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Significant van der Waals Effects in Transition Metal Complexes

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Abstract: There is, in general, very good experience using hybrid DFT to study mechanisms of enzyme reactions containing transition metals. For redox reactions, the B3LYP* functional, which has 15% exact exchange, has been shown to be particularly accurate. Still, there are some cases which have turned out to be quite difficult with large errors. In the present study, the effects of van der Waals interaction have been investigated for these cases, using the empirical formula of Grimme. The results are encouraging.

Introduction

Hybrid density functional theory has been an extremely successful tool in studying mechanisms for enzymatic reactions involving transition metals.[1−3] Barriers and reaction energies within 3−5 kcal/mol from experimental results have generally been found, provided the chemical model is large enough. Still, there are continuous reports of failures of hybrid DFT for transition metal complexes. For example, the energy differences between the peroxo and bis-μ-oxo isomers of copper dimer complexes appear to show big errors of 10−15 kcal/mol.[4] Also, the binding of methyl and adenosyl to cobalamin[5] as well as the binding of small molecules to heme groups have been reported to be underestimated by the same, or even larger, magnitude.[6] The most common explanation for the DFT failures has been the inability to describe multireference effects, since DFT is inherently a single determinantal method.[6,7] That explanation, implying that B3LYP should very often be distrusted for transition metal complexes, is in sharp contrast to the excellent experience obtained when studying chemical reactions with this method. In the present letter, these failures for transition metal complexes are reinvestigated using recent improvements of hybrid DFT, where van der Waals effects are empirically included.[8] A significant advantage of this improvement is that it can be applied on top of the results of a well established DFT method, such as B3LYP.[9] Since it has been argued that the fraction of exact exchange is a way to tune nondynamical correlation effects in DFT,[10] another advantage is that these effects and van der Waals effects, which have different origins, can be separated. This type of improvement is in contrast to suggestions to improve the results in difficult cases by selecting a different functional depending on the problem investigated. In that approach, the hybrid B3LYP functional could be used for molecules containing first and second row atoms, while a nonhybrid functional like BP86 should be used for binding methyl and adenosyl to cobalamin, and M06 functionals should be used for copper complexes.[4−7] There are some previous investigations on the inclusion of explicit van der Waals effects for 3d transition metal complexes. For example, significant improvements were demonstrated for noncovalent ligand binding energies in some chromium complexes.[11] In a benchmark test containing 3d transition metals, the inclusion of a dispersion correction on top of the B97 functional essentially removed cases with large errors.[12] Also, the M06-L functional has been demonstrated to show much improved results for noncovalent interactions in 3d complexes.[13]

Methods

In the calculations performed here, the B3LYP* functional[14] has been used if not otherwise indicated. This is a slight modification of the original B3LYP functional[9] with 15% exact exchange (rather than 20%), which has been found to

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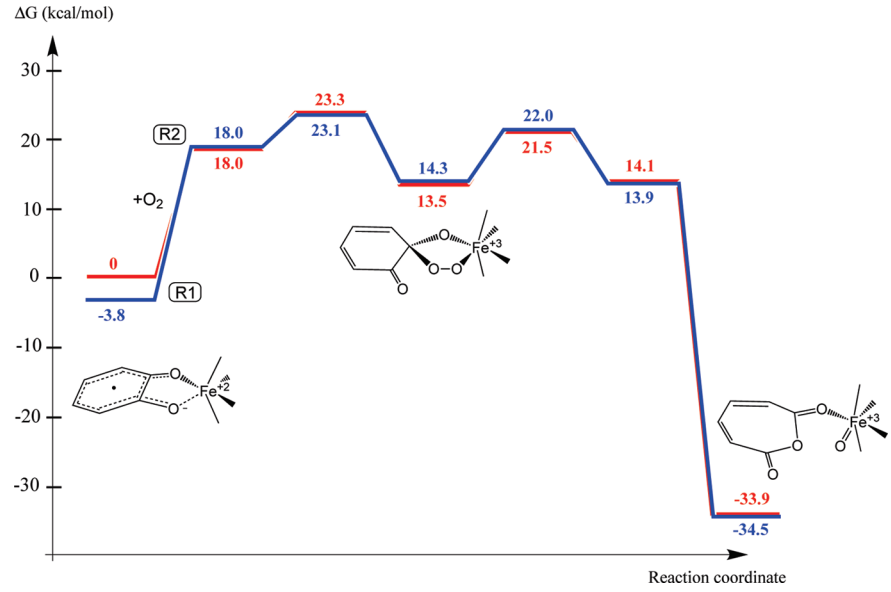

Figure 1. Energy diagram for the biomimetic intradiol-cleaving dioxygenase discussed in the text. The red line is without, the blue line with van der Waals effects.

be superior in most cases for describing oxidations of transition metals.[2,14,15] The energetics discussed were obtained using large, nearly saturated basis sets (cc-pvtz(-f)) in single point calculations at geometries optimized using a smaller basis set. Solvent effects were included with a dielectric constant chosen from case to case. They were not found to be significant in the reactions discussed below. The calculations were performed using the Jaguar program.[16]

A Typical Energy Diagram. The discussion of the results will start with a typical example of a reaction mechanism involving a transition metal complex, taken from a recent application.[17] This reaction is for a biomimetic intradiol-cleaving dioxygenase, where the details do not matter in the present context. The energy diagram obtained at the B3LYP* level for the suggested mechanism is shown in Figure 1. The starting point of the reaction is an Fe(III) complex with a bound catechol substrate. In the first step of the mechanism in the figure, O_2 binds to the complex. The mechanism then proceeds by formation of a bridging peroxide, and the cleavage of the O−O bond. Finally, the ring of the catechol substrate is opened in between the carbons carrying the hydroxyl groups, an intradiol cleavage. The competing mechanism is an extradiol ring opening, and the main question asked is why one mechanism is preferred and not the other. This and other questions were answered by the model calculations, and the barriers computed were reasonable compared to experiments. In short, there was no sign of any failure of B3LYP* in spite of the redox chemistry occurring.

Also shown in Figure 1 are the relative effects (set to zero for **R2**) from adding van der Waals interactions through the empirical formula. The most striking feature is that these effects are almost perfectly constant throughout the reaction, except for the step from **R1** to **R2** when O_2 becomes bound, where there is a significant relative effect of −3.8 kcal/mol, which is expected since two additional atoms are added to the complex. The conclusion drawn is that, apart from this effect, which has been pointed out before,[18,19] the energy diagram is almost unaffected by adding van der Waals effects. The most important mechanistic issues, such as the choice of the intradiol or extradiol pathway, are therefore also unaffected.

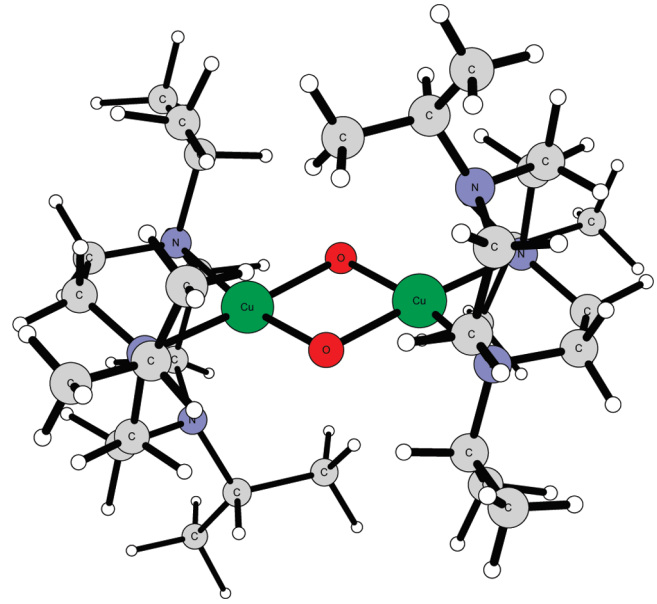

Figure 2. Optimized Cu_2(III,III)-bis-μ-oxo structure with iPr_3TACN ligands.

Dicopper Complexes. The discussion of dicopper complexes will start with the case with iPr_3TACN ligands, shown in Figure 2. This is an interesting system experimentally, for which it has been shown that the bis-μ-oxo (in the figure) and the peroxo complexes are in equilibrium.[20] The experimental estimate of the energy difference is 0.9 kcal/mol favoring the peroxo complex. The previously calculated B3LYP value is 15.0 kcal/mol, favoring the peroxo complex, and was claimed to show "some of the worst agreement between pure and hybrid functionals" ever reported.[4] The pure functional value was in good agreement with experiments, and this type of functional was therefore strongly

recommended for these systems. The present B3LYP* value is 4.2 kcal/mol. Adding the van der Waals effect of −3.6 kcal/mol leads to an energy difference of only 0.6 kcal/mol. The solvent effects (already included) favor the bis-μ-oxo structure by −1.7 kcal/mol. The zero-point effects of +2.0 kcal/mol (not included) favor the peroxo structure, while the relativistic effects of −3.9 kcal/mol (not included)[21] are in the opposite direction. Overall, the present result is in quite reasonable agreement with experiments. The difference between the present and the previous results is partly explained by the use of B3LYP*, which favors the bis-μ-oxo structure by 5.7 kcal/mol compared to B3LYP, and the van der Waals effects of 3.6 kcal/mol, also favoring the bis-μ-oxo structure. However, this is not the full explanation, since these corrections only sum up to 9.3 kcal/mol and the difference amounts to 14.4 kcal/mol. The larger basis set used here also appears to play a role. For the corresponding case with iPr_2TACD ligands, the present calculations favor the peroxo structure by 5.3 kcal/mol, including a van der Waals effect of −5.8 kcal/mol. This result is also in qualitative agreement with experiments, even though the exact energy difference is not known in that case. For another type of ligand, termed DBED, the experimental energy difference is shifted slightly (by 1 kcal/mol) toward the peroxo complex, compared to the case with iPr_3TACN ligands.[22] The present calculations give an energy difference of 2.7 kcal/mol favoring the peroxo structure, where the van der Waals contribution is −2.8 kcal/mol. The calculated difference from the case with iPr_3TACN ligands is thus +2.1 kcal/mol in favor of the peroxo structure, in comparison with the experimental preference by about +1.0 kcal/mol.

Since the above results are in such good agreement with experiments, it is interesting to investigate what the same level of treatment gives for the energy difference between the peroxo and the bis-μ-oxo structure of the dicopper complexes appearing in the hemocyanin, tyrosinase, and catechol oxidase enzymes, which has been a strongly debated issue.[23] In these cases, there are three histidine ligands on each copper. Modeling these by imidazoles leads to an energy difference of 14.1 kcal/mol favoring the peroxo structure, which includes a van der Waals effect of −3.2 kcal/mol. This result is in qualitative agreement with the fact that only the peroxo complex has been observed. The previous conclusion that the bis-μ-oxo structure does not enter into the mechanisms in these enzymes,[23] therefore, still appears to hold.

Binding of Methyl and Adenosyl to Cobalamin. The cleavage of the Co−C bond in methyl- or adensoyl-cobalamin, see Figure 3, is a common first step in many reactions catalyzed by enzymes including the vitamin B_{12} cofactor. In the case of adenosyl, the cleavage is homolytic, and the resulting radical abstracts a hydrogen atom from the substrate in the second step. In the case of methyl, the cleavage is heterolytic, resulting in a methyl cation. A major problem in quantum chemical studies of these enzymes has been that it has turned out to be difficult to obtain a proper homolytic bond dissociation energy for the Co−C bond. B3LYP has been found to underestimate the bond strength by 10−15 kcal/mol. In contrast, nonhybrid methods like BP86 have given values much closer to experiments but have instead had problems in describing the energetics of the subsequent reaction steps.

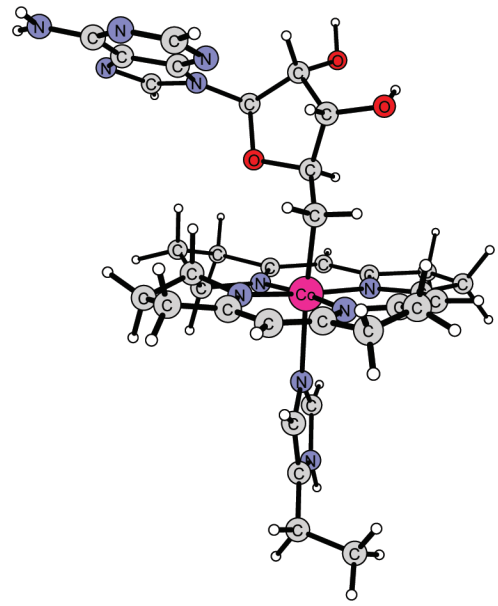

Figure 3. Optimized structure for cobalamin with a bound adenosyl ligand.

Using the model in Figure 3, a B3LYP value for the Co−C bond strength for methyl of 16.2 kcal/mol (including zero-point and solvent corrections) was obtained in ethyleneglycol ($\varepsilon = 40$),[24] compared to the experimental value of 37 ± 3 kcal/mol.[25] A discrepancy of as much as 20 kcal/mol is thus obtained, in line with previous bad experience using hybrid DFT. At the B3LYP* level, the bond strength increases to 20.7 kcal/mol, which is still a severe underestimation. However, in this case, the van der Waals effects turn out to be quite large with 11.3 kcal/mol increasing the bond strength. The resulting bond strength of 32.0 kcal/mol is at least in reasonably good agreement with experiments. For adenosyl, the corresponding results are 16.7 kcal/mol at the B3LYP* level, and 29.5 kcal/mol with van der Waals effects added. This result agrees very well with the experimental value of 30 kcal/mol.[26] The van der Waals contribution of 12.8 kcal/mol for adenosyl is remarkably large. The reason is the large number of rather short atom−atom distances between the substrate and the cobalamin. The van der Waals contribution from the metal is very small due to the cutoff value in the empirical formula. It is clear that the mechanisms of these cobalamin-containing enzymes cannot be described without van der Waals interactions.

Small Molecule−Heme Interactions. The binding of molecular oxygen to heme-iron is important in several biological processes, for example, in oxygen transport and in respiration. Also, the binding of other small molecules, such as CO and NO, to heme-iron plays an important role, for example, as inhibitors for O_2 binding. As has been pointed out before, the binding energies of these small molecules to heme-Fe(II) as calculated using the B3LYP functional are significantly too small,[6] at the same time as it was shown that CASPT2 calculations gave good agreement with experimental results. Since this failure of the DFT calculations

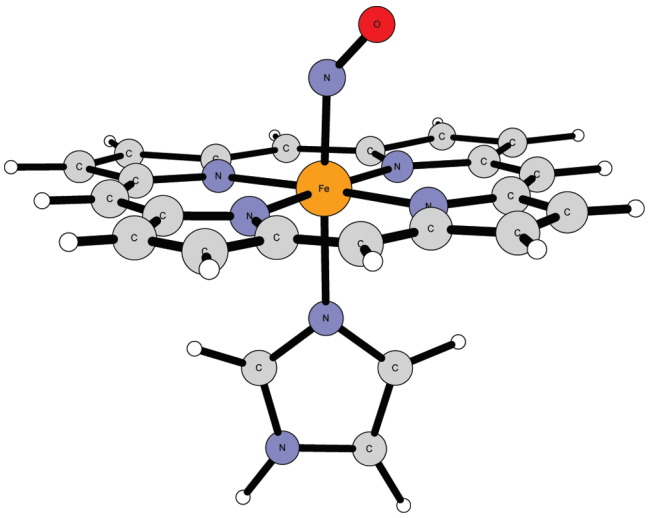

Figure 4. Model used in the calculations of small molecule−heme complexes.

Table 1. Calculated Fe−X Binding Energies in Six-Coordinated Heme, Where X is CO, NO, or O_2 (Zero-Point Effects Included)

	Fe−CO (kcal/mol)	Fe−NO (kcal/mol)	Fe−O_2 (kcal/mol)
B3LYP	10.9	7.6	1.1 (5.9)[c]
B3LYP-D	20.6	16.9	8.8 (13.6)[c]
B3LYP*	16.6	16.3	5.5 (10.3)[c]
B3LYP*-D	26.3	25.6	13.2 (18.0)[c]
exp[a]	19.5 (18.5)	22.8 (22.8)	10.1 (16.1)
exp[b]	18.1		12.3

[a] From dissociation barriers in myoglobin corrected for "the protein effect",[6] uncorrected myoglobin values in parentheses. [b] Dissociation barriers in protoheme. [c] Values within parentheses are spin-corrected.

can be due to the lack of both multireference and van der Waals effects, new calculations have been performed using both the B3LYP and the B3LYP* functionals, and adding the empirical van der Waals corrections according to Grimme, giving rise to four calculated binding energies for each system: B3LYP, B3LYP-D, B3LYP*, and B3LYP*-D. The model used in the calculations is shown for the NO case in Figure 4, and the results are summarized in Table 1.

As can be seen from Table 1, the attractive van der Waals effects are quite significant, 9.7 kcal/mol for CO, 9.3 kcal/mol for NO, and 7.7 kcal/mol for O_2. This is due to the interaction between the binding molecule and the large number of atoms in the heme group. The B3LYP-D values therefore come quite close to the experimental values for both CO and O_2, while the binding of NO is still much too small, 16.9 kcal/mol compared to the experimental value of 22.8 kcal/mol. Reducing the amount of exact exchange in going from B3LYP to B3LYP* gives quite large increases in the binding energy, 5.7 kcal/mol for CO, 8.6 kcal/mol for NO, and 4.4 kcal/mol for O_2. In the case of (heme)Fe−O_2, which has an antiferromagnetically coupled open shell singlet ground state, there is also a calculated spin-correction of 4.8 kcal/mol, and in the table all values are given with and without this spin correction. The spin correction and the reduction of exact exchange are partly related effects, connected to the multiconfigurational character of the wave function, and if both effects are applied, the calculated binding energy is clearly too large, 18.0 kcal/mol (with van der Waals correction) as compared to the experimental values of 10−12 kcal/mol. Without spin correction, the B3LYP*-D value of 13.2 kcal/mol is in good agreement with the experimental values. For NO, the B3LYP*-D value of 25.6 kcal/mol is a bit too large compared to the experimental value (22.8 kcal/mol), but it is still the best calculated value for NO binding.

In summary, for these heme systems, the situation is more complicated than for the other systems discussed above. The van der Waals effects are large and important, but for some systems, B3LYP-D gives better agreement with experimental values, while for others, B3LYP*-D gives better results. Further investigations are therefore needed to find out how these systems should be best described.

Conclusions

In a few important cases, taken from studies of enzyme mechanisms, van der Waals effects have been shown to be quite significant. In most cases they appear in the step where a substrate becomes bound to the metal cofactor. Apart from this step, the van der Waals effects are normally small. By including the van der Waals effects, and reducing the amount of exact exchange to 15%, the results are in good agreement with experiments even for most of these difficult cases. The most significant improvements appear for the binding of adenosyl to cobalamin and for biomimetic dicopper complexes, where very good results are obtained. Interestingly, the previous exclusion of the Cu_2(III,III) state in the mechanism of tyrosinase[23] still appears to hold. The exceptions to the excellent results are the cases when a small molecule is bound to a heme group, where the results are still not quite satisfactory. For these systems, more work and experience are needed to improve the situation.

Supporting Information Available: Coordinates for all the structures discussed in the present paper. This information is available free of charge via the Internet at http://pubs.acs.org/.

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