrogen atoms, at a distance of 1.08 Å in the direction of the bond in the 2-(acetylamino)benzamide minima at the corresponding level of theory.

kJ mol^{-1}. (This may be an overestimate, as part of the energy difference is likely due to the stabilizing electrostatic contribution of the OHO(Tyr) hydrogen bond in the more folded structure. In addition, MP2 calculations are known to overestimate the dispersion relative to CCSD(T) calculations for stacked π systems.[19,34]) A similar observation that commonly used density functional methods fail to predict the correct structure of the phenylalanyl−glycyl−glycine tripeptide due to the inaccurate London dispersion contribution has recently been reported by Řeha et al.[35]

3. Further Analysis on Two Crystalline Conformers of 2-(Acetylamino)benzamide

The intramolecular BSSE and dispersion errors could be explored in more detail in the case of 2-(acetylamino)benzamide. This molecule has two crystal structures:[36] the α-polymorph has an internal hydrogen bond that is replaced in the β-polymorph by an elongated intermolecular hydrogen bond formed by the NH donor of the acetamide chain. Molecular modeling estimates[37,38] of the relative lattice energies of the two crystals, calculated as the sum of the intermolecular lattice energy and ab initio or semiempirical estimates of the conformational energy differences, were significantly greater than the conventionally accepted limit of about 10 kJ mol^{-1}.[39] Although a determination of the exact stability difference between the two polymorphs requires accurate models for the intermolecular interactions, the accurate estimation of the intramolecular energy differences was expected to be more straightforward. On the contrary, Figure 2 shows that the energy difference between the two molecular conformations greatly depends on the electronic structure method applied.

The two main causes for the different results predicted by MP2 and B3LYP are again the large intramolecular BSSE in the former method and the severe underestimation of dispersion in the latter. MP2/6-31G(d,p) calculations estimating the intramolecular BSSE by considering two complexes of formamide with acetamide in the relative spatial arrangements of the two side chains in the polymorphs of 2-(acetylamino)benzamide (Figure 3) show that BSSE effects are significant. The BSSE values are −12.17 and −15.89 kJ mol^{-1} for the complexes representing the α- and β-conformers, respectively. Thus, for the complex representing the α-conformer, counterpoise correction changes the interaction from attractive (−1.18 kJ mol^{-1}) to repulsive (10.99 kJ mol^{-1}), whereas counterpoise correction increases the (repulsive) interaction energy of the β-complex from 9.00 to 24.89 kJ mol^{-1}. The relative stability of the two formamide−acetamide complexes (α − β) is thus −10.3 kJ mol^{-1} (uncorrected) and −13.9 kJ mol^{-1} (CP-corrected), indicating that intramolecular BSSE artificially favors the β-form of 2-(acetylamino)benzamide.

Although the absolute BSSE values are still significant at the MP2/6-311++G(2d,2p) level, they are of similar magnitude for the complexes modeling the α- and β-conformers (−6.59 and −6.86 kJ mol^{-1}, respectively), and thus, the effect on the relative interaction energies is minimal (−12.32 kJ mol^{-1} uncorrected; −12.59 kJ mol^{-1} counterpoise-corrected). It is worth noting that both formamide−acetamide complexes have the same short distance (1.8 Å) between the two hydrogens added to saturate the dangling bonds left behind when the phenyl ring in 2-(acetylamino)benzamide is removed. Such a short intermolecular H···H distance is rarely observed in crystal structures.[40] The repulsive interaction in formamide−acetamide is probably due to this short distance and does not necessarily indicate that the interaction between the formamide and acetamide fragments in 2-(acetylamino)benzamide is repulsive. However, this short contact will give a constant contribution to the BSSE, and so the variation between the conformations is a meaningful estimate of the BSSE artifact on the relative conformational energies. Accordingly, the use of the 6-311++G(2d,2p) basis set appears to be sufficient to evaluate the relative energy differences of the two 2-(acetylamino)benzamide polymorphs without significant artifacts from BSSE. This contrasts with Tyr−Gly, where at this level of theory the BSSE effect was found to differ substantially for the two conformations. This difference correlates with the nature of the varying

close contacts (O−H···aromatic interaction and N−H···O═C hydrogen bond) in the two molecules.

Figure 2 shows that, even when using this basis set to virtually eliminate the relative intramolecular BSSE, MP2 and two commonly used DFT methods still give very different results for the relative stability of the two 2-(acetylamino)benzamide structures. As further confirmation, the df-LMP2[41−44] method, implemented in Molpro,[45] which produces much reduced BSSE values as compared with canonical MP2[46] while including dispersion, yields results almost identical to those obtained with MP2 for an aug-cc-pVTZ basis set. For sufficiently large basis sets, we can attribute most of the discrepancy in the results obtained with MP2 and B3LYP to the difference in the intramolecular dispersion energy between the different parts of the molecule, i.e., the contribution that is modeled as nonbonded C_6/R^6 in most force fields.

4. Conclusion

The conformations of flexible molecules and their relative stabilities can be very sensitive to the type of electron correlation used, because of the importance of dispersion contributions, and to the basis set employed, as large basis sets are required to avoid intramolecular BSSE. The relative importance of intramolecular BSSE and inaccuracies in the dispersion description is so conformation dependent as to be a cause for concern in many applications of molecular modeling. This warning of the intramolecular energy sensitivity to the electronic structure level of theory is particularly important for fields, such as crystal structure prediction, where the focus is generally on other aspects of the computational model and only one electronic structure method is typically used.[47−49] Commonly used DFT methods, such as B3LYP/6-31G(d), may not give reliable results for molecular systems where the intramolecular dispersion energy is likely to be a major factor in determining the conformation.

Unfortunately, the more reliable calculations reported in this paper required considerable computational resources which are not readily available for many molecular systems where the balance of BSSE and dispersion errors is likely to be problematic. However, the recently proposed df-LMP2 method, employing the aug-cc-pVTZ basis set, gave a relative energy difference for the two conformers of 2-acetylamino-benzamide of −36 kJ mol^{-1}, in good agreement with the MP2/aug-cc-pVTZ value, but in less than a tenth of the computer time. This method, which includes dispersion[46] and produces much smaller BSSE values than MP2, therefore appears to be a promising new tool for molecular modeling.

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