The Carboxylation of Active Methylene Compounds with Carbon Dioxide in the Presence of Diphenylcarbodiimide and Potassium Carbonate[1]

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Active methylene compounds were effectively carboxylated with carbon dioxide in the presence of diphenylcarbodiimide (DPC) as a biotin model and potassium carbonate. Fluorene was carboxylated even under a nitrogen atmosphere in the presence of DPC, indicating that a carbonate ion was the carbon source. The reaction occurred even in the presence of water. It was considered that reaction intermediates are stable to water and that the concentration of the carbonate ion is important for carboxylation.

The fixation of carbon dioxide has been attempted by many researchers, since carbon dioxide is a considerable natural source of carbon.[2–6] Furthermore, the greenhouse effect due to carbon dioxide has gained much attention and decreasing atmospheric carbon dioxide is a critical problem.[7] Carbon dioxide can be converted into useful forms of organic compounds by coupling with an organic substance. However, in order to do so, carbon dioxide and/or the organic substances must be activated. One example of the former way is the activation of carbon dioxide by a transition metal.[2,3] The photocarboxylation of aromatic compounds represents latter examples in which the anion radicals of aromatic compounds react with carbon dioxide.[8,9]

It has been well established that biotin is required as a cofactor in a number of enzymatic carboxylation reactions.[6] One of us has already reported that active methylene compounds are carboxylated by employing a reagent system, 1,3-diphenylurea (DPU), as a biotin model compound, potassium carbonate and carbon dioxide.[10,11] Also, Otsuji and co-workers have reported that a number of active methylene compounds are carboxylated by employing the reagent system benzyltrimethylammonium hydroxide–dicyclohexylcarbodiimide and carbon dioxide.[12] In these carboxylations, carbon dioxide is activated at the imidazole moiety. We recently found that diphenylcarbodiimide (DPC) is an effective biotin model as a carrier of carbon dioxide to active methylene compounds.[1] We have undertaken to construct a model reaction for biotin-promoted carboxylations, whereby the chemical mechanism of the reaction may be elucidated. Mainly, we used fluorene as an active methylene compound, since fluorene-9-carboxylic acid (9-FLC) is easy to treat after the reaction.

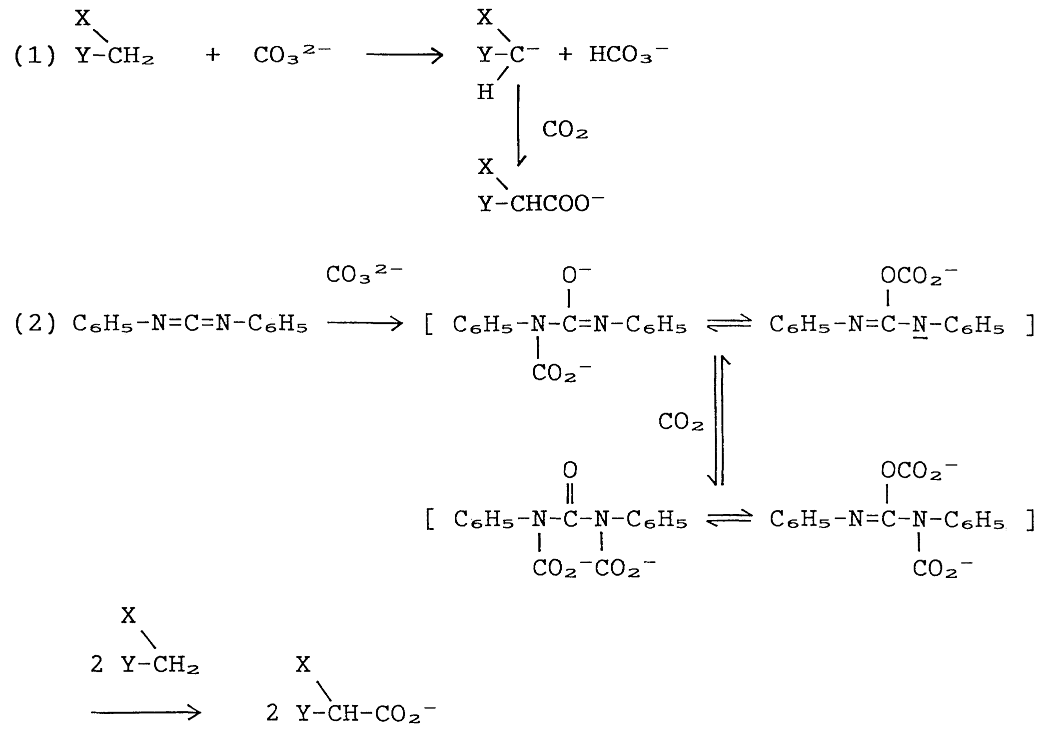
Results and Discussions

Carboxylation of Fluorene with Imine and Carbon Dioxide. Fluorene was carboxylated with carbon dioxide and potassium carbonate to yield 9-FLC, even if no biotin model (imine) was present. However, the yield was as low as 4.8% (Table 1). It is well known that a strong base, like 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU), abstracts a proton from an active methylene compound.[13,14] In this reaction carbonate ion might abstract a proton from fluorene, while producing the fluorenyl anion ((1) in the Scheme). Since fluorenyl anion reacts with carbon dioxide to give carboxylic acid, water must be an inhibitor. Certainly, no 9-FLC was obtained when water was added. It is reported that dicyclohexylcarbodiimide was an effective imine for the carboxylation of an active methylene compound in the presence of quaternary ammonium salt.[12] However, a low yield was obtained when potassium carbonate was used instead of quaternary ammonium salt. Also, phenyl isocyanate was not a good biotin model for this carboxylation. More than 35% of the fluorene was carboxylated with carbon dioxide in the presence of DPC. The yield was seven-times larger than that using dicyclohexylcarbodiimide. Furthermore, fluorene was carboxylated even under a nitrogen atmosphere. Without DPC, no 9-FLC was obtained if under a nitrogen atmosphere. These facts indicate that if DPC was present, potassium carbonate was able to be a source of carbon dioxide. We considered reaction mechanism (2) in the Scheme. A carbonate ion attacks an imine carbon to give anionic intermediates. The results in a non-carbon dioxide atmosphere indicated that such intermediates can donate carbon dioxide to an active methylene compound. The high yield under a carbon dioxide atmosphere suggested that such intermediates react further with carbon dioxide to give the reactive intermediates shown in the Scheme. These results are interesting examples of carboxylation under a nitrogen atmosphere as the model of an enzyme system. The yield of 9-FLC in air was 18.1%. The value was larger than 6.6% in a nitrogen atmosphere. Air might include moisture. Drying of air decreased the yield, indicating that water was a positive factor. The effect

Table 1. Carboxylation of Fluorene Using Imine as a Model of the Biotin Enzyme Active Site[a)]

Imine	Atmosphere (1 atom)	Reaction time/h	Yield of 9-FLC/%[b)]
None	CO_2	2	4.8
None[c)]	CO_2	2	0.0
None	N_2	2	0.0
Dicyclohexylcarbodiimide	CO_2	2	4.8
Diphenylcarbodiimide	CO_2	2	35.2
Diphenylcarbodiimide	Air	2	18.1
Diphenylcarbodiimide	Closed[d)]	2	10.5
Diphenylcarbodiimide	N_2	2	6.6
Diphenylcarbodiimide	N_2	5	5.7
Diphenylcarbodiimide[e)]	CO_2	2	10.3
Bis(*o*-methylphenyl)carbodiimide	CO_2	2	0.0
Bis(*m*-methylphenyl)carbodiimide	CO_2	2	32.2
Bis(*p*-methylphenyl)carbodiimide	CO_2	2	42.6
Bis(*o*-chlorophenyl)carbodiimide	CO_2	2	5.5
Bis(*o*-chlorophenyl)carbodiimide	N_2	2	0.0
Bis(*m*-chlorophenyl)carbodiimide	CO_2	2	23.8
Bis(*p*-chlorophenyl)carbodiimide	CO_2	2	15.1
Phenyl isocyanate	CO_2	5	5.2

a) Fluorene, 5 mmol; imine, 16.8 mmol; potassium carbonate, 30 mmol; DMSO, 25 ml; reaction temp, 20 °C. b) The yields were calculated on the basis of fluorene used. c) Water was added. d) Reaction was carried out with closing the reactor. e) Dimethylforamide was used as a solvent.



Scheme.

of water addition is discussed later. *o*-Substituents in the phenyl moieties of DPC were harmful for carboxylation, the same results as those using DPU.[10)]

If carbon dioxide is activated by transference to the imidazole moiety, as shown in the Scheme (2), *o*-substituents in the phenyl moieties of DPC interferred with the carboxylation reaction. Such a steric effect may be present.

Carboxylation of Active Methylene Compounds with DPC and Carbon Dioxide. Twelve active methylene compounds were carboxylated with carbon dioxide in the presence of DPC and potassium carbonate (Table 2). The highest yield was obtained in the carboxylation of indene. Though the yields were from 0.0 to 53.8%, there was no correlation between pK_a and the yield. In the case that a strong base is used

Table 2. Carboxylation of Active Methylene Compounds in a Carbon Dioxide Atmosphere$^{a)}$

Substrate (p$K_a$$^{16,17)}$)	Yield of carboxylic acid/%$^{b)}$
Indene (21)	53.8
Indanone	45.5
Fluorene (25)	35.2
Phenylacetonitrile	29.2
Acetophenone (19)	28.7
1-Tetralone	21.5
p-Methoxyacetophenone	14.4
Cyclohexanone	14.0
Xanthene (29)	0.5
Acetonitrile (25)	Trace
Diphenylmethane (35)	0.0
4,4′-Dinitrodiphenylmethane (16)	0.0

a) Substrate, 5 mmol; diphenylcarbodiimide, 16.8 mmol; K_2CO_3, 30 mmol; DMSO, 25 ml; reaction temp, 20 °C; reaction time, 2 h. b) The yields of carboxylic acid were calculated on the basis of substrate used. The products were monocarboxylic acids. They were identified by comparison of IR spectra with those of the authentic samples, after esterification with diazomethane, if necessary.

without a biotin model, proton abstraction by the base should be a rate-determining step and pK_a an important factor.[14] Our results indicate that since proton abstraction is not a rate-determining step it is not an important factor. After the reaction we confirmed the presence of DPU. In the case of fluorene, one fourth of the DPC converted to DPU after a 2 hour reaction. Though we measured the ^{1}H NMR of the reaction solution, we could not confirm the presence of DPU during the reaction. During the post-treatment, the reaction mixture was poured into ice-cold water. There is a possibility that the reaction intermediates reacted with protons at this point to give DPU.

The Effects of Reaction Time and Carbon Dioxide Pressure on the Carboxylation of Fluorene. In the case of DPU, the yield of carboxylic acid increased with an increase in the reaction time.[10,11] However, the maximum yield of 9-FLC was obtained at ca. 2 h in the case of DPC; the yield decreased slightly after 2 h (Table 3). This suggests the presence of undesirable reactions, such as a reverse reaction and/or an adduct reaction between DPC and 9-FLC. Actually, 55% of 9-FLC changed to unknown compounds in the reaction of 9-FLC with DPC for 2 h, although no reaction was observed when 9-FLC alone was reacted in DMSO. Although the reaction mechanism is not clear, the production of fluorenone was confirmed. We could also obtain the trimer of DPC by a reaction at 80 °C for 9 h. The production was confirmed by MS. The yield of 9-FLC when the DPC trimer was used instead of DPC was only 10.1% at 20 °C for 2 h. If the oligomerization of DPC occurs, elongation of reaction time is not preferable.

Table 3. Effects of the Reaction Time and CO_2 Pressure on the Carboxylation of Fluorene Using Diphenylcarbodiimide$^{a)}$

Pressure	Reaction time/h					
MPa$^{b)}$	0.5	1	2	4	5	7
0	15.2	28.7	35.2	22.5	16.1	16.0
	25.2	24.3		29.7		
1		20.8	10.5	13.9		15.9
2		25.3	16.5		10.4	12.0
			17.6			
4		8.7	9.8	18.6	12.3	12.3

a) Fluorene, 5 mmol; diphenylcarbodiimide, 16.8 mmol; K_2CO_3, 30 mmol; DMSO, 25 ml; reaction temp, 20 °C. b) Gauge pressure.

Table 4. Effects of Alkali Carbonate on the Carboxylation of Fluorene Using Diphenylcarbodiimide (DPC)$^{a)}$

Alkali carbonate	Solubility$^{b)}$ mmol	Amounts of CO_2 absorption$^{c)}$	Yield of 9-FLC$^{d)}$ %
None		17.1	0.0
Li_2CO_3	0.32	18.3	6.3
Na_2CO_3	0.62	16.8	1.9
K_2CO_3	3.68	15.1	35.2
$K_2CO_3$$^{e)}$			38.3
Rb_2CO_3	12.6	18.3	26.8
Cs_2CO_3	13.8	64.0	71.6

a) Fluorene, 5 mmol; diphenylcarbodiimide, 16.8 mmol; alkali carbonate, 30 mmol; DMSO, 25 ml; reaction temp, 20 °C; reaction time, 2 h. b) Solubility of alkali carbonates in DPC and DMSO 100 ml. c) The amount of CO_2 absorption (mmol) in the solution of alkali carbonate, DPC, and DMSO 100 ml. d) The yields of fluorene-9-carboxylic acid (9-FLC) were calculated on the basis of fluorene used. e) 60 mmol of K_2CO_3 was used.

It has been reported that carboxylation using DBU is influenced by the pressure of carbon dioxide.[6] Active methylene compounds give carboxylated products in much higher yield under higher pressure carbon dioxide. However, in the case of DPC, the carbon dioxide pressure was not effective on the yield of 9-FLC (Table 3). It has already been reported that in the absence of any catalyst equilibrium between two phenyl isocyanate molecules and DPC, carbon dioxide exists far on the side of phenyl isocyanate.[15] There is a possibility of a reaction of DPC with carbon dioxide to give phenyl isocyanate. Phenyl isocyanate was not a good imine, as mentioned earlier (Table 1).

The Effects of Alkali Carbonate on the Carboxylation of Fluorene. The yield of 9-FLC depended upon the nature of alkali carbonate (Table 4). Lithium and sodium carbonates were not effective; cesium salt was the most effective. The yields are well related to the solubility of alkali carbonate and the amount of

Table 5. Effects of Water Addition on the Yield of 9-FLC in Carboxylation for 2 h Using Diphenylcarbodiimide and K_2CO_3[a)]

Conditions	Amount of water added/mmol					
	0	5	10	15	20	30
A	10.5	13.5	24.3	10.8	0.1	
B	35.2	35.4	42.8	41.6	37.5	30.5
C	27.4	29.9	42.6	44.4	25.3	19.2

A; reactor was closed. B; reactor was bubbled by CO_2. C; reactor was pretreated by bubbling CO_2 for 1 h before adding fluorene and after then closed. a) Fluorene, 5 mmol; diphenylcarbodiimide, 16.8 mmol; K_2CO_3, 30 mmol; DMSO, 25 ml; reaction temp, 20 °C.

carbon dioxide absorbed in the reaction solution. The solubility of potassium carbonate was 3.68, larger than those of lithium and sodium carbonates by a factor of five to ten. The solubilities of rubidium and cesium carbonates were about three- to four-times larger than that of potassium carbonate. The concentration of carbanion is critical. Without an alkali carbonate, 17.1 mmol of carbon dioxide was absorbed in DMSO. This indicates that the carbonates, except cesium carbonate, did not contribute to the increase in the amount of carbon dioxide absorption. The highest yield of 71.6% with cesium carbonate is attributable to the high solubility in DMSO and the great ability to absorb carbon dioxide in conjunction with DPC.

The Effects of Water Addition on the Carboxylation of Fluorene. 1 g of potassium carbonate is soluble in 2.8 g of water. The solubility of potassium carbonate increased from 3.68 to 8.79 upon the addition of 10 mmol water to the DMSO solution of DPC. Water is known to be an inhibitor in many carboxylation reactions, as mentioned previously. However, the yield of 9-FLC in air was larger than that in drying air (Table 1), indicating that, at least, water was not an inhibitor. We have found the very interesting fact that in this study the addition of water accelerated the carboxylation yield (Table 5). Though without carbon dioxide the yield of 9-FLC without water was 10.5%, the value increased to 24.3% upon the addition of 10 mmol water. A maximum yield was obtained at 10 to 15 mmol addition of water in the case of bubbling carbon dioxide. The addition of more water than 15 mmol was not effective. The solubility of potassium carbonate increased upon the addition of water. Although the concentration of carbonate ions increased upon the addition of water, water addition lowered the solubility of fluorene in DMSO. Carbanion reacted with a proton to give a less-reactive compound. Our results suggest that if the reaction intermediates, as shown in the Scheme (2), reacted with water, their carboxylation activity did not become lower.

Conclusions

DPC was an effective carbon dioxide carrier for the carboxylation of active methylene compounds as a biotin model. Carboxylation of fluorene, even under a nitrogen atmosphere, is a very interesting reaction, since DPC can react with the carbonate ion directly, although DPU can not.[10,11)] This indicates the possibility of an effective usage of carbonate ions in which more than 99.9% of the carbon dioxide exists as calcium carbonate. The carboxylation reaction of fluorene occurred even in the presence of water, suggesting that the reaction intermediates shown in the Scheme are stable to water. It was considered that the concentration of carbonate ions determined the reaction. In a biological system, the carboxylation reaction occurs in the presence of water without carbon dioxide. Our results indicate that the carboxylation of fluorene using DPC occurs under similar conditions as those of biological systems.

Experimental

DPC and substituted DPC were synthesized according to a method of Campbell et al.[15)] 1-Ethyl-3-methyl-3- phospholene 1-oxide was used as a catalyst. Active methylene compound and DPC were dissolved in DMSO (25 ml); to this solution powdered alkali carbonate was added. Dry carbon dioxide was then passed into the mixture. The reaction mixture was poured into ice-cold water and the precipitate filtered off (active methylene compound and DPU etc.). The filtrate was extracted with ether. Acidification of the aqueous solution with hydrochloric acid gave a white precipitate. The precipitate was carboxylic acid. The ether extract was dried over anhydrous sodium sulfate and the solvent evaporated. The residue and above-mentioned precipitate were identified by a comparision of the IR spectra and melting points with those of carboxylic acids. A reaction under pressure was carried out using a 100 ml magnet-driven autoclave and treated in the same manner as mentioned above. The solubilities of alkali carbonates were determined by titration using HCl after filtration.

The amounts of carbon dioxide absorption in a DMSO solution containing DPC were determined by measuring the weight both before and after carbon dioxide bubbling.

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