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Vitamin B_{12} catalysis - probing the structure/efficacy relationship

Maksymilian Karczewski,[a] Michał Ociepa,[a] Katarzyna Pluta,[a] Keith ó Proinsias,[a]* Dorota Gryko[a]*

Abstract: Vitamin B_{12} is a cofactor for many enzymes but it also functions as a catalyst in C-C bond forming reactions. In the present study, the impact of corrin structural modifications on their catalytic efficacy was examined. Derivatives with various substituents at *c*-, *d*-, and *meso*-positions were synthesized using traditional and new microwave methodologies and then tested in the model reaction of 1,1-diphenylethylene with EDA. To complement our experimental data, CV and DFT calculations were performed. Mainly alterations at the *c*- or *d*-positions influence both the reaction yield and selectivity.

Introduction

Over the years vitamin B_{12} (**1**, cobalamin, Cbl) has attracted a lot of attention mainly because of its biological role as a cofactor in enzymatic reactions: methyl transfer, rearrangements, or dehalogenation (Figure 1).[1-3] However, its use as a catalyst in synthetic organic chemistry has been less explored. The catalytic activity of cobalt corrinoids is inherently connected with the metal ion, its redox properties, and their ability to form Co-C bond. One of the most crucial steps in all vitamin B_{12} catalyzed reactions involves the homolytic cleavage of this bond in alkyl-cobalamins, which is influenced by the ligand structure and reaction conditions. In the field of catalysis, the fine tuning of the catalyst efficacy, via proper ligand design, has always been among the top priorities.[4-6] However, in the case of vitamin B_{12} and its derivatives, a comprehensive understanding of the role of axial and equatorial ligands and their ligation under thermal and photolytic conditions has not yet been fully exploited.

In alkyl-cobalamins, the basicity of the *trans*-axial ligand (corrin) weakly changes the dissociation energy of the Co-C bond. However, the situation becomes more complex when the *cis*-effect is additionally involved. In this regard, two main factors should be considered: 1) modifications of the corrin ring affect the character of the cobalt centre, and/or 2) modifications of the peripheral groups not only affect the cobalt ion but through interactions with substrates, for example via hydrogen bonding, affect the catalyst' efficiency. In this regard, NMR experiments showed that an exchange of an axial ligand on the cobalt ion impacts the chemical shift of the *meso*-proton resonance, indicating the influence of the *cis*-effect.[7,8] Moreover, the comparison of *meso*-X-Cbl bond lengths in *meso*-Cl-Cbl, *meso*-NO-Cbl, and *meso*-H-Cbl bearing different Co-L (L = H_2O, Me or CN) substituents revealed that they are different.[9,10] Marques and Knapton's DFT calculations unveiled the effect of *meso*-substituents on the electron density on the central cobalt ion.[11-13] The introduction of a chlorine atom at the *meso*-position causes the delocalization of charge density from the axial donor atom to the metal and Cl resulting in the stronger binding of anionic ligands.[11]

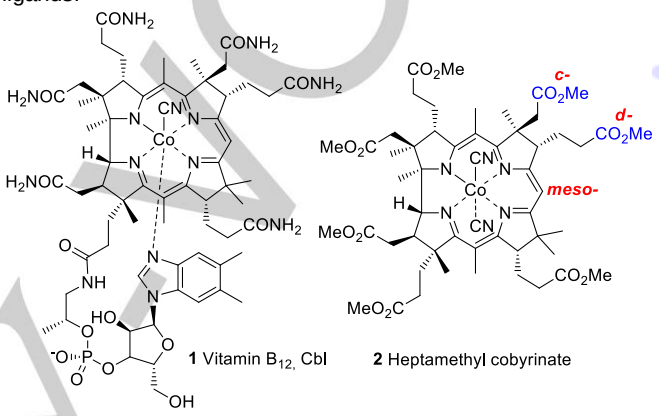

Figure 1. Structures of corrins **1** and **2**.

We wondered whether and how functional groups present on the periphery of the vitamin B_{12} corrin ring, would affect the catalytic property of a derivative. One of the only cases, reported by Murakami *et al*, of intentional modification of a vitamin B_{12} derived catalyst was achieved by linking *c*- and *meso*-positions with 1,3-diphenylenediacetal.[14] A so called "strapped" derivative was alkylated at the β-axial site with racemic 3-bromo-2-methylpropionic esters. An increase in the enantioselectivity compared to the reaction catalysed by the parent heptamethyl cobyrinate **2** was observed. Based on the electrochemical studies and DFT calculations, it was concluded that the electronic state of the central cobalt ion remained unchanged but the steric hindrance imposed by the strap effectively created a stereospecific microenvironment at the β-face of the macrocycle. Furthermore, Zelder *et al.* corroborated the influence of the peripheral groups in the substitution of the cobalt-coordinated water molecule with the cyanide ligand in diastereoisomerically pure aquacyanoheptmethyl cobyrinates.[15] Kinetic studies revealed that the two faces of heptamethyl cobyrinate (**2**) are indeed different due to the diverse stereochemical environments imposed by the remote side chains. Moreover, peripheral groups influence corrinoids' binding properties due to the hydrogen bonding between an axial ligand at the β-face of the macrocycle and the carbonyl moiety at the *c*-side chain.[16] This interaction has also been reported by O'Connor and Kräutler.[17] In the crystal structure of spirolactone, bearing *c*-ethanolamide and *d*-lactone, Gryko *et al.* observed the existence of hydrogen bonding between the β-axial cyanide ligand and the terminal -OH group of the *c*-ethanolamide

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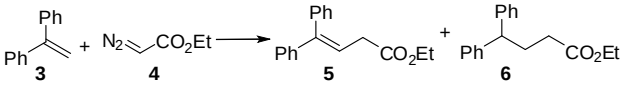
Supporting information for this article is given via a link at the end of the document.

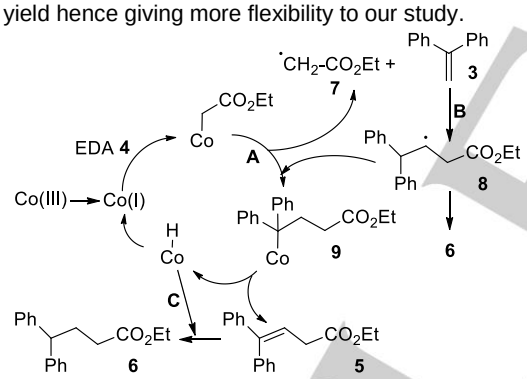
moiety.[18] Even though these evidences clearly suggest that remote structural modifications of the macrocycle affect vitamin B_{12} physicochemical properties, a study on how these changes impact catalytic efficacy of vitamin B_{12} derivatives has yet to be undertaken. Herein, the influence of modifications at the *c*-, *d*- and *meso*-positions of vitamin B_{12} derivatives on their catalytic efficacy in the model reaction of 1,1-diphenylethene (**3**) with ethyl diazoacetate (**4**) is presented (Scheme 1).



Scheme 1. Model reaction of 1,1-diphenylethene with EDA.[19]

Results and Discussion

The influence of different functional groups present at the periphery of the macrocycle on the catalytic activity of corrin derivatives **10-26** was studied in the model reaction of 1,1-diphenylethylene with ethyl diazoacetate (EDA, **4**). This reaction is known to be catalysed by an amphiphilic cobalamin derivative - cobalester giving a mixture of olefin **5** and its hydrogenated analogue **6** in overall 91% yield (Scheme 1).[19] For the purpose of our project, heptamethyl cobyrinate (**2**) was used as a catalyst with the loading being decreased to 1 mol%. The reaction furnished a mixture of products **5** and **6** with a desirable decreased yield (61%) thus allowing for a larger gap of variability in the yield hence giving more flexibility to our study.



Scheme 2. Proposed mechanism for the C-H alkylation of an olefin using a B_{12} catalyst.[19]

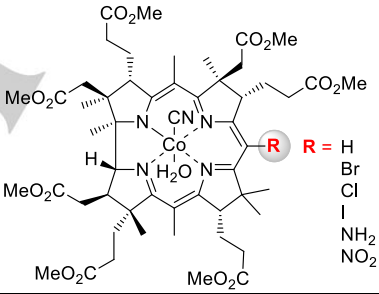
According to the proposed mechanism[19] (Scheme 2) post-generation of the Co(I) species and reacting with EDA **4**, radical **7** is generated (**A**). Upon reacting with 1,1-diphenylethene (**3**) affording intermediate **8**, which subsequently undergoes recombination with the catalyst in its +2 oxidation state (Co(II)form), either alkylcobalamin **9** or compound **6** (**B**) is obtained. Subsequent dehydrocobaltation gives product **5**, which can also transform into compound **6** by reacting with hydridoderivative[20] (**C**).

The synthesis of Cby(OMe)$_7$ **2**, Cby(OMe)$_6$(*c*-lactone) **16** and Cby(OMe)$_6$(*c*-lactam) **17**, the three main starting materials required for the preparation of all catalysts, was performed using newly developed methodology. It was found that utilizing microwave irradiation for the methanolysis of vitamin B_{12} allowed for a substantial decrease in the reaction time from 6 days to 40 min. and rapid generation of desired derivatives (for full optimization and experimental details see supporting information).

All catalysts were transformed into their aqua-form **2**, **10**-**26** ((CN)(H_2O)Cby) to facilitate the reduction of the central cobalt ion in the model reaction.

Firstly, we focused on derivatives modified at the *meso*-position. As it is known that such modifications *via* the *cis*-effect, influence the nature of the central cobalt atom.[23] The presence of *meso*-Br- (**10**), -Cl (**11**), or -NH_2 (**13**) substituents in the catalyst structure had little to no effect on the model reaction yield but fluctuation in the products' ratio (**5**:**6**) was observed (Table 1, entry 2, 3, 5). This suggests that such modifications affect either the rate of hydrogenation of olefin **5** (Figure 2, step **C**) or the recombination rate of intermediate **8** with the catalyst (Figure 2, step **B** decreased rate), both steps that heavily influence the selectively of the studied reaction. Unfortunately, data obtained for corrins **12** and **14** could not be used for comparison as both catalysts were not stable under reaction conditions (entries 4, 6).

Table 1. Yields and ratios for the model reaction with *meso*-position modified catalysts [a]



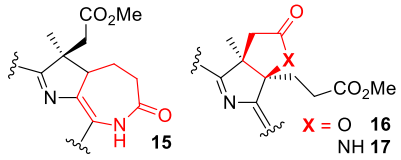
Entry	Catalyst	Yield [%]	Ratio (**5**:**6**)
1	**2**	61	17:1
2	**10**[21]	62	11:1
3	**11**[21]	51	8:1
4	**12**[22]	-	-
5	**13**[23]	62	9:1
6[b]	**14**[23]	61	7:1

[a] Conditions: diphenyl ethylene (90 µL, 0.5 mmol), ethyl diazoacetate (156 µL, 1.3 mmol), catalyst (1 mol%), Zn (196 mg, 3.0 mmol), NH_4Cl (90 mg, 1.7 mmol), ACN (5 mL), rt, under light irradiation (2x300 Lm LED warm light), 18 h, Ar atmosphere. [b] Possible reduction to compound **13**.

Subsequently, to examine the effect of the peripheral groups a series of *c*- and *d*-modified catalysts was prepared. First, restrained *c*- **15** and *d*-modified catalysts **16**, **17** were examined. Catalyst **15** with a lactam between the *d*- and *meso*- positions, resulted in a significant drop in the yield of products (27%) and a decrease in the selectivity (4:1) (Table 2, entry 1). An even more pronounced result was obtained with *c*-lactam **17**, the reaction yield dropped to 32% and no selectivity was observed (entry 3). Although these results do adhere to our theory, still there may be some interactions between the remaining, protruding carbonyl groups. Therefore, catalysts with no substituents at *c*-

and *d*-positions were prepared to give a more comprehensive view.

Table 2. Yields and ratios for the model reaction with restrained *c*-/*d*-catalysts [a]

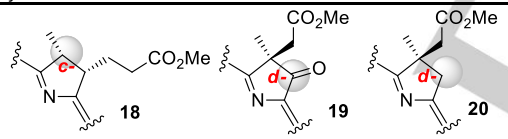


Entry	Catalyst	Yield [%]	Ratio (**5**:**6**)
1	**15**[23]	27	4:1
2[b]	**16**	37	4:1
3	**17**	32	1:1

[a] Conditions: diphenyl ethylene (90 µL, 0.5 mmol), ethyl diazoacetate (156 µL, 1.3 mmol), catalyst (1 mol%), Zn (196 mg, 3.0 mmol), NH_4Cl (90 mg, 1.7 mmol), ACN (5 mL), rt, under light irradiation (2x300 Lm LED warm light), 18 h, Ar atmospehere. [b] Possible reduction to compound **21**.

Surprisingly, removal of the substituent at the *c*-position (catalyst **18**, Table 3, entry 1) did not have a major impact on the yield (51%), although a 19% increase in the yield was observed as compared to *c*-lactam **17**. In reactions catalyzed by corrins **19** and **20** (entry 2-3), lacking the *d*-peripheral side chain, the effect was even more pronounced as a larger decrease in the yield, 45% and 31% respectively, and an almost complete loss in selectivity was observed. This emphasizes the importance of the *d*-side chain in the catalyst structure. Therefore, further studies into modifying *c*- and *d*-positions to empower the catalyst efficacy and possibility steer towards an optimal catalyst were conducted.

Table 3. Obtained yields and ratios for the model reaction with nor-*c*- and *d*- catalysts [a]

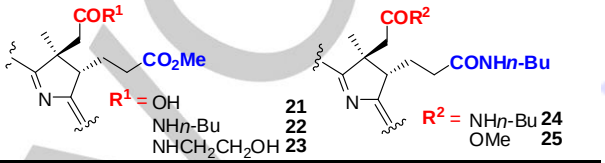


Entry	Catalyst	Yield [%]	Ratio (**5**:**6**)
1	**18**[25]	51	4:1
2	**19**[26]	45	4:1
3	**20**[27]	31	2:1

[a] Conditions: diphenyl ethylene (90 µL, 0.5 mmol), ethyl diazoacetate (156 µL, 1.3 mmol), catalyst (1 mol%), Zn (196 mg, 3.0 mmol), NH_4Cl (90 mg, 1.7 mmol), ACN (5 mL), rt, under light irradiation (2x300 Lm LED warm light), 18 h, Ar atmosphere.

At this stage of the research, the best catalyst for our model reaction possesses the original ester groups at the *c*- and *d*-positions at the periphery of the corrin ring (catalyst **2**, Table 1, entry 1); however, any modification imposed on the catalyst only gave a decrease in the yield and ratio of products. Since reported data indicate that hydrogen bonding between axial ligands and the *c*-side chain amide group was shown to form stronger hydrogen bonds than with ester group, consequently amide derivatives were prepared and tested. The replacement of the *c*-methyl ester group with -CO_2H in the catalyst structure (catalyst **21**) led to both a substantial decrease in the yield and ratio (Table 4, entry 2). Next, two particular amides, *n*-butylamide **22** and ethanolamide **23** (entry 3 and 4) were tested as the later one is known to interact with the cyano ligand bound to the cobalt ion.[18] In both cases the isolated yield increased to 77-78%. Moreover, major differences were observed in the ratio of products, 9:1 for catalyst **22** (entry 3) and 12:1 for catalyst **23** (entry 4). Presumably, this was the result of the presence of the terminal -OH group, hence hydrogen bonding can facilitate the formation of desired product **5** and hinders the generation of compound **6**. Unfortunately, a complete selectivity in the studied reaction has not yet been achieved.

Table 4. Yields and ratios for the model reaction with *c*- and *d*- modified catalysts [a]



Entry	Catalyst	Yield [%]	Ratio (**5**:**6**)
2	**21**[26]	30	3:1
3	**22**	78	9:1
4	**23**	77	12:1
5	**24**	53	5:1
6	**25**	69	9:1

[a] Conditions: diphenyl ethylene (90 µL, 0.5 mmol), ethyl diazoacetate (156 µL, 1.3 mmol), catalyst (1 mol%), Zn (196 mg, 3.0 mmol), NH_4Cl (90 mg, 1.7 mmol), ACN (5 mL), rt, under light irradiaton (2x300 Lm LED warm light), 18 h, Ar atmospehere.

As the significance of the substituent at the *d*-position in the catalyst structure was confirmed (see Table 3), catalyst **25**, bearing the *n*-butylamide group at this position, was synthesized and tested. Interestingly, the yield dropped to 69%, compared to catalyst **22** (78%), but was still higher than the one obtained for parent catalyst **2** (61%). This suggests the importance of the distance between the amide group and the cobalt ion or the configuration at the *d*-position. However, when di-*n*-butylamide catalyst **24** was applied, the model reaction furnished products with a decreased yield (53%) and selectivity (5:1) (entry 5). Although each group influences the reaction course in a specific manner, interactions between neighbouring groups also hinder the catalyst. To further elaborate on this hypothesis, heptamide **26** was prepared and tested. In this case the reaction yield increased to 71% with the highest ratio of products being recorded (13:1) compared to all the catalysts studied.

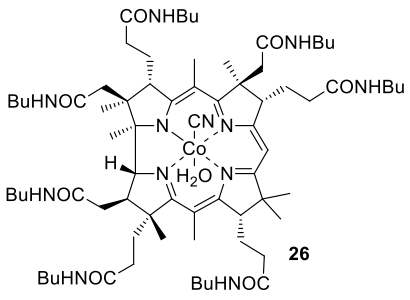


Figure 2. Structure of catalyst **26**.

To complement our data and further elaborate the structure/efficacy relationship, a series of electrochemical and computational experiments were performed.

Table 5. Reduction potential values [V] of synthesized catalysts [a] (*vs.* Ag/AgCl)

Entry	Cat.	$(H_2O)(CN)Co(III)/(H_2O)Co(II)$	$(H_2O)Co(II)/Co(I)$	$(CN)_2Co(III)/(CN)Co(II)$	$(CN)Co(II)/Co(I)$
1	**2**[b]	-	-	-1.30	-1.50
2	**2**[c]	-0.43	-0.64	-1.30	-1.51
3	**10**	-0.35	-0.54	-1.18	-1.39
4	**11**	-0.34	-0.53	-1.13	-1.34
5	**13**	-0.39	-0.62	-1.30	-1.54
6	**14**	-0.48	-	-1.27	-1.53
7	**15**	-0.33	-0.56	-1.21	-1.44
8	**16**	-0.37	-0.54	-1.15	-1.33
9	**17**	-0.62	-0.62	-1.25	-1.48
10	**18**[e]	-0.36	-0.92	-1.35	-1.57
11	**19**[e]	-0.36	-0.91	-1.52	-1.52
12	**20**	-0.42	-0.63	-1.30	-1.51
13	**21**	-0.39	-0.65	-	-
14	**22**	-0.36	-0.69	-	-
15	**23**	-0.33	-0.64	-1.21	-1.46
16	**24**	-0.42	-0.64	-1.23	-1.47
17	**25**	-0.46	-0.64	-1.31	-1.58
18	**26**	-0.37	-0.68	-1.24	-1.46

[a] Measurements conditions: catalyst (c = 0.2 M); electrolyte (NBu_4ClO_4, c = 0.1 M); solvent: dry, degassed acetonitrile; potential sweep rate: 100 mV/s; working electrode: GC; auxiliary electrode: Pt wire; reference electrode: Ag/AgCl; all measurements were carried out at room temperature and under Ar atmosphere; [b] $(CN)_2Cby(OMe)_7$, [c] $(CN)(H_2O)Cby(OMe)_7$, [d] Dicyano form of the catalyst, [e] Unusual voltammogram was recorded

The influence of structural changes on a catalyst redox property was studied with the means of cyclic voltammetry (Table 5). The results clearly indicate that the incorporation of the halogen substituent at the *meso*-position gave less negative values of reduction potentials compared to heptamethyl cobyrinate **2**. Surprisingly, the presence of strong electron donating (-NH_2 **13**, entry 5) or electron withdrawing (-NO_2 **14**, entry 6) substituents at this position did not change E_{pc} substantially indicating that the effect of the halogen on the cobalt cannot be purely electronic. Interestingly, in the case of catalyst **14** the peak corresponding to the redox couple Co(II)/Co(I) for the aqua form was not observed hence Co(II) complex exists in solution mainly in the (CN)Co(II) form. This can be explained by the fact that the incorporation of the -NO_2 group at the *meso*-position induces stronger affinity of the cobalt centre towards the cyanide ligand, which is consistent with constant values of the complex formation ($pK_{Co\text{-}CN}$) reported by Marques.[28] Contrary, for catalysts **21** and **22** (entry 13-14) the redox couples Co(III)/Co(II) and Co(II)/Co(I) for dicyano form were not observed. Hence, the formation of complexes **21** and **22** in the dicyano form in acetonitrile solution is much slower in comparison to other cobyrinates studied, which is advantageous when using mild reducing agents (Figure 3). This could also contribute to the increase in yield observed for catalyst **22**, but the conflicting results found for catalyst **21**, bearing the *c*-acid moiety, further expresses the complexity of the reaction. In the case of catalyst **24** (entry 16) having very similar structural features to **22** did not show analogous behaviour, this can be further attested to their yield and product ratio that vary substantially.

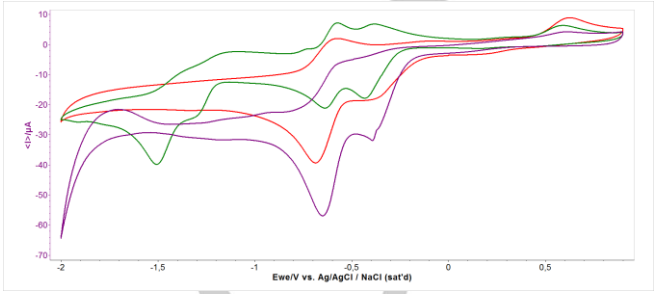


Figure 3. Comparison of catalysts **2** (green), **21** (purple) and **22** (red).

On the other hand, the voltammogram of complex **17** (entry 9) showed not separated redox couples Co(III)/Co(II) and Co(II)/Co(I) for their aqua forms, which is distinctively different from typical cobyrinates,[29] but similar to the redox behaviour observed for cobalamins (e.g. cyanocobalamin, cobalester).[30] For other studied catalysts, the value of redox potentials are varying in the range of +/- 0.1 V, indicating that in those cases structural changes have minor influence on the redox properties of the cobalt centre.

The *trans* effect's influence can be exploited using DFT calculations (considering the second step of the mechanism). We wondered whether the electron density, as computed by Gausian 09, localized on the central metal ion might be proportional to the reaction yield.[31,32] As the Co(I) species has a pseudo square planar geometry and its two faces, α and β, are capable of acting catalytically the absolute value of the arithmetic mean of minimum electron density at the cobalt atom was calculated. For highly complex molecules DFT calculations are often performed on simplified models. Kozłowski *et al.* proved that in the case of vitamin B_{12}, a simplified structure of cobyrinate, bereft of peripheral groups, could be used to compute dissociation energies of the axial ligands (Figure 4).[33,34] We have additionally incorporated *c*- and *d*- moieties. For the initial dataset, the electron densities of catalysts – **2**, **10**, **13**, **15**, **18**, **20**, and **22** were assigned. At first the B3LYP/6-31G(d) level of theory was used, incorporating the solvent effect (acetonitrile) as implemented in the PCM. As well as the LANL2DZ basis set which takes heavy atoms, i.e. cobalt, into account. Furthermore, BP86 and M062x functionals were also investigated.

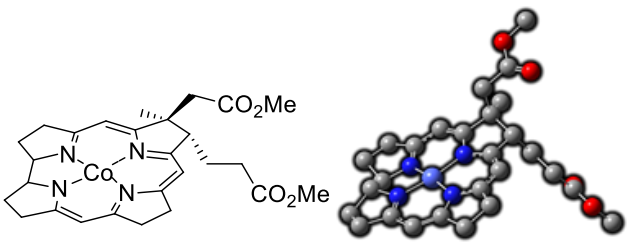
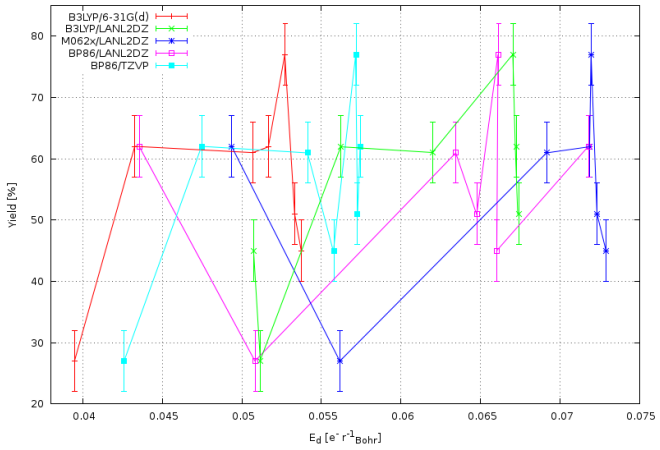


Figure 4. Simplified and optimized structure of cobyrinates.

The absolute value of the mean electron density (E_d) was plotted against the yield, assuming error of ±5% (Table 6). (Please see supporting information for a more detailed graph.) Catalyst **21**, bearing a free carboxylic group, was exempt from this study since it is not inert and can be present in its anion form.

Table 6. Absolute value of mean electron densities of cobalt for different basis/set functional.

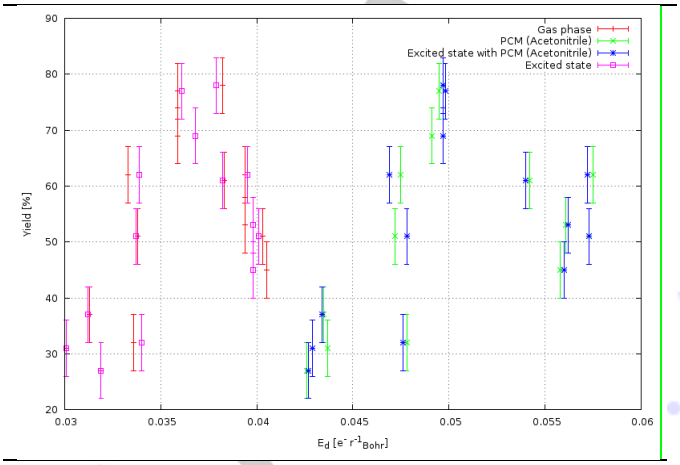


Entry	Cpd	|E.@Co(I)| [e r-1Bohr]			
		TZVP	6-31G(d)	LANL2DZ	
		BP86	**B3LYP**	**B3LYP**	**M062x**
1	**2**	0.0542	0.0507	0.0620	0.0691
2	**10**	0.0475	0.0433	0.0562	0.0493
3	**13**	0.0575	0.0517	0.0673	0.0718
4	**15**	0.0426	0.0395	0.0512	0.0562
5	**18**	0.0573	0.0533	0.0674	0.0723
6	**20**	0.0558	0.0537	0.0507	0.0729
7	**22**	0.0572	0.0527	0.0670	0.0719

With the B3LYP functional an unusual plateau was observed and therefore was disregarded, while employing B3LYP/LANL2DZ a vast difference in electron densities was found for catalysts **18** and **20** (Table 6, entry 5 and 6), which is in contradiction to their chemical character and yields. The combination of BP86 and M062x with LANL2DZ gave a large error for catalyst **10** compared to other results (entry 2). Consistent data were obtained using B3LYP/6-31G(d) or BP86/TZVP and upon expansion of the dataset the latter proved superior (Table 7).

In order to present a more realistic view, different environmental aspects were taken into consideration, including optimized geometries in the gas phase, first excited state with PCM included or solely first excited state. However, gas phase and PCM calculations were discarded due to over or under estimation of electron densities for catalyst **10** and **13** respectively (Table 7, entry 4 and 10). Hence, we have concluded that the excited state optimized geometry was paramount in describing the relationship between minimum of the electron density and the yield.

Table 7. Calculated electron densities using BP86/TZVP.



|E.@Co(I)| [e r-1Bohr]

Entry	Compound	gas phase	PCM	PCM/ex. state	ex. state
1	**18**	0.0301	0.0437	0.0429	0.0301
2	**16**	0.0313	0.0435	0.0434	0.0312
3	**15**	0.0319	0.0426	0.0427	0.0319
4	**10**	0.0338	0.0472	0.0478	0.0337
5	**11**	0.0333	0.0475	0.0469	0.0339
6	**17**	0.0336	0.0478	0.0476	0.0340
7	**22**	0.0359	0.0495	0.0498	0.0361
8	**25**	0.0382	0.0497	0.0497	0.0379
9	**2**	0.0383	0.0542	0.0540	0.0382
10	**13**	0.0394	0.0575	0.0572	0.0395
11	**20**	0.0405	0.0558	0.0560	0.0398
12	**18**	0.0403	0.0573	0.0573	0.0401

Although the geometry of the *c*- and *d*-peripheral side chains have previously been calculated, in our case reliable results for catalysts possessing amide groups were not obtained. Utilizing catalyst **23**, bearing *c*-ethanolamide group, the conformation in relation to electron density vs yield was examined. It was discovered that the conformation of the *c*-side chain with the nitrogen atom facing the corrin plane, was superior when compared to an oxygen atom (see supporting information for a detailed graph regarding conformation vs electron density). Using the electron densities for the optimized structure a complete plotted graph was assigned (Figure 5).

DFT calculations indicate that with none of our catalyst could furnish products **5** and **6** exceeding 80%, even with the assumed error of 5%. In the case of catalyst **18** a larger deviation was observed, giving a 10% error. When compared to Murakami's work,[14] the effect of steric bulkiness could not be considered, since when the structures of catalyst **2** and **15** are overlaid the angle of the *d*-side chain is the same for both compounds (see supporting information for comparison of structures). Therefore, the instability of the catalysts under the reaction conditions should be considered. This is also true for catalyst **17**, **18** and **19**.

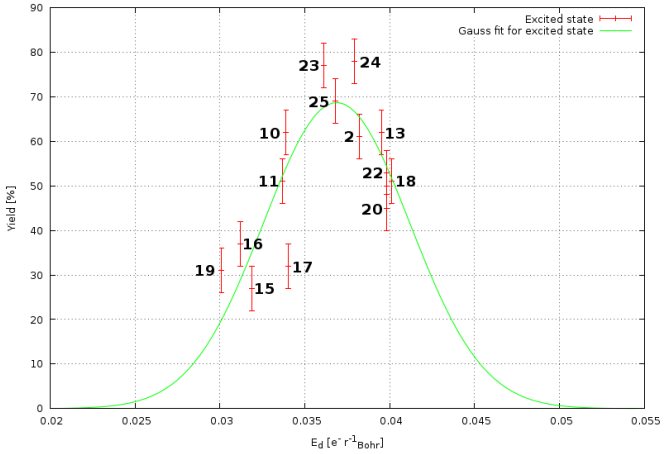


Figure 5. The electron density plotted against yield and Gauss fit.

Conclusions

In conclusion, vitamin B_{12} derivatives were prepared using standard and new microwave methodologies, specifically focusing on modifications at the *c*-, *d*- and *meso*-positions. The hydrophobic vitamin B_{12} structure/efficacy relationship was studied on the model reaction of 1,1-diphenylethylene (**3**) and EDA (**4**). It was found that the introduction of halogens or electron donating/withdrawing groups at the *meso*-position had little to no effect on the reaction yield, though halogenation at the *meso*-position (**10**, **11**, **12**) did have an impact on the cobalt redox properties. Thus, we assume that the reduction step has a minor effect on the overall reaction outcome. However, differences in the ratio of saturated and unsaturated products were observed.

In the case of the B-ring peripheral groups, restraint of either the *c*- or *d*-positions, via lactam formation, resulted in a large drop in the yield of products **5** and **6**, and a complete loss of selectivity, highlighting the importance of the B-ring side chains on the catalysts efficacy. The removal of either *c*-acetate or *d*-propionate resulted in a decrease in the yield and selectivity of the model reaction. On the other hand, the incorporation of amide moieties at the *c*-position (namely ethanolamide or *n*-butylamide) had a positive effect, increasing the yield and giving selectivity close to that of the original heptamethyl cobyrinate (**2**) due to possible interactions of the amide or other terminal groups with the ligand bound to cobalt.

Furthermore, the relationship between the electron density of the central cobalt metal and the actual yield was established using BP86/TZVP which proved the best for calculating the efficacy of our catalysts. Geometries of the peripheral groups were considered, with the implementation of the excited state geometries proving superior. The accumulated results gave a Gauss distribution curve with a 5-10% error, depending on the catalyst, with a possible optimum yield of 80%.

The accumulation of all results leads us to reconsider our view on exactly how a cobalamin catalyst operates in a chemical reaction. Even though previous reports gave us a glimpse into the catalysts activity in a specific situation, one must view the reaction as a whole, combining the effect of catalyst modification with the subsequent effect the catalyst has on the surrounding reactants. This work shows only the beginning of our investigatory journey into viewing real-life vitamin B_{12} catalysis.

Experimental Section

General procedure for the model reaction: Into a dry tube (30 mL Pyrex borosilicate glass with ground socket) catalyst (1 mol%), activated Zn (196 mg, 3.0 mmol) and NH_4Cl (90 mg, 107 mmol) was added with a magnetic stirrer. The flask was sealed using a septa and flushed with Ar. MeCN (5.0 mL) was added and the mixture degassed for 10 min by bubbling Ar under sonication. Subsequently, diphenyl ethylene (90 µL, 0.5 mmol) and ethyl diazoacetate (156 µL, 1.5 mmol) were added and the mixture irradiated with visible light from LEDs (300 Lm; warm light) for 18 h. The reaction was then diluted with DCM and filtered through a silica plug to remove the catalyst and zinc, and then concentrated in vacuo. Purification using flash column chromatography, 2% AcOEt in hexane gave the desired product as a clear oil.

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Keywords: vitamin B_{12} • Co-catalysis • corrins • diazo compounds • olefins

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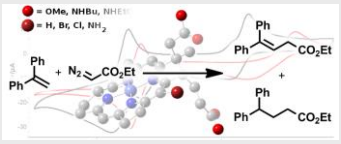
Layout 2:

FULL PAPER



Vitamin B_{12} catalysis: Vitamin B_{12} derivatives modified at *c*-, *d*-, and *meso*- were synthesized using new microwave methodology and tested as catalysts in the model reaction of 1,1-diphenylethylene with EDA. Experimental results, CV measurements and DFT calculations showed that mainly alterations at *c*- and *d*-positions influence the catalytic efficacy of vitamin B_{12} derivatives.

*one or two words that highlight the emphasis of the paper or the field of the study

Co-catalysis, vitamin B_{12}

Maksymilian Karczewski, Michał Ociepa, Katarzyna Pluta, Keith ó Proinsias, and Dorota Gryko**

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Vitamin B_{12} catalysis - probing the structure/efficacy relationship