

Redox and linkage isomerism with ligands relevant to oxidative and nitrosative stress in cobalamin



Mihai Surducan^{a,*}, Sergei V. Makarov^b, Radu Silaghi-Dumitrescu^{a,*}

^aDepartment of Chemistry and Chemical Engineering, "Babes-Bolyai" University, Str. Arany Janos Nr. 11, RO-400028 Cluj-Napoca, Romania

^bState University of Chemistry and Technology, Engels str., 7, 153000 Ivanovo, Russia

ARTICLE INFO

Article history:

Received 1 July 2013

Accepted 5 March 2014

Available online 20 March 2014

Keywords:

Density-functional theory

Cobalamin

Nitrogen monoxide

Dioxygen

CASSCF

ABSTRACT

Presented here is an extensive DFT study on the interaction of both Co(II) and Co(III), base-on and base-off cobalamins with such ligands as dioxygen, superoxo, hydroperoxo, NO, NO⁺, HNO and NO₂⁻. Dioxygen is predicted to bind to Co(II) but unlikely to form a stable complex with Co(III)cobalamins, in line with the fact that such an adduct has not been observed experimentally. Formally hexacoordinated Co(II) models bound to anions (hydroperoxo, superoxo) are predicted to be possible, but partial charges show that such adducts would instead contain a Co(III) state, with the extra electron either on the corrin or the ligand, and not a 'true' Co(II). Binding of a nitro group to Co(III)cobalamins is thermodynamically favored over nitrito binding, in line with the complexes thus far characterized by X-ray crystallography, which only give the Co(III)–N bound isomer. NO is predicted here to bind to both Co(II) and Co(III), with the first preferred. Although it is known that NO will not react with Co(III)–H₂O cobalamins (the actual species present in neutral or acidic media), which is in accordance with experimental data, HNO appears more favored to bind to cobalamins (both Co(II) and Co(III)) compared to water and hence these complexes are a viable target for the future. Furthermore, CASSCF calculations were performed in order to obtain more detailed views on problematic electronic structures; these are discussed in comparison (and, mostly in agreement) to the DFT results.

© 2014 Elsevier Ltd. All rights reserved.

1. Introduction

Vitamin B₁₂ is a cofactor for methionine synthase, a key enzyme in folate metabolism. Nitric oxide (NO) inhibits methionine synthase in mammalian cells *in vitro* [1–3] and *in vivo* at physiological concentrations and pH [4]. The effectiveness of the reaction between NO and cobalamin strongly depends on the oxidation state of the cobalt atom. In neutral and acidic aqueous solutions, NO reacts very effectively with Co(II) and Co(I)cobalamins [5–7], but not directly with Co(III)cobalamin. In strongly acidic solutions, Co(III)cobalamin reacts with NO through reductive nitrosylation leading to the Co(II) adduct, but through a mechanism dependent on nitrite impurities present in NO aqueous solutions [8]. NO₂⁻ was also shown to react with Co(III)cobalamins. [9]. Reduced cobalamin (containing a Co(II) state) also reacts with hydrogen peroxide [10] and O₂ [11,12]. Co(II)cobalamin was also observed to react very rapidly with superoxide in a SOD (superoxide dismutase) type reaction [13]. Crystal structures have been determined for the nitro

adduct of Co(III)cobalamin [14,15], and for NO [16,17] and O₂ Co(II)cobalamins [11]. DFT calculations were employed extensively to study not only the alkyl-cobalamins directly relevant for enzyme mechanisms [18–24], spectra [25–27] and cobalamins within proteins [28–30], but also for cobalamins bound to oxygen, nitrite and NO [8,31–33]. This set of reactions, involving nitrite, nitric oxide, dioxygen and its reduced congeners, is reminiscent of the ones seen with hemoproteins, and in which such issues as electromerism, high- or low-valent states and linkage isomerism were discussed [34,35]. Presented here is an extensive DFT study on cobalamins, with the metal atom in two oxidation states (+2, +3) with such ligands as dioxygen, superoxo, hydroperoxo, nitroxyl, nitrozo, nitro and nitrito, aiming to examine linkage and redox isomerism. In the case of dioxygen, nitroxyl and nitrozo, which were found to be problematic cases, CASSCF calculations were performed and comparisons to the DFT results are given.

2. Materials and methods

The models used in the present study are shown in Fig. 1. An anionic corrin ring without any lateral substituents (noted from now on as C) was bound to a formally Co(II) or Co(III) metal center.

* Corresponding authors. Tel.: +40 264593833; fax: +40 264590818.

E-mail addresses: mihai.surducan@ubbcluj.ro (M. Surducan), rsilaghi@chem.ubbcluj.ro (R. Silaghi-Dumitrescu).

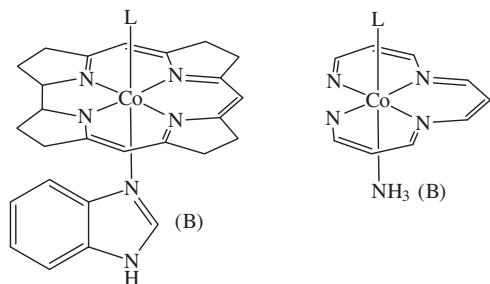
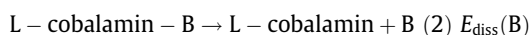


Fig. 1. Theoretical models employed for the cobalamins. Full corrin model (left) for DFT studies with $L = O_2, O_2^-, OOH^-, NO_2^-, ONO^-, NO^0, NO^+, HNO$; corrin reduced in size (right) for CASSCF studies with $L = O_2, NO^0, HNO$.

An unsubstituted benzimidazole (denoted in the figure as **B**) was used as an axial ligand and the sugar bound to the nitrogen atom in cobalamins was replaced with a hydrogen atom. “Base-on” and “base-off” models signify here the presence and absence of the benzimidazole ligand in the models employed. Sets of extra axial ligands were used (denoted as **L** in Fig. 1 and exemplified later in the text) trans to the benzimidazole ligand.

Full geometry optimizations were performed for all models at the BP86/6-31G** and B3LYP/6-31G** level of theory, as implemented in Spartan [36] using standard convergence criteria. As recent computational studies showed the superiority of GGA functionals compared to hybrid functionals on geometric parameters and dissociation energies for the methylcobalamin, adocobinamide and methylcobinamide benchmarks [37–39], all results pertaining to the latter functional are placed in the Appendix section. A discussion related to the B3LYP functional is only given in the case where this functional performs better than BP86 or in the case of spin densities. Partial atomic charges and spin densities were obtained from Natural Population Analyses (NPA) as implemented in Spartan. This methodology was applied in our group with reasonable results on iron-heme models and also on corrin models [40,41]. Single point energies were recomputed in Gaussian 09 [42]. Frequency calculations were performed at the same level of theory using Gaussian 09 [42] and no imaginary frequencies were found, confirming the structures are local minima on the potential energy surface. Dissociation energies (E_{diss}) for the hexacoordinated complexes were computed according to the equations:



As solvent corrections were shown to improve the computed bond dissociation energy in methylcobalamin compared to experimental values [18], they were accounted for by using the CPCM solvation model, as employed in Gaussian 09, using water [42]. Additionally, single point energies were computed using the larger basis set 6-311+G** as implemented in Gaussian [42]. Thermochemistry data extracted from vibrational analysis is presented in the Appendix. Thermal corrections do not change the value of the ZPE corrected energy by more than 1 kcal/mol and do not significantly improve the results, where experimental data is available for comparison. Dispersion energy corrections were also found to improve the BDE of methylcobalamin compared to the experimental results [20] and were determined here by using the software DFT-D3 [43] using the Becke Johnson damping function [44,45]. These are presented as corrections to the SCF energy in the Appendix. As a general note, dispersion corrections for $E_{diss}(B)$ tend to increase this value by 14–18 kcal/mol, regardless of the functional. Because of the lack of experimental data for the enthalpy for equation (2), this data will not be commented on further.

Selected smaller models (Fig. 1) were used to compute spin densities at the CASSCF level of theory. These were constructed as follows: the cobalamin was reduced in size by replacing all sp^3 carbon atoms by hydrogen, while maintaining the conjugated system in the original corrin. In the case of the base-on models, the benzimidazole was replaced by ammonia. Although the models do not contain the full corrin ring or axial base, the same naming (“cobalamin”, “base-on” and “base-off”) will be used in the discussion. Full geometry optimizations followed by frequency calculations were carried out in Gaussian 09 [42] using BP86/6-31G**. CASSCF calculations were performed afterwards on these optimized geometries in the MOLCAS 7.7 software [46–48]. The ANO-S basis set library was used, with the following contraction scheme: 6s5p3d1f for Co, 3s2p1d for N and O, 3s2p for C and 2s1p for H. All details of the active spaces employed are given in the Results and discussions section. Mulliken spin densities for the DFT results were computed with Gaussian 09 [42], while for the CASSCF calculations they were computed with MOLCAS [46–48].

3. Results and discussions

3.1. Reactions of cobalamins with dioxygen and related species

Results for the geometry optimizations for different oxygen cobalamins are given in Tables 1 and 2 and the Appendix. All hexacoordinated Co(III) models are predicted to be possible. As a general observation, dioxygenic ligands exert a stronger trans effect on the axial base compared to water (elongating the Co–N(B) distance), and in line with the trans effect of ligands studied before at the same level of theory, of which hydroxo, thiocyanato and isothiocyanato ligands can be exemplified [40].

Of the models employed in this section, the formal O_2^- –Co(III)cobalamin is an electromer of O_2^0 –Co(II)cobalamin and was the only one characterized by X-ray crystallography. Diffraction data indicate that the first electromer is the best description for the model based on comparisons with other oxygen bound cobalt species [11]. Also, EPR measurements on similar O_2 –Co(II)cobyrinates [49] and O^{17} enriched O_2 –Co(II)cobalamin reveal almost one full spin unit on the ligand [12], supporting the superoxo description. BP86 results attribute 1.09 spin units on the dioxygenic ligand, consistent with the superoxo model, but B3LYP results show a completely different picture: half of a negative spin unit on the cobalt antiferromagnetically coupled with 1.5 spin units on the ligand, suggesting a possibly hidden mixed Co(III)–superoxo/Co(II)–diradicalic dioxygen state; Fig. 2 shows the spin densities predicted by the two functionals.

The situation is even more accentuated in the base-off model, where almost a full negative spin unit is found on the metal and almost two full spin units are predicted on the ligand by B3LYP. The bond lengths given by BP86 are closer to the experimentally determined ones (Co–O = 1.93 Å, O–O = 1.31 Å, Co–N(B) = 2.06 Å) [11], giving credit to the electromer proposed by this functional. For the Co–O–O angle, the experimentally determined value is 120°, very close to the value of 118° predicted here.

On comparing to the results obtained by DFT in other studies, one can see that the geometrical parameters obtained by LDA–VWN are similar (Co–O = 1.91 Å, O–O = 1.27 Å, Co–N(B) = 1.99 Å, Co–O–O = 116°) [32,33] but BP86 still predicts values closer to the experimental values. On the other hand, in reference [33], B3LYP predicted a broken Co–O bond, a result not observed here when using this functional.

Both functionals employed here indicate local minima corresponding to an interaction between O_2 and Co(III)cobalamin with geometrical parameters predicting bonding. It is, however,

Download English Version:

<https://daneshyari.com/en/article/1337825>

Download Persian Version:

<https://daneshyari.com/article/1337825>

[Daneshyari.com](https://daneshyari.com)