Structure and Bonding Nature of Carboxyimidazolidone, a Model of Carboxybiotin. Ab Initio MO/MP4, SD-CI, and CCD Studies

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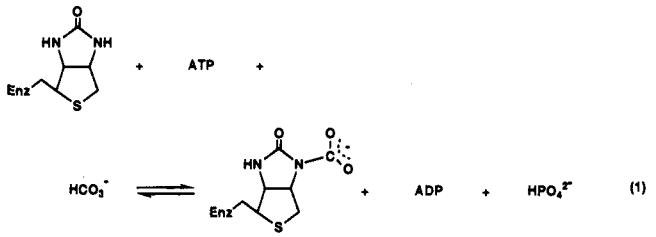
Abstract: *N*-Carboxyimidazolidone (**1**) and *O*-carboxyimidazolidone (**2**) were theoretically investigated as a model of carboxybiotin. The planar structure of **1** including CO_2 on the molecular plane is more stable than the perpendicular one by 5.0 kcal/mol (MP4SDQ/6-31+G*). The CO_2 binding energy is 26 kcal/mol for **1** and 15 kcal/mol for **2** (MP4SDQ/6-31+G*), where a standard (energy 0) is the sum of CO_2 and deprotonated imidazolidone (abbreviated as imidazolidone$^-$ hereafter) taking their equilibrium structures. When solvated species such as imidazolidone$^-$−$3H_2O$ and CO_2−$3H_2O$ systems are taken as standard, the CO_2 binding energy is 27 kcal/mol for **1** and −3 kcal/mol for **2** (SCRF-HF/6-31+G*). These results are in accord with the experimental result that only *N*-carboxybiotin was isolated in the biotin-dependent enzymic reaction. Population analysis indicates that the charge transfer from imidazolidone$^-$ to CO_2 is of particular importance in carboxyimidazolidone and this charge transfer is greater in **1** than in **2**. Because of this charge transfer interaction, the CO_2 part in **1** and **2** is considerably activated for electrophile like transition metal η^1-C coordinated CO_2 complexes. Various simple model compounds of carboxybiotin are compared with **1** and **2**, and their reliabiltiy is discussed in detail.

Introduction

The reaction mechanism of the biotin-mediated CO_2 metabolism has been actively investigated as reviewed recently,[1] because biotin serves as a cofactor in a number of important enzymic carboxylation reactions of organic substrates.[2−4] For instance, the pioneering work of Lynen et al. clearly indicated that enzymic carboxyl-transfer reaction proceeds via a carboxybiotin intermediate.[2] The reaction mechanism accepted now is summarized as follows:[1] (1) *N*-carboxybiotin is formed from biotin, bicarbonate, and ATP (eq 1), accompanied with conversion of ATP to ADP and inorganic phosphate,[2,3] and then (2) the carboxyl group transfers from *N*-carboxybiotin to an organic substrate with the deprotonation of substrate by either enzyme or biotin itself (eq 2).[4−6] Although many elegant experimental works have been carried out to clarify the reaction mechanism,[1] there still remain several important issues to be examined. One of those issues is the reactivity of *N*-carboxybiotin. Because *N*-carboxybiotin is considered to be inherently unreactive,[7] it must be activated to perform the carboxyl-transfer reaction. Kluger et al.[8] proposed that the carboxyl group became reactive by the rotation around the N−CO_2 bond because such rotation would destroy the resonance preserved in the most stable planar conformation. The other proposal was presented by Perrin and Dwyer, in which the CO_2 group of carboxybiotin is considered to be activated by proton donor or cationic species.[9] Detailed knowledge on geometry, stability, bonding nature, and electron distribution of carboxybiotin would be helpful to discuss the reaction mechanisms. Not only experimental works but also theoretical works are necessary to obtain such knowledge. However, only a few of the theoretical works have been carried out to our knowledge,[8,10] in which rather simple compounds were adopted as a model of biotin.

In this work, we carried out ab initio MO/MP4, SD-CI, and coupled cluster with double substitution (CCD) calculations of



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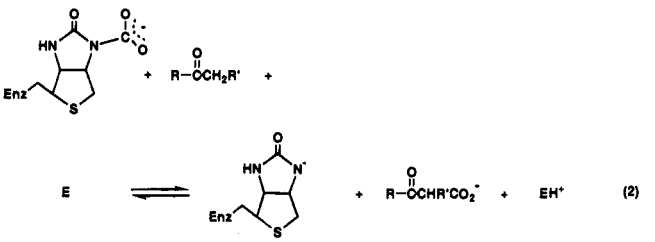

(2)

[⊗] Abstract published in *Advance ACS Abstracts*, November 1, 1995.

(1) (a) Knowles, J. R. *Annu. Rev. Biochem.* **1989**, *58*, 195. (b) Thatcher, G. R. J.; Kluger, R. *Adv. Phys. Org. Chem.* **1989**, *25*, 99. (c) Kluger, R. *Chem. Rev.* **1990**, *90*, 1151.

(2) Lynen, F.; Knappe, J.; Lorch, E.; Jütting, G.; Ringelmann, E. *Angew. Chem.* **1959**, *71*, 481.

(3) For instance: (a) Kluger, R.; Taylor, S. D. *J. Am. Chem. Soc.* **1991**, *113*, 996. (b) Taylor, S. D.; Kluger, R. *J. Am. Chem. Soc.* **1993**, *115*, 867. References are therein.

(4) Rétey, J.; Lynen, F. *Biochem. Z.* **1965**, *342*, 256.

(5) (a) Stubbe, J.; Abeles, R. H. *J. Biol. Chem.* **1977**, *252*, 8338. (b) Stubbe, J.; Frish, S.; Abeles, R. H. *J. Biol. Chem.* **1980**, *255*, 236.

(6) (a) Kuo, D.; Rose, I. A. *J. Am. Chem. Soc.* **1989**, *104*, 3235. (b) Kuo, D.; Rose, I. A. *J. Am. Chem. Soc.* **1993**, *115*, 387. References are therein.

(7) (a) Caplow, M. *J. Am. Chem. Soc.* **1965**, *87*, 5774. (b) Caplow, M.; Yager, M. *J. Am. Chem. Soc.* **1967**, *89*, 4513. (c) Guchhait, R. B.; Polakis, S. E.; Bimroth, P.; Stoll, E.; Moss, J.; Lane, M. D. *J. Biol. Chem.* **1974**, *249*, 6633.

(8) Thatcher, G. R. J.; Poirier, R.; Kluger, R. *J. Am. Chem. Soc.* **1986**, *108*, 2699.

(9) Perrin, C. L.; Dwyer, T. J. *J. Am. Chem. Soc.* **1987**, *109*, 5163.

(10) Andres, J.; Moliner, V.; Krechl, J.; Silla, E. *J. Chem. Soc., Perkin Trans.* **1993**, *2*, 521.

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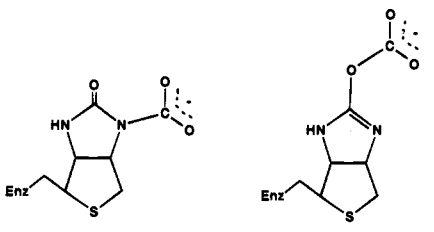
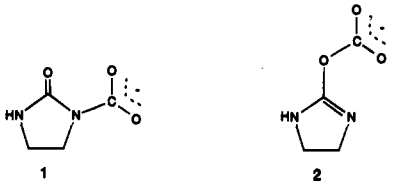
Chart 1





N-carboxyimidazolidone (**1**) and *O*-carboxyimidazolidone (**2**), where **1** and **2** were adopted here as a model of carboxybiotin (Chart 1). The purpose of this work is (1) to provide fundamental knowledge necessary for systematic theoretical investigation of biotin (for instance, reliability of model, and basis set effects and correlation effects on stability), (2) to present such detailed information on deprotonated imidazolidone and carboxyimidazolidone as geometry, bonding nature, electron distribution, and reactivity, and (3) to make a clear comparison between *N*-carboxyimidazolidone and *O*-carboxyimidazolidone, because *O*-carboxybiotin was proposed previously[11] but no information has been reported on it.

Computational Details

Ab initio closed-shell Hartree−Fock (HF), MP2 to MP4SDQ, SD-CI, and CCD calculations were carried out with Gaussian 86[12] and 92[13] programs. In SD-CI calculations, the contribution of higher-order excited configurations was estimated, according to Davidson,[14] Davidson−Silver,[15] and Pople et al.[16] In CCD calculations, the contribution of single and triple substitutions was evaluated through forth order with CCD wave functions.[17] In all the calculations at the correlated level, core orbitals were excluded from the active space.

Geometry optimization was performed with the energy gradient method at the MP2 level, using the 6-31G* set,[18,19] where a d-polarization function was added on all the first-row elements. In the optimization, no constraint was considered; for instance, the five-member ring of imidazolidone was not assumed to be planar, while it was experimentally reported to be planar.[20] A better basis set, 6-31+G*,[18,19,21] was used for investigating energy change, electron distribution, bonding nature, etc. As will be discussed later, interaction of water molecules with deprotonated imidazolidone and carboxyimidazolidone is indispensable for estimating the stability of carboxyimidazolidone. Positions and orientations of water molecules were optimized at the HF level,[22] using the 6-31G* basis set, where geometries of water, deprotonated imidazolidone, and carboxyimidazolidone were not reoptimized but were fixed to be the same as those of the free molecules.

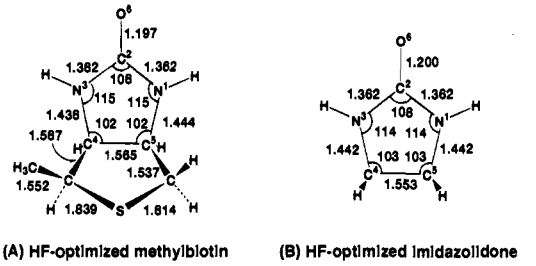


Figure 1. Optimized geometries (HF/6-31G* optimization) of methylbiotin and imidazolidone.

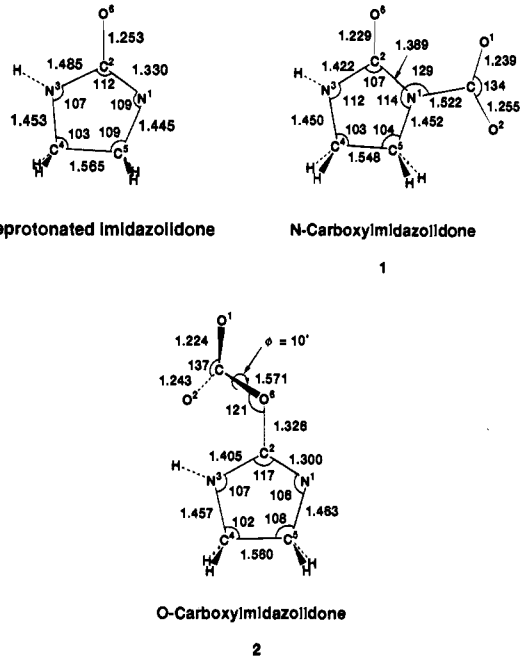


Figure 2. Optimized geometries (MP2/6-31G* optimization) of *N*-carboxyimidazolidone and *O*-carboxyimidazolidone.

Results and Discussion

A Comparison of Biotin with Imidazolidone. First, we will examine whether imidazolidone can be adopted as a reasonable model of biotin or not. As shown in Figure 1A, the HF-optimized geometry of methylbiotin agrees well with the experimental structure of *d*(+)-biotin.[20] Also, the HF-optimized geometry of imidazolidone (Figure 1B) is almost the same as the corresponding part of the HF-optimized methylbiotin. Furthermore, imidazolidone has π and π^* orbitals at similar energy levels to those of biotin, as compared in Table 1. Also, N and O atomic populations[23] in imidazolidone are almost the same as those in biotin, indicating that the CO_2 binding site of

(11) Hegarty, A. F.; Bruice, T. C. *J. Am. Chem. Soc.* **1970**, *92*, 6561.
(12) Frisch, M. J.; Binkley, J. S.; Schlegel, H. B.; Raghavachari, K.; Melius, C. F.; Martin, R.; Stewart, J. J. P.; Borowicz, F. W.; Röhlfing, C. M.; Kahn, L. R.; DeFrees, D. J.; Seeger, R.; Whiteside, R. A.; Fox, D. J.; Fleuder, E. M.; Pople, J. A. *Gaussian 86*; Carnegie-Mellon Quantum Chemistry Publishing Unit: Pittsburgh, PA, 1987.
(13) Frisch, M.; Trucks, G. W.; Gordon, M. H.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; DeFrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. *Gaussian 92*; GAUSSIAN Inc.: Pittsburgh, PA, 1992.
(14) Langhoff, S. R.; Davidson, E. R. *Int. J. Quantum Chem.* **1974**, *8*, 61.
(15) Davidson, E. R.; Davidson, D. W. *Chem. Phys. Lett.* **1977**, *52*, 403.
(16) Pople, J. A.; Seeger, R.; Krishnan, R. *Int. J. Quantum Chem. Symp.* **1977**, *11*, 149.
(17) (a) Pople, J. A.; Krishnan, R.; Schlegel, H. B.; Binkley, J. S. *Int. J. Quantum Chem.* **1978**, *14*, 545. (b) Ragavachari, K. *J. Chem. Phys.* **1985**, *82*, 4607.
(18) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys.* **1972**, *56*, 2257.
(19) (a) Pietro, W. J.; Francl, M. M.; Hehre, W. J.; DeFrees, D. J.; Pople, J. A.; Binkley, J. S. *J. Am. Chem. Soc.* **1982**, *104*, 5039. (b) Hariharan, P. C.; Pople, J. A. *Theor. Chim. Acta* **1973**, *28*, 213.
(20) DeTitta, G. T.; Edmonds, J. W.; Stallings, W.; Donohue, J. *J. Am. Chem. Soc.* **1976**, *98*, 1920.
(21) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comp. Chem.* **1983**, *4*, 294.
(22) MP2/6-31G* optimization could not be carried out because disk space greater than 2G bite was required.
(23) (a) Foster, J. P.; Weinhold, F. *J. Am. Chem. Soc.* **1980**, *102*, 7211. (b) Reed, A. E.; Weinhold, F. *J. Am. Phys.* **1983**, *78*, 4066. (c) Reed, A. E.; Curtiss, L. E.; Weinhold, F. *Chem. Rev.* **1988**, *88*, 899. References are therein.

Table 1. Atomic Population and Energy Levels of π and π^* Orbitals ($\epsilon(\pi)$ and $\epsilon(\pi^*)$) of Methylbiotin and Imidazolidone[a]

	methylbiotin	imidazolidone
	Atomic Population[b]	
N^1	7.85	7.79
C^2	5.09	5.02
N^3	7.83	7.79
C^4	5.91	6.21
C^5	5.78	6.21
O^6	8.70	8.71
	Orbital Energy (eV)	
$\epsilon(\pi)$	−10.84	−10.95
$\epsilon(\pi^*)$	6.85	6.89

[a] The 6-31+G* basis set was used. [b] NBO populations[23] are given.

imidazolidone is in the situation similar to that of biotin. C^4 and C^5 atomic populations are much different between imidazolidone and biotin, since these two atoms are in much different situations between imidazolidone and biotin. However, this difference has little influence on the other part, as described above. From the above results, imidazolidone seems to be a reasonable model of biotin.

Geometries and CO_2 Binding Energies (BE) of *N*-Carboxyimidazolidone (1) and *O*-Carboxyimidazolidone (2). Optimized geometries of **1** and **2** are shown in Figure 2. Several interesting features are observed: (1) The CO_2 part significantly distorts in both **1** and **2**; the C=O distance is considerably longer than that of the free CO_2 molecule and the OCO angle is remarkably closed. The CO_2 part is more distorted in **1** than in **2**. (2) It is noted that the geometry of CO_2 in **1** and **2** resembles well the η^1-C coordinated CO_2 ligand in transition metal complexes, such as $M[Co^I(R\text{-salen})(CO_2)]$,[24] $Rh^ICl(diars)_2(CO_2)$,[25] and $Ru(bpy)_2(CO)(\eta^1\text{-}CO_2)$.[26] (3) In **1**, the CO_2 part is on the molecular plane of imidazolidone, whereas in **2** the CO_2 part slightly rotates around the $C-O^6$ bond by 10° from the molecular plane of imidazolidone. (4) The five member ring of imidazolidone is almost planar like the experimental structure of *d*(+)-biotin,[20] whereas the N^3-H bond is displaced from the plane by about 35°.

The perpendicular structure of **1** is less stable than the planar one by 5 kcal/mol at the MP4SDQ/6-31+G* level. This energy difference is much smaller than that calculated previously for the simple model compound, $H_2NCONH-CO_2$.[8] There are several reasons for this difference; the basis sets used are different, electron correlation is included in this work but was not in the previous work, and a more realistic model is adopted here than in the previous work.[8] Thus, the energy difference evaluated here seems more reliable.

The binding energy (BE) of CO_2 in **1** and **2** was calculated with MP4SDQ/6-31G, MP4SDQ/6-31G*, MP4SDQ/6-31+G*, SD-CI/6-31G*, and CCD/6-31G* methods. Although the BE value more or less fluctuates at MP2 and MP3 levels, almost the same value was calculated at MP4SDQ, SD-CI(DS), SD-CI(P), and CCD levels (see Table 2). However, the SD-CI method with Davidson correction gives a somewhat different BE value from others (see the SD-CI(D) value in Table 2). Interestingly, correlation effects depend considerably on the kinds of basis set used: Although introduction of electron correlation significantly decreases the BE value in the 6-31G calculation, it only slightly changes the BE value in the 6-31G*

Table 2. Correlation and Basis Set Effects on the CO_2 Binding Energy (BE, kcal/mol) of *N*-Carboxyimidazolidone (**1**) and *O*-Carboxyimidazolidone (**2**)

	BE		
	1	**2**	ΔBE[a]
	6-31G		
HF	47.2	26.9	20.3
MP2	28.5	14.9	13.6
MP3	39.2	25.8	13.4
MP4DQ	36.5	22.2	14.3
MP4SDQ	34.3	19.7	14.6
	6-31G*		
HF	27.9	15.5	12.4
MP2	24.8	16.0	8.8
MP3	28.8	20.4	8.4
MP4DQ	27.7	18.4	9.3
MP4SDQ	26.5	17.0	9.5
SDCI(D)[b]	29.3	15.1	14.2
SDCI(DS)[c]	27.6	18.8	8.8
SDCI(P)[d]	27.8	18.8	9.0
CCD	27.5	18.5	9.0
CCD+ST(CCD)	25.5	17.4	8.1
	6-31+G*		
HF	26.5	12.5	14.0
MP2	23.6	13.3	10.3
MP3	28.0	18.2	9.8
MP4DQ	26.7	15.9	10.8
MP4SDQ	25.6	14.6	11.0
HF(SCRF)	32.4	13.1	19.3
MP2(SCRF)	28.6	14.1	14.5

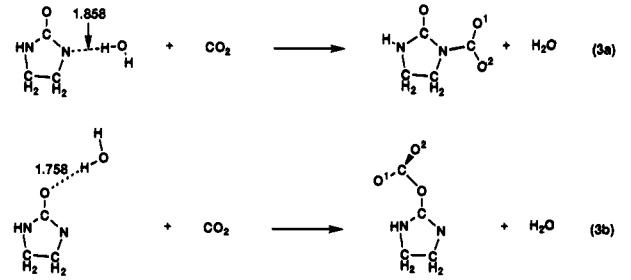
[a] ΔBE = difference in binding energy between **1** and **2**. [b] D = Davidson's correction for higher order excitations.[14] [c] DS = Davidson–Silver's correction for higher order excitations.[15] [d] P = Pople's correction for higher order excitations.[16]

and 6-31+G* calculations. This means that significantly large correlation effects observed in the 6-31G calculation seem to be artificial due to the poor basis set. Moreover, the BE value changes little upon going to 6-31+G* from 6-31G*, indicating that 6-31G* and 6-31+G* sets seem reliable for investigating these compounds. Hereafter, we discuss relative stabilities of **1** and **2**, based on MP4SDQ/6-31+G* calculations.

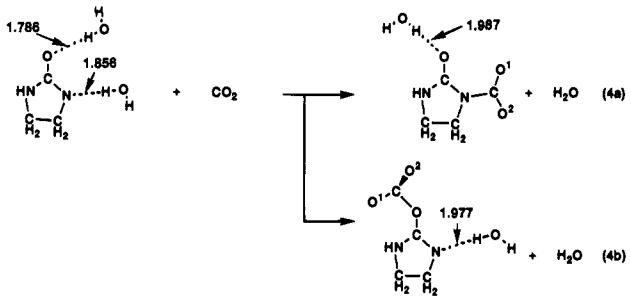
Although the BE value becomes smaller upon going from 6-31G to 6-31G* and 6-31+G*, the energy difference between **1** and **2** seems to converge to 10−11 kcal/mol, and the BE value of **1** is much larger than that of **2** in all the calculations. Therefore, it should be clearly concluded that *N*-carboxyimidazolidone is more stable than *O*-carboxyimidazolidone. This conclusion is in accord with the experimental result that *N*-carboxybiotin was isolated in the biotin-dependent enzymic reaction.[7c]

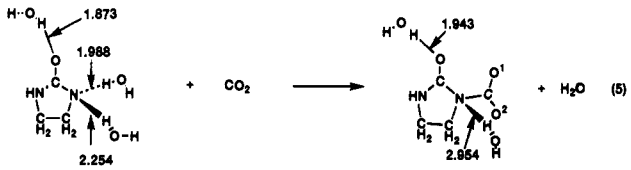
The binding energy of *N*-carboxybiotin was experimentally estimated to be ca. 20 kcal/mol.[27] This experimental value is somewhat smaller than the binding energy calculated here by 5−6 kcal/mol (see the BE value calculated with the MP4SDQ/6-31+G* method in Table 2). Because *N*-carboxybiotin exists in water, solvent effects were estimated with the SCRF method.[28] However, the binding energy increases to 32 kcal/mol at the SCRF-HF/6-31+G* level and 29 kcal/mol at the SCRF-MP2/6-31+G* level, and the discrepancy from the experimental value enlarges. This result suggests that not only the Onsarger model but also microsolvation effects are important. Also, we must note that the binding energy should be estimated as an energy difference between *N*-carboxyimidazolidone and the imidazolidone$^--H_2O$ adduct (deprotonated imidazolidone is abbreviated as imidazolidone$^-$ hereafter), because the binding energy was measured in water. Thus, we estimated BE as an energy difference between *N*-carboxyimidazolidone and the imidazolidone$^-$–H_2O adduct (eq 3). The

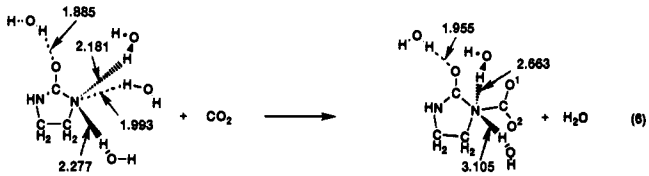
(24) (a) Fachinetti, G.; Floriani, C.; Zanazzi, P. F. *J. Am. Chem. Soc.* **1978**, *100*, 7405. (b) Gambarotta, S.; Arena, F.; Floriani, C.; Zanazzi, P. F. *J. Am. Chem. Soc.* **1982**, *104*, 5082.
(25) Calabrese, J. C.; Herskovitz, T.; Kinney, J. B. *J. Am. Chem. Soc.* **1983**, *105*, 5914.
(26) Tanaka, H.; Nagao, H.; Peng, S. M.; Tanaka, K. *Organometallics* **1992**, *11*, 1450.

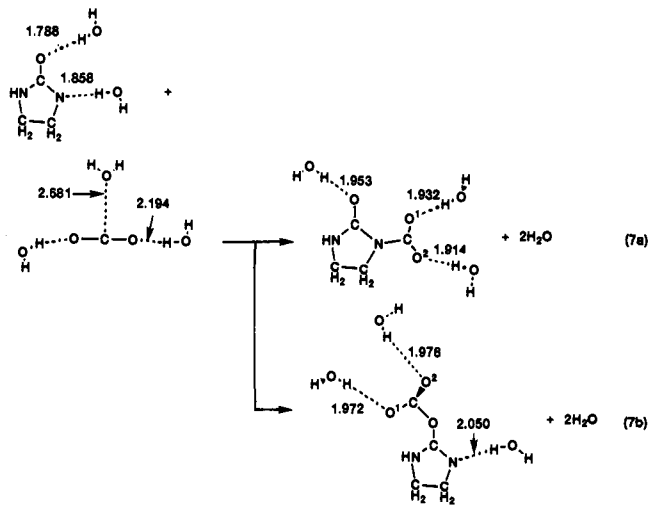


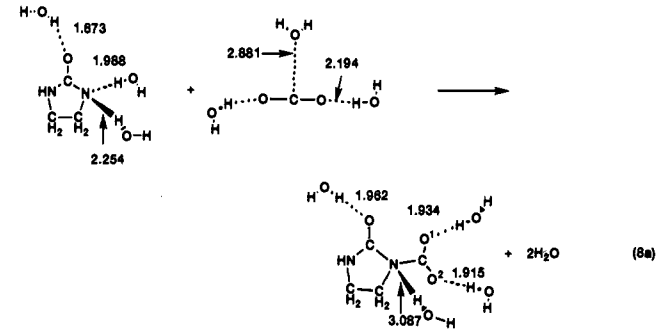
BE value is ca. 12 kcal/mol at the HF/6-31+G* level, 19 kcal/mol at the SCRF-HF/6-31G* level, and 13 kcal/mol at the SCRF-MP2/6-31G* level, as shown in Table 3. Then, two to six water molecules are considered in estimating the BE value (eqs 4−9).

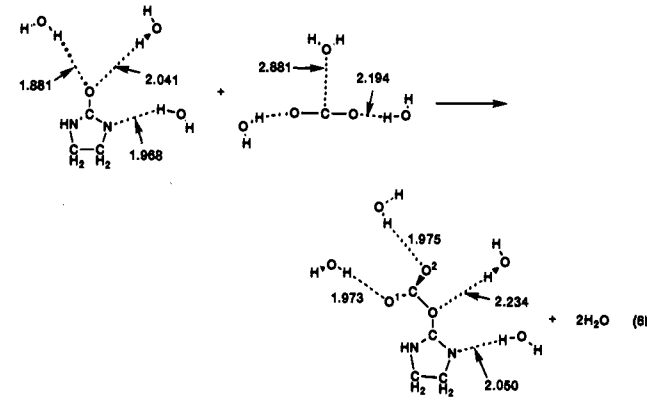


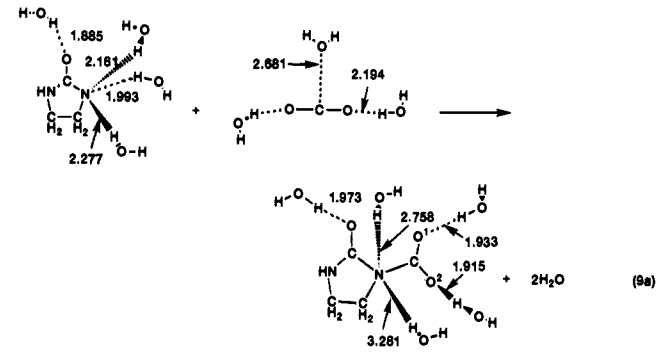


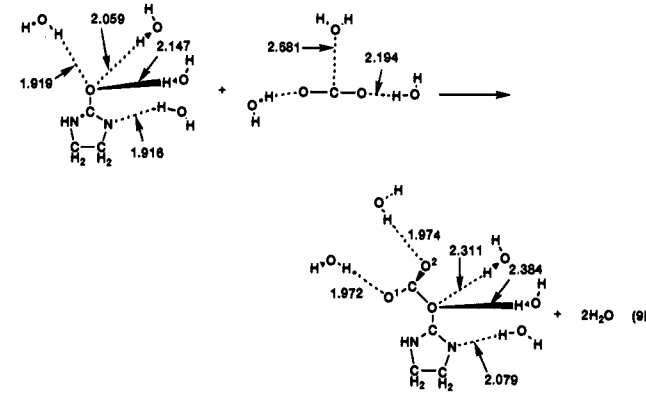












From eq 4−6, microsolvation to the imidazolidone part was considered. As schematically shown in eqs 4−6, one water molecule interacting with the N^1 atom of imidazolidone is considered to dissociate from imidazolidone upon formation of carboxyimidazolidone, since the CO_2 binding with imidazolidone would inhibit the solvent interaction with imidazolidone. In this case, the BE value considerably decreases and finally

(27) Green, N. M. *Biochem. J.* **1963**, *89*, 599.

(28) (a) Wong, M. W.; Frisch, M. J.; Wiberg, K. B. *J. Am. Chem. Soc.* **1991**, *113*, 4776. (b) $\epsilon(H_2O) = 78.54$, Solute radius; a_0(imidazolidone$^-$) = 3.79 bohr, $a_0(CO_2)$ = 2.93 bohr, $a_0(H_2O)$ = 2.54 bohr, a_0(*N*-carboxyimidazolidone) = 4.06 bohr, a_0(*O*-carboxyimidazolidone) = 4.13 bohr, and a_0(imidazolidone−H_2O) = 4.04 bohr.

Table 3. Solvation Effects on the CO_2 Binding Energy (BE, kcal/mol) of *N*-Carboxyimidazolidone (**1**) and *O*-Carboxyimidazolidone (**2**)

	1	**2**
$Imd-H_2O^a + CO_2 \rightarrow Imd-CO_2 + H_2O$ (3)		
HF	12.3	−1.6
HF(SCRF)	19.8	4.3
MP2(SCRF)	12.8	3.3
$Imd-2H_2O^a + CO_2 \rightarrow H_2O-Imd-CO_2 + H_2O$ (4)		
HF	22.8	9.0
HF(SCRF)	20.6	2.7
$Imd-3H_2O^a + CO_2 \rightarrow 2H_2O-Imd-CO_2 + H_2O$ (5)		
HF	5.1	
HF(SCRF)	14.8	
$Imd-4H_2O^a + CO_2 \rightarrow 3H_2O-Imd-CO_2 + H_2O$ (6)		
HF	−1.2	
HF(SCRF)	10.5	
$Imd-2H_2O^a + CO_2-3H_2O \rightarrow H_2O-Imd-CO_2-2H_2O + 2H_2O$ (7)		
HF	21.0	8.7
HF(SCRF)	36.0	14.1
$Imd-3H_2O^a + CO_2-3H_2O \rightarrow 2H_2O-Imd-CO_2-2H_2O + 2H_2O$ (8)		
HF	21.3	4.8
HF(SCRF)	25.8	8.5
$Imd-4H_2O^a + CO_2-3H_2O \rightarrow 3H_2O-Imd-CO_2-2H_2O + 2H_2O$ (9)		
HF	14.6	−3.6
HF(SCRF)	27.0	−2.7

[a] Positions and orientations of water molecules are given schematically in eqs 3−9.

becomes unreasonably small (for instance, BE = 10.5 kcal/mol for eq 6; Table 3), as the number of water molecule increases. Then, microsolvation to both imidazolidone and CO_2 parts is taken into consideration. In this case, one water molecule interacting with C of CO_2 also dissociates from CO_2 upon formation of carboxyimidazolidone. The BE value increases considerably upon introducing microsolvation to the CO_2 part, and this BE value moderately changes as the number of water molecules increases. In particular, the BE value of **1** at the SCRF-HF/6-31+G* level seems to converge to 26−27 kcal/mol. As calculated for eq 3, the BE value at the SCRF-MP2 level is smaller than that at the SCRF-HF level by ca. 7 kcal/mol. Thus, the BE value for eq 9a would approach 20 kcal/mol, if we introduce electron correlation. On the other hand, the BE value of **2** becomes unreasonably small, as shown in eqs 8 and 9, even if the microsolvation to CO_2 is taken into consideration. This result clearly shows that *O*-carboxybiotin cannot be formed in water and only *N*-carboxybiotin can be formed as an intermediate.

Electron Distribution of *N*-Carboxyimidazolidone (1) and *O*-Carboxyimidazolidone (2). Several interesting changes in NBO populations[23] are observed in Table 4: (1) The electron population of the CO_2 part increases upon formation of carboxyimidazolidones **1** and **2**, which indicates that the charge transfer from imidazolidone$^-$ to CO_2 occurs strongly. (2) The CO_2 electron population in **1** is greater than that in **2**, which corresponds to the greater binding energy of CO_2 in **1**. (3) The O^1 and O^2 atomic populations increase considerably, while the C atomic population increases less than the O^1 and O^2 atomic populations. This result is contrary to our expectation that the C atomic population increases more than the O atomic population because the CO_2 π^* orbital involves the greater p_π orbital of C than that of O. All these features of the electron distribution are the same as those reported in η^1-C-coordinated CO_2 complexes of transition metals.[29]

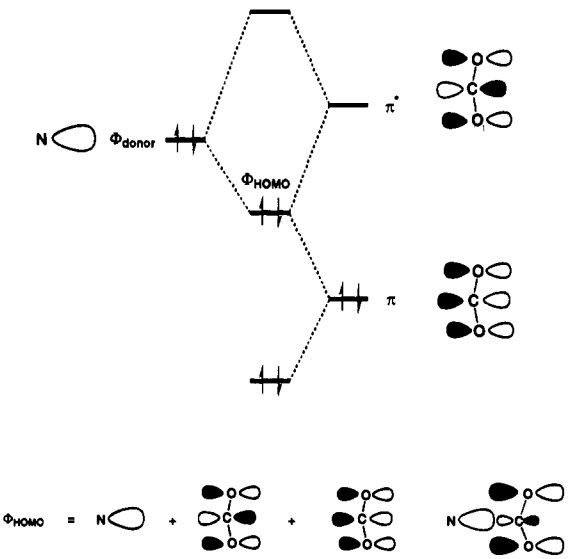
The above electron distribution is interpreted in terms of the orbital mixing shown in Chart 2. The HOMO of imidazolidone$^-$ interacts little with the CO_2 π^* orbital because the HOMO is a

Table 4. Electron Redistribution[a] by the Formation of Carboxyimidazolidone

	1	**2**		**1**	**2**
CO_2	+0.59	+0.45	O^2	+0.27	+0.18
C	+0.11	+0.02	N^1	−0.14	−0.13
O^1	+0.21	+0.25	O^6	−0.12	−0.16

[a] The positive values mean an increase of electron population. The 6-31+G* set was used. The NBO populations[23] are given.

Chart 2



π-type orbital. The donor orbital (ϕ_{donor}) of imidazolidone$^-$ is the next HOMO (Figure 3A), which is a lone pair type orbital expanding from both N and O atoms. The orbital interaction is mainly composed of the bonding overlap between the ϕ_{donor} orbital and the CO_2 π^* orbital. Because the ϕ_{donor} orbital expands outside of the N^1 atom to a greater extent than from the O^6 atom, the $\phi_{donor}-\pi^*$ overlap is larger in **1** than in **2**, which leads to the greater CO_2 electron population and the stronger CO_2 binding in **1** than in **2**. The $\phi_{donor}-\pi^*$ bonding overlap undergoes the mixing of the CO_2 π orbital in an antibonding way with ϕ_{donor} because the π orbital lies at a lower energy than ϕ_{donor}. As clearly shown in Chart 2, this orbital mixing reduces the contribution of the C p_π orbital but enlarges the contribution of the O p_π orbitals. The $26a_1$ orbital of **1** and **2** arises from this orbital mixing (Figures 3B and 3C), in which the C p_π orbital almost disappears but the O p_π orbitals are considerably large, according to the above-described orbital mixing. As a result, the C atomic population increases less than the O^1 and O^2 atomic populations upon formation of carboxyimidazolidone.

Reactivity of CO_2 in Carboxyimidazolidone. The knowledge of the reactivity of CO_2 in carboxyimidazolidone is potentially useful in understanding the enzymic function of biotin. The reactivity would strongly depend on electron distribution and frontier orbitals. The O atom of CO_2 becomes much more negatively charged in carboxyimidazolidone (vide supra). This means that the Columbic interaction between the O atom and a cationic species would be easily formed in carboxyimidazolidone. Frontier orbital energies are given in Table 5. The $26a_1$ orbital receives considerable contribution from the O p_π orbitals (Figure 3B and 3C). This $26a_1$ orbital lies at a considerably higher energy than the nonbonding π ($n\pi$) orbital (HOMO) of the free CO_2 molecule like the HOMO of $NiF(NH_3)_4(\eta^1\text{-}CO_2)$ which was calculated as a model of the Ni^I-

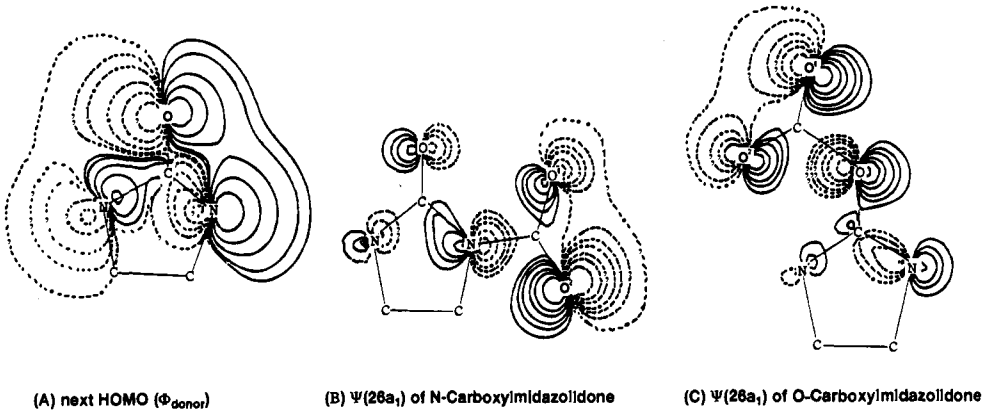


Figure 3. Contour maps of the next HOMO of deprotonated imidazolidone and next HOMO ($26a_1$) of *N*- and *O*-carboxyimidazolidone. Contour values are ±0.3, ±0.2, ±0.15, ±0.1, ±0.075, and ±0.05.

Table 5. Frontier Orbital Energies (eV) of Carboxyimidazolidone[a]

compounds	Frontier orbitals	
N-carboxyimidazolidone (**1**)	$26a_1$[b]	−6.8
	$n\pi_\perp$[c]	−6.1
	$n\pi_\parallel$[c]	−6.5
O-carboxyimidazolidone (**2**)	$26a_1$[b]	−7.9
	$n\pi_\perp$[c]	−7.2
	$n\pi_\parallel$[c]	−7.5
$NiF(NH_3)_4(\eta^1\text{-}CO_2)$[29b]	HOMO[d]	−8.2
	$n\pi$	−11.0
free CO_2	$n\pi$	−14.6

[a] The 6-31+G* set was used. [b] See Figures 3B and 3C. [c] $n\pi$; nonbonding π orbital of the CO_2 part. The subscripts "⊥" and "∥" represent the $n\pi$ orbital perpendicular to the molecular plane of carboxyimidazolidone and the $n\pi$ orbital on the molecular plane, respectively. [d] The HOMO corresponds to the $26a_1$ orbital of **1** and **2** (see ref 29c).

(cyclam)(CO_2) complex.[29c] Furthermore, the $n\pi$ orbitals localized on the CO_2 part of carboxyimidazolidone lie much higher in energy than that of the free CO_2 molecule, probably because of strong charge transfer from imidazolidone$^-$ to the CO_2 π^* orbital. In conclusion, CO_2 in **1** and **2** is much more activated to an electrophile in both charge and frontier controlled reactions. This suggests the possibility that the CO_2 part in carboxybiotin would interact with some electrophile or cationic center.

Also, we mention here that the above-described feature of CO_2 is similar to that observed in η^1-C-coordinated CO_2 complexes of transition metals,[29] as compared in Table 5. Considering that η^1-C-coordinated CO_2 complexes of transition metals serve as a catalyst in many electrocatalytic reductions of CO_2,[30] we can expect that carboxyimidazolidone is useful as an organic catalyst for the electrochemical reduction of CO_2 like transition metal complexes.

Reliable Model of Carboxybiotin. It is necessary to adopt a simple but reliable model for investigating theoretically the function of biotin. $CH_3\overline{NH(CO_2)}^-$ (**3**), $CH_3\overline{N(CHO)(CO_2)}^-$ (**4**), $CH_3N{=}C(H)O(CO_2)^-$ (**5**), $CH_3\overline{N(CONH_2)(CO_2)}^-$ (**6**), and $CH_3N{=}C(NH_2)O(CO_2)^-$ (**7**) are considered to be candidates for a model of carboxybiotin. However, little is known on the CO_2 binding energy, electron distribution, and energy levels of their frontier orbitals. We carried out MP4SDQ/6-31+G*//MP2/6-31G* calculations on them and compared them with those of carboxyimidazolidone.

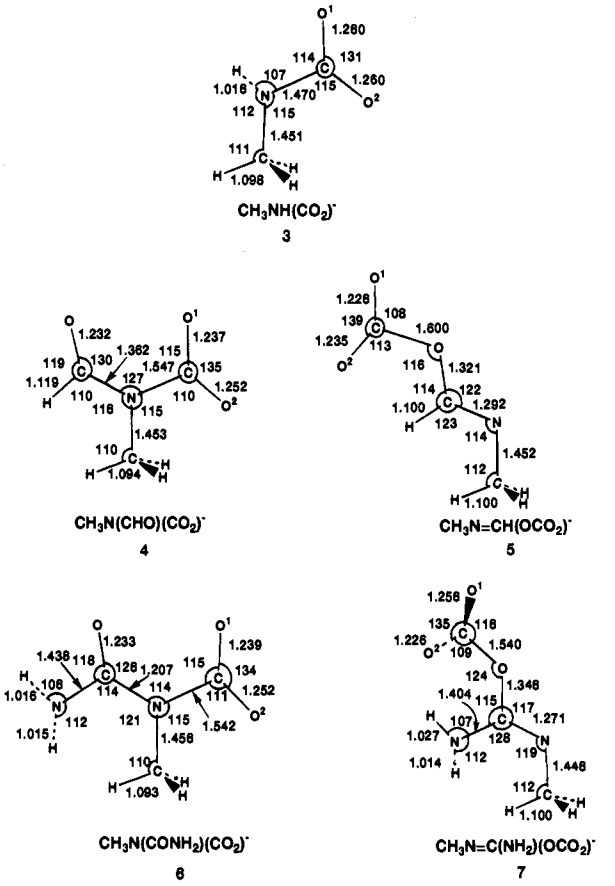


Figure 4. Optimized geometries (MP2/6-31G* optimization) of $CH_3\overline{NH(CO_2)}^-$ (**3**), $CH_3\overline{N(CHO)(CO_2)}^-$ (**4**), and $CH_3N{=}CH(OCO_2)^-$ (**5**), $CH_3\overline{N(CONH_2)(CO_2^-)}$ (**6**), and $CH_3N{=}C(NH_2)(OCO_2)^-$ (**7**).

As shown in Figure 4, the N−CO_2 distance of **3** is considerably different from those of the other complexes studied. Furthermore, the binding energy (BE) of **3** is much greater than that of **1** (Table 6). Also, the CO_2 electron population of **3** is considerably larger than that of **1** (Table 6). The HOMO and next HOMO (NHOMO) of **3** which are nonbonding π ($n\pi$) orbitals localized on the CO_2 part lie at considerably higher energies than those in **1**. These results indicate that **3** is not appropriate as a model of carboxybiotin.

4 is considered to be a better model than **3** because the carbonyl group exists at the neighboring position of the active N atom like biotin (see Figure 4). The CO_2 binding energy in

(29) (a) Sakaki, S.; Dedieu, A. *Inorg. Chem.* **1987**, *26*, 3278. (b) Sakaki, S.; Aizawa, T.; Koga, N.; Morokuma, K.; Ohkubo, K. *Inorg. Chem.* **1989**, *28*, 103. (c) Sakaki, S. *J. Am. Chem. Soc.* **1990**, *112*, 7813; **1992**, *114*, 2055.

(30) For instance: (a) Beley, M.; Collin, J.-P.; Ruppert, R.; Sauvage, J.-P. *J. Am. Chem. Soc.* **1986**, *108*, 7461. (b) Ishida, H.; Terada, T.; Tanaka, K.; Tanaka, T. *Inorg. Chem.* **1990**, *29*, 905.

Table 6. Binding Energy (BE, kcal/mol),[a] Electron Population, and Frontier Orbital Energy (eV) of CO_2 in $CH_3\overline{NH(CO_2)}^-$ (**3**), $CH_3\overline{N(CHO)(CO_2)}^-$ (**4**), $CH_3N{=}C(H)(OCO_2)^-$ (**5**), $CH_3\overline{N(CONH_2)(CO_2)}^-$ (**6**), and $CH_3N{=}C(NH_2)(OCO_2)^-$ (**7**)

	3	4	5	6	7
BE(MP4SDQ)	69.7	23.6	16.8	26.8	15.7
CO_2[b]	+0.72	+0.58	+0.46	+0.58	+0.47
$\epsilon(1+\pi^*)$[c]	−6.5	−6.8	−7.8	−6.8	−8.0
$\epsilon(n\pi_\perp)$[d]	−5.4	−6.1	−7.2	−6.0	−7.2
$\epsilon(n\pi_\parallel)$[d]	−5.8	−6.4	−7.6	−6.5	−7.5

[a] MP4SDQ/6-31+G*//MP2/6-31G* calculations. [b] The NBO population.[23] [c] The $(1+\pi^*)$ orbital corresponds to the $26a_1$ orbital of *N*- and *O*-carboxyimidazolidones (Figure 3). This orbital mainly consists of bonding overlap between the lone pair type orbital of the model compound and the CO_2 π^* orbital into which the CO_2 π orbital mixes in an antibonding way with the lone pair orbital. [d] $n\pi$; nonbonding π orbital of the CO_2 part. The subscripts "$\perp$" and "$\parallel$" represent the $n\pi$ orbital perpendicular to the molecular plane of carboxyimidazolidone and the $n\pi$ orbital in the molecular plane, respectively.

4 is about 3 kcal/mol smaller than that of **1**. The N−CO_2 distance is only 0.025 Å longer than in **1**, and the CO_2 geometry of **4** is almost the same as in **1**. The HOMO, NHOMO, and $(1 + \pi^*)$ orbitals of **4** lie at almost the same energies as those in **1** (see Table 6), where the $(1 + \pi^*)$ orbital is corresponding to the $26a_1$ orbital of **1** and mainly consists of the bonding overlap between the lone pair type orbital of $CH_3N(CHO)^-$ and the CO_2 π^* orbital into which the CO_2 π-orbital mixes in an antibonding way with the lone pair type orbital. From these results, **4** would be a better model than **3**. **5** is also examined as a model of **2**. The CO_2 binding energy is 2 kcal/mol larger than that of **2**, the O−CO_2 distance is only 0.03 Å longer than in **2**, and the CO_2 geometry of **5** is also almost the same as in **2**. However, the BE difference (ΔBE) between **4** and **5** is still much smaller than that between **1** and **2**.

6 is considered to be a better model than **4**, because **6** has an urea structure like **1** (Figure 4). In fact, the N−CO_2 distance and CO_2 geometry of **6** are almost the same as those of **1**. Its CO_2 binding energy is only 1.2 kcal/mol larger than that of **1**. **7** is also examined as a model of **2**. The CO_2 binding energy of **7** is only 1.1 kcal/mol larger than that of **2**. As a result, the BE difference between **6** and **7** (11.1 kcal/mol) is almost the same as the difference between **1** and **2** (11.0 kcal/mol). Moreover, **6** and **7** have a CO_2 electron population similar to those of **1** and **2** and HOMO, NHOMO, and $(1 + \pi^*)$ orbitals at almost the same energies as those of **1** and **2**, respectively. These results show that **6** and **7** are considered as reasonable models of **1** and **2**, respectively, and that the urea structure of biotin is important in the CO_2-binding function of biotin.

Concluding Remarks

Imidazolidone can be adopted as a reasonable model of biotin because imidazolidone and methylbiotin have very similar geometry, electron distribution, and π and π^* orbital energies. However, simple compounds such as $CH_3\overline{NH(CO_2)}^-$ and $CH_3\overline{N(CHO)(CO_2)}^-$ are considered not to be good models unlike carboxyimidazolidone. $CH_3\overline{N(CONH_2)(CO_2)}^-$ (**6**) seems a reasonable model of carboxybiotin from the CO_2 binding energy, electron distribution, and frontier orbital energies. These results suggest that the urea structure is important in the CO_2 binding function of biotin.

In *N*-carboxyimidazolidone (**1**), CO_2 lies on the molecular plane. The perpendicular structure of **1** is less stable than the planar one by ca. 5 kcal/mol at the MP4SDQ/6-31+G*//MP2/6-31G* level. The CO_2 binding energy of **1** is much greater than that of **2** by ca. 10 kcal/mol, indicating that **1** is more stable than **2**. When microsolvation of six water molecules to CO_2 and imidazolidone is considered, the CO_2 binding energies of **1** and **2** are calculated to be about 27 and −3 kcal/mol, respectively, with the SCRF-HF/6-31+G* method. These results are in accord with the experimental result that only *N*-carboxybiotin was isolated in the biotin-dependent enzymic reactions.[7c]

In carboxyimidazolidone, the charge transfer from imidazolidone$^-$ to CO_2 occurs strongly. The electron population of CO_2 is larger in **1** than in **2**. The O^1 and O^2 atomic populations increase more than does the C atomic population upon formation of carboxyimidazolidones (**1** and **2**). This electron distribution can be interpreted in terms of the bonding interaction between ϕ_{donor} of imidazolidone$^-$ and the CO_2 π^* orbital into which the π orbital of CO_2 mixes in an antibonding way with ϕ_{donor}.

Geometries, electron distribution, and frontier orbitals of **1** and **2** resemble well those of η^1-C-coordinated CO_2 complexes of transition metals such as $[Co(alcn)_2(\eta^1\text{-}CO_2)]^-$ (alcn = HNCHCHCHO$^-$), $RhCl(AsH_3)_4(\eta^1\text{-}CO_2)$, and $NiF(NH_3)_4(\eta^1\text{-}CO_2)$.[29] Considering that the several η^1-C-coordinated CO_2 complexes of transition metal serve as a key intermediate in electrochemical reduction of CO_2,[30] we can expect that biotin, imidazolidone, and their analogues would be useful as an organic catalyst for CO_2 reduction.

The CO_2 part in **1** is considerably activated for an electrophile. Thus, there is a possibility that the electrophile or cationic species interacts with the O atom of CO_2.

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