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Synthesis of α-oximinoketones, Precursor of CO_2 Reduction Macrocyclic Coenzyme F430 Model Complexes

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Abstract Ni(II) containing coenzyme F430 catalyzes the reduction of CO_2 in methanogen. Macrocyclic Ni(II) complexes with N,O shiff bases have been received a great attention since metal ions play an important role in the catalysis of reduction. The reducing power of metal complexes are supposed to be dependent on oxidoreduction state of metal ion and structural properties of macrocyclic ring moiety that can enhance electrochemical properties in catalytic process. Six different α-oximinoketone compounds, precursor of macrocyclic ligands used in CO_2 reduction coenzyme F430 model complexes, were synthesized with yields over 90% and characterized by NMR. The molecular geometries of α-oximinoketone analogues were fully optimized at Beck's-three-parameter hybrid (B3LYP) method in density functional theory (DFT) method with 6-31+G* basis set using the ab initio program. In order to understand molecular planarity and substitutional effects that may enhance reducing power of metal ion are studied by computing the structure-dependent ^{13}C-NMR chemical shift and comparing with experimental results.

Keywords Coenzyme F430, Ab initio, NMR, CO_2 reduction

Introduction

F430 is a Ni(II)-containing coenzyme that functions in the two electron reduction of methyl coenzyme M (2-(methylthio)-ethane sulfonate) to methane and coenzyme M (2-mercaptoethane) in methanogenic bacteria.[1-4] The coenzyme consists of a tetrapyrrole corphin macrocycle with a centrally bound, square planar Ni atom as shown in Figure 1.[5,6] Similar to the corrin macrocycle in coenzyme B_{12}, the corphin is not fully conjugated and is thus able to bend or ruffle.[7,8] Although knowledge of the mechanistic details of F430-dependent catalysis is primitive,[9,10] XAFS[11] and resonance Raman[12] studies on the F430-methyl reductase holoenzyme point to the formation of additional bonds to Ni to yield either 5- or 6-coordinate species. In addition, Jaun and Pfaltz[13] recently presented data suggesting that organonickel intermediates may be formed during F430-dependent catalysis.

A central question in F430 catalysis (and for that matter, B_{12} catalysis) is the role of a flexible equatorial macrocycle. In the widely studies B_{12} system, proposed mechanisms dealing with axial bond formation and cleavage invoke steric interactions between the equatorial and axial ligands as the dominant function of a flexible macrocycle.[14] In NMR and X-ray crystallography studies, F430 has the thermally unstable derivatives 13-monoepimeric F430 and 12,13-diepimeric F430. These two derivatives form a tetraaza ring, which called corphin due to its structural similarity to porphyrin and corrin.[15] It is reported corphin was not fully conjugated and it thus able to bend or ruffle, similar to the corrin macrocycle in coenzyme B_{12}.[16]

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The structural modification of macrocycle by epimerization can play and important roles in oxidation of central metal Ni(II), and this charac terization is important information to under stand the catalytic process of F430 in the cell.

In this study, various α-oximinoketone compounds, precursor of macrocyclic ligands used in CO_2 reduction coenzyme F430 model complexes, were synthesized in order to address molecular planarity and substitutional effects by comparing the structure dependent ^{13}C-NMR chemical shift obtained from molecular geometries optimized with ab initio quantum computations.

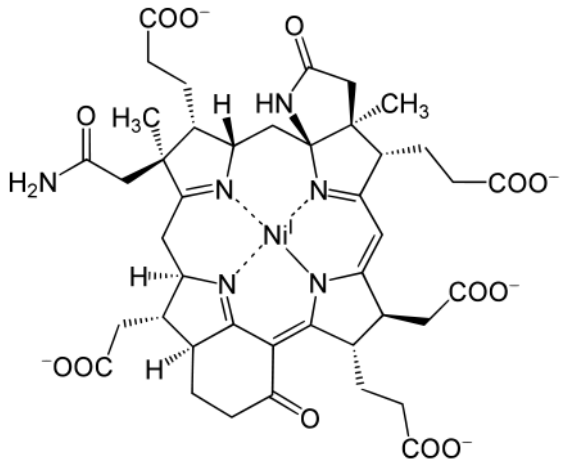

Figure 1. Structure of native coenzyme F430

Experimental Methods

Material and Synthesis of α-oximinoketones – All chemicals were purchased from Sigma Aldrich and used without further purifications. The NOCl was synthesized by reacting chlorotrimethylsilane with isoamyl nitrite at low temperature, and product subsequently added to propiophenones carrying various substituents. As shown in Figure 2, the NOCl can attack the labile hydrogen atom near ketone when ketone and enol are under chemical equilibrium, and finally enable to produce α-oximinoketone. By using propiphenone moiety with various substituents, 6 different α-oximino propiphenone derivatives were synthesized.[15] The oximimino macrocyclic ligands can be synthesized by adding 0.5 equivalents of diamine. These tetradentate macrocyclic ligands can bind with metal ions such as Ni(II), and these metal complexes can be used as F430 model complexes.

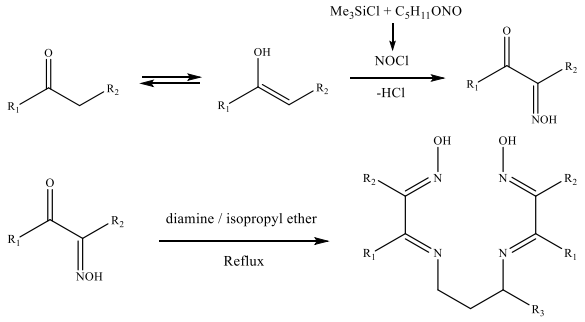

Figure 2. Synthesis of α-oximinoketone and macrocyclic tetradentate ligand with different substituents (R_1 : phenyl group, R_2 and R_3 : methyl group)

The detail synthetic procedure of α-oximinoketone compounds are as follows; 30 mL of methylene chloride and acetophenones with various substituents were added to the jacketed round-bottom flask equiped with low temperature circulator and reflux condensor. The addition of 1.2 g of Me_3SiCl (0.011 mol) and 1.4 g of isoamyl nitrite (0.0112 mol) gave rise to α-oximinoketones at -20 ℃. In order to synthesize α-oximinoketones, six different aceto phenone derivatives with various substituents were independently used as follows; 1.17 mL of aceto phenone(**1**), 1.33 mL of propiophenone(**2**), 1.49 g of 4-methyl propiophenone(**3**), 1.69 g of 4-chloropropio phenone(**4**), 1.69 g of 3-chloropropiophenone(**5**), 1.48 g of 1-phenylbutane-1-one(**6**).

Yields of α-oximinopropiphenone, 4'-methyl-α-ox iminopropiphenone, 4'-chloro-α-oximinopropio phen ome were over 93%. The cryatalline precipitates were then filtered with rotary evaporator and recrystallized from hexane and toluene, respectively. The structure and elements labeling of the synthesized derivatives were shown in Figure 3. [17,18]

NMR experiments - All ^{13}C NMR measurements for α-oximinopropiphenones were obtained with Varian 500 MHz FT-NMR spectrometer. The NMR data were processed and analyzed by using VNMRJ and

NMRpipe software. ^{13}C-NMR chemical shifts were referenced to DMSO-d_6 (39.51 ppm), and used in the comparison with those of computational results.

Ab initio calculations - The molecular geometries of α-oximinoacetophenone and its analogues were fully optimized at Beck's-three-parameter hybrid (B3LYP) method in density functional theory (DFT) method with 6-31+G* basis set using the ab initio program Gaussian 98 without any geometrical restrictions.[19,20]

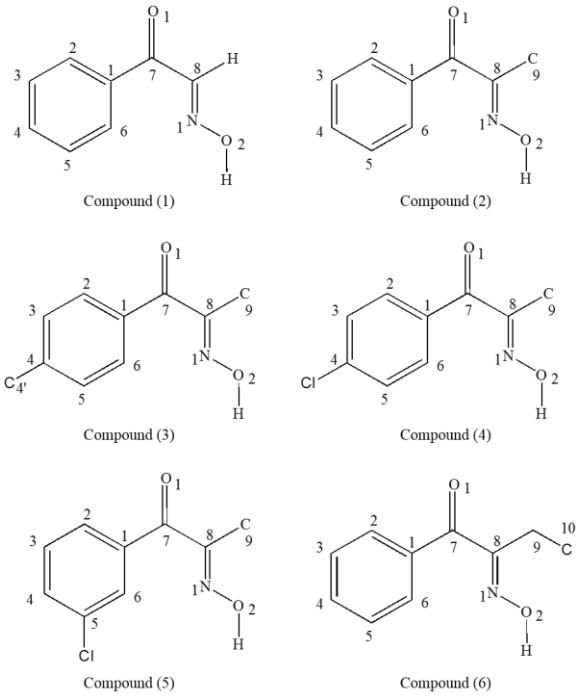

Figure 3. Molecular structures of six different α-oximino-ketones

Results and Discussion

Ab initio calculations - The optimized geometrical parameters for compounds **1 ~ 6** at B3LYP/6-31+G* are summarized in Table 1. Compared with geometrical parameters of compounds **1**, **2**, and **6**, most par meters are well consistent one another. But the parameters of C_7-C_8-N_1 angle, C_2-C_1-C_7-O_1, C_1-C_7-C_8-N_1 dihedral angle of compound **1** are different from those of compounds **2** and **6**. Through the effect of alkyl substituents in compounds **2** and **6**, the C_7-C_8- N_1 angle decrease about 6.5° ~ 6.8°, both the C_2-C_1- C_7-O_1 and C_1-C_7-C_8-N_1 dihedral angles increase about 5.2° ~ 6.3°. Also, the geometries of compound **3** and compound **4** with different substituents at C_4 differ in benzene ring geometry. Among C-C bond lengths in benzene ring, C_3-C_4 and C_4-C_5 bond lengths of compound **3** are somewhat longer than those compound **4**. Both the C_2-C_3-C_4 and C_4-C_5-C_6 angles of compound **3** are about 2° larger than those of compound **4**, but C_3-C_4-C_5 angles is about 3.2° smaller than that of compound **4**. Additionally, C_2-C_1-C_7-O_1 dihedral angle of compound **3** was computed to be 20.1°, which is about 1.2° less than that of com- pound **4**. Conversely, C_1-C_7-C_8-N_1 dihedral angle of compound **3** is calculated to be 27.1°, which is about 2.1° more than that of compound **4**. The geometrical parameters of compound **5** is similar to those of compound **4**, but C_2-C_1-C_7-O_1 and C_1-C_7-C_8-N_1 dihedral angles are somewhat different from those of com- pound **4**.

^{13}C-NMR chemical shifts were calculated by using the gauge-independent atomic orbital (GIAO) method[21,22] at both the HartreeFock (HF) and B3LYP levels. Though Gauss[23,24] has recently developed the GIAO-MP2 and GIAO-CCSD methods which provide shielding constant that are consistently in close agreement with experiment, an enormous computational cost beyond HF approximations has still prevented us from computing molecular properties of large molecules at high level of theory. The B3LYP method in DFT has been shown to be successful in predicting various molecular properties, [25-27] often giving results of a quality comparable or even better than MP2. It therefore seems reasonable to investigate in detail how well B3LYP predict NMR chemical shifts in particular for large molecules. Table 2 and Table 3 show the calculated values for these com pounds and TMS are obtained using GIAO method at the HF/6-311+G** and B3LYP/6-311+G** level with the B3LYP/6-31+G* optimized geometry. Though chemical shifts are generally a little difference, B3LYP/6-311+G** level predicts that ^{13}C chemical shifts are much closer to experimental

values than those obtained using the HF/6-311+G** level. In Table 3, the calculated ^{13}C-NMR chemical shift of C_8 in compound **1** is about 8~9 ppm more shielding than that in compounds **2** ~ **5** and chemical shift of C_8 in compound **6** is 13 ppm more deshielding than that in compound **1**. Additionally, chemical shift of C_4 with methyl substituent in compound **3** is about 12 ppm, chemical shift of C_4 with chlorine substituent is about 15 ppm more deshielding than that in compounds **1**, **2**, **5**, and **6**. These chemical shift differences can be explained with deshilding effect originated from the ring current of benzene ring moiety, and with substitution effects from electron widrawing group and electron donating groups. The dihedral angles of C_2-C_1-C_7-O_1 and O_1-C_7-C_8-C_9 are given to the range of 17.4 ~ 23.8 and 19.5 ~ 22.7, respectively. Molecular planarity and ruffling of macrocyclic ring are considered to be important in metal ion mediated CO_2 reduction. These variation of dihedral angles in spite of sp2 hybridization on C7, C8 carbon atoms exhibit that side chains and the benzene ring moiety with various substituents may be flipped around even in macro-cyclic metal complex formation. By using ab initio computation, structural features and dynamic properties of α-oximinoketone derivatives were determined. In addition, ^{13}C-NMR chemical shifts computed by using GIAO method at the HF/6-311 +G** and B3LYP/6-311+G** level for the molecular geometries optimized with the B3LYP /6-31+G* basis set appear to be sufficient enough to compare with experimental chemical shifts for these compounds. Although calculated ^{13}C-NMR chemical shifts are not exactly matched with experimental values, there are consistency that can address chemical shift changes originated from substituents and local molecular structures.

Based on these structural informations, further electrochemical CO_2 reduction studies on the synthesis Ni(II)-containing macrocyclic model complexes[28,29] including various alkyl, aryl groups and inorganic axial ligands will be made in detail.

Table 1. Geometrical Parameters for six α-oximinketone analogues (Distances (Å) ; Angles (deg))

Parameter	Compound **1**	Compound **2**	Compound **3**	Compound **4**	Compound **5**	Compound **6**
C_1-C_2	1.408	1.407	1.407	1.406	1.405	1.406
C_2-C_3	1.393	1.392	1.390	1.391	1.392	1.393
C_3-C_4	1.399	1.400	1.406	1.398	1.399	1.400
C_4-C_5	1.398	1.397	1.401	1.395	1.394	1.397
C_5-C_6	1.396	1.396	1.396	1.395	1.393	1.396
C_6-C_1	1.405	1.405	1.404	1.405	1.404	1.405
C_6-C_7	1.494	1.495	1.493	1.495	1.499	1.496
C_7-C_8	1.496	1.510	1.511	1.510	1.508	1.509
C_8-C_9	-	1.502	1.503	1.502	1.501	1.508
C_7-O_1	1.229	1.228	1.228	1.227	1.226	1.228
C_8-N_1	1.280	1.287	1.286	1.287	1.288	1.288
N_1-O_2	1.393	1.398	1.400	1.397	1.396	1.400
∠C_1-C_2-C_3	120.5	120.6	120.7	121.1	120.3	120.5
∠C_2-C_3-C_4	120.0	120.0	121.0	119.0	120.4	120.0
∠C_3-C_4-C_5	119.9	119.9	118.0	121.2	118.9	119.9
∠C_4-C_5-C_6	120.3	120.3	121.3	119.3	121.6	120.3
∠C_5-C_6-C_1	120.2	120.2	120.4	120.7	119.3	120.2
∠C_6-C_1-C_2	119.2	119.1	118.5	118.8	119.5	119.1
∠C_1-C_7-C_8	123.1	122.0	122.0	122.0	122.0	122.3
∠C_7-C_8-C_9	-	119.2	119.0	119.1	119.2	118.4
∠C_1-C_7-O_1	121.2	120.6	120.8	120.4	120.2	120.6
∠C_7-C_8-N_1	122.6	116.1	116.3	116.0	116.0	115.8
∠C_8-N_1-O_2	111.2	111.6	111.6	111.6	111.6	112.2
∠O_1-C_7-C_8	115.8	117.4	117.2	117.5	117.8	117.1
∠N_1-O_2-H	103.5	102.9	102.9	103.1	103.1	102.8
∠C_2-C_1-C_7-O_1	17.4	22.6	20.1	21.3	23.8	22.4
∠C_1-C_7-C_8-N_1	19.3	25.6	27.1	25.0	23.1	25.2
∠C_7-C_8-N_1-O_2	175.8	175.2	175.1	175.4	175.5	175.2
∠C_9-C_8-N_1-O_2	-	0.6	0.7	0.6	0.5	0.9
∠C_1-C_7-C_8-C_9	-	159.4	158.1	159.9	161.7	160.0
∠O_1-C_7-C_8-C_9	-	21.4	22.7	21.0	19.5	20.6

Table 2. ^{13}C-NMR chemical shifts calculated with HF/6-311+G** basis set for geometry optimized structures of α-oximino-ketone analogues with B3LYP/6-31+G* Level[a]

	Carbon								
	C_1	C_2	C_3	C_4	C_5	C_7	C_8	C_9	C_9'
Compound **1**	135.77[b] (148.39)[c]	138.90 (129.50)	130.01 (133.47)	140.20 (128.40)		195.09 (188.06)	161.19 (150.36)		
Compound **2**	137.20 (136.42)	138.99 (129.88)	129.94 (132.12)	139.37 (127.22)		197.69 (190.17)	169.68 (155.03)	7.86 (9.98)	
Compound **3**	133.55 (142.40)	139.72 (131.09)	129.66 (128.06)	151.85 (137.38)		197.19 (191.21)	169.79 (155.40)	7.98 (10.12)	
Compound **4**	135.20 (139.15)	140.11 (128.32)	130.60 (132.79)	151.39 (134.61)		196.44 (190.16)	169.58 (156.82)	7.72 (10.38)	
Compound **5**	138.51	136.81 (132.32)	130.88 (128.21)	139.18 (129.59)	139.71 (138.71)	196.84 (189.04)	169.24 (154.91)	7.56 (9.39)	
Compound **6**	137.50 (137.75)	138.94 (129.78)	129.02 (132.13)	139.30 (127.79)		198.47 (199.72)	173.07 (159.02)	17.26 (17.23)	9.47 (10.23)

[a] Relative to TMS. [b] Calculated values. [c] Experimental values. Shifts of symmetric carbons are ommited.

Table 3. ^{13}C-NMR chemical shifts calculated with B3LYP/6-311+G** basis set for geometry optimized structures of α-oximinoketone analogues with B3LYP/6-31+G* Level[a]

	Carbon								
	C_1	C_2	C_3	C_4	C_5	C_7	C_8	C_9	C_9'
Compound **1**	137.52[b] (148.39)[c]	132.79 (129.50)	129.57 (133.47)	134.96 (128.40)		190.25 (188.06)	153.13 (150.36)		
Compound **2**	138.59 (136.42)	133.13 (129.88)	129.18 (132.12)	134.30 (127.22)		192.98 (190.17)	162.07 (155.03)	6.81 (9.98)	
Compound **3**	135.97 (142.40)	133.16 (131.09)	129.88 (128.06)	146.87 (137.38)		192.23 (191.21)	162.03 (155.40)	6.96 (10.12)	
Compound **4**	136.39 (139.15)	134.35 (128.32)	129.93 (132.79)	151.04 (134.61)		191.53 (190.16)	161.93 (156.82)	(10.38)	
Compound **5**	140.00	130.79 (132.32)	130.10 (128.21)	134.22 (129.59)	144.08 (138.71)	192.05 (189.04)	161.75 (154.91)	6.42 (9.39)	
Compound **6**	138.73 (137.75)	132.93 (129.78)	129.44 (132.13)	134.05 (127.79)		193.67 (199.72)	166.32 (159.02)	19.41 (17.23)	8.74 (10.23)

[a] Relative to TMS. [b] Calculated values. [c] Experimental values. Shifts of symmetric carbons are omitted.

Acknowledgements

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