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Mechanism of the Carboxylation of Cyclohexanone with Carbon Dioxide Catalyzed by 1,8-Diazabicyclo[5.4.0]undec-7-ene

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The dependence of the rate of carboxylation upon the concentration of the reactant was investigated in dimethyl sulfoxide. The reaction rate depended upon the concentration of cyclohexanone and 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU) in the first order, respectively. The reaction also followed first-order kinetics regarding the CO_2 pressure in the range 50—400 Torr. From these reaction characteristics, it is suggested that carboxylation proceeds via a reaction between CO_2 dissolved in dimethyl sulfoxide and the anion of cyclohexanone, rather than between the CO_2 adduct with DBU and cyclohexanone. The results of carboxylation by the CO_2 adduct with DBU and by CO_2 dissolved in dimethyl sulfoxide also support the above conclusion. The formation of the cyclohexanone anion by a reaction of cyclohexanone with DBU was verified by the UV spectrum of a solution of concentrated DBU and cyclohexanone.

A number of carbon dioxide fixation reactions catalyzed by a base is known in organic chemistry. In these reactions, compounds containing active methylene are transformed to carboxylic acids. The bases used as the

$$RH + CO_2 + B^- \rightarrow RCO_2^- + BH$$

catalyst are classified into two groups. One of them contains metal oxides such as sodium[1] or potassium[2,3] phenoxide or magnesium methoxide.[4] Another group includes nitrogen bases. Strong bases such as 1,8-diazabicyclo[5.4.0]undec-7-ene(DBU)[5] or tetramethylguanidine[6] are used in the absence of metal ions, and weak bases such as triethylamine[7] and 2-imidazolidinone[8] are used in the presence of metal ions.

We have investigated carboxylation using potassium phenoxide (PhOK).[2,3] With regard to the mechanism of this reaction, it was suggested[3] that the CO_2 complex with PhOK served as the CO_2 source of the carboxylate. We are now interested in the catalysis of nitrogen bases. Among nitrogen bases, DBU has been extensively studied by Haruki et al.[9] and was established as an effective carboxylating agent in synthetic chemistry. In a preliminary experiment, we found that the carboxylation of cyclohexanone using this base in dimethyl sulfoxide (DMSO) gives 2-oxocyclohexanecarboxylic acid in a homogeneous reaction system. We therefore selected this reaction system as a typical carboxylation by a nitrogen base, and studied it from a mechanistic view point. Iwatani et al.[10] studied this system under a high pressure of CO_2. In the present paper, the kinetics of carboxylation with CO_2 under a pressure lower than atmospheric are reported, and a reaction mechanism under this condition is proposed.

Experimental

Material and Glassware. DBU was dried with NaOH for several days at room temperature and distilled under nitrogen at a reduced pressure prior to use. Cyclohexanone was distilled under atmospheric pressure. DMSO was refluxed with CaH_2 for about 3 h, and distilled under a reduced nitrogen pressure. Well-dried glassware was used for the uptake of CO_2 by DBU and for carboxylation.

The Uptake of CO_2 by DBU. The uptake of CO_2 by DBU was investigated with a 0.2-M (1 M=1 mol dm^{-3}) DMSO solution at 20 °C in the vacuum system described in a previous paper.[3] The amount of CO_2 taken up by DBU was calculated by subtracting the amount dissolved in DMSO from the total amount taken up by the DMSO solution of DBU.

Carboxylation of Cyclohexanone with DBU and CO_2. CO_2 at atmospheric pressure was passed through a DMSO solution of DBU for 1 h at 20 °C. Then, cyclohexanone was added to this solution. A portion of the mixture was withdrawn at predetermined intervals, acidified with diluted HCl, and extracted with ether. The ethereal layer was dried with anhydrous sodium sulfate and treated with diazomethane. The methyl ester of the carboxylic acid was determined by means of gas chromatography. In a study of the dependence of the reaction rate upon the concentration of DBU, varying amounts of DBU in the ranges of 5—40 mmol and 10 mmol of cyclohexanone were used with 100 cm^3 of DMSO. Similarly, to study the dependence upon the concentration of cyclohexanone, 10 mmol of DBU and 5—40 mmol of cyclohexanone were used. In a study regarding the dependence upon the CO_2 pressure, mixtures of N_2 and CO_2 in varying ratios were used. The amounts of DBU and cyclohexanone used in this experiment were 20 and 10 mmol, respectively, with 100 cm^3 of DMSO.

Spectral Measurement. Infrared (IR) spectra were measured with a Hitachi EPI-G3 spectrophotometer, and electronic spectra, with a Hitachi 100-50 spectrophotometer.

Results and Discussion

Regarding carboxylation with PhOK, we suggested[3] that CO_2 complexed with PhOK plays the role of a CO_2 source. Accordingly, we first investigated the reaction between DBU and CO_2 in DMSO. After CO_2 was passed through a DMSO solution of DBU, a new absorption was observed at 1642 cm^{-1} in the IR spectrum. This fact indicates that CO_2 forms an adduct with DBU. In Fig. 1 is shown the uptake of CO_2 by

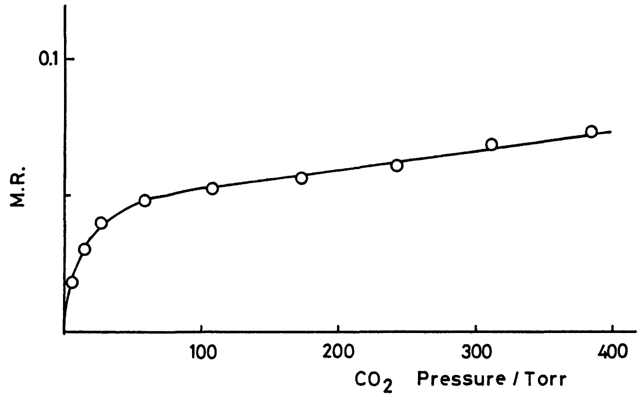

Fig. 1. The uptake of CO_2 by DBU at 20°C under various CO_2 pressure (0.2 M DMSO solution).

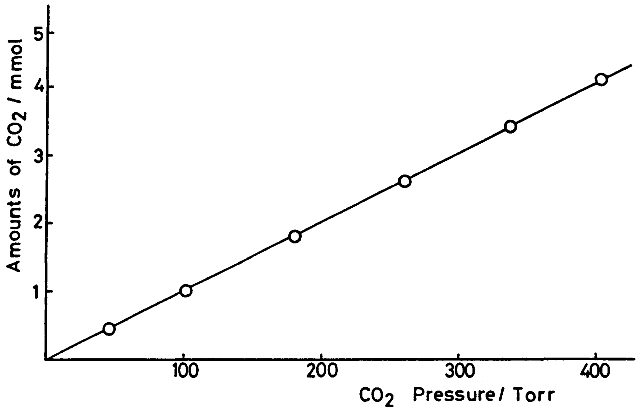

Fig. 2. The solubility of CO_2 in 50 cm^3 of DMSO at various CO_2 pressure at 20°C.

DBU in DMSO under various CO_2 pressures. The amount of CO_2 taken up by DBU was obtained by subtracting the amount of CO_2 dissolved in DMSO (Fig. 2, slope=2.05×10^{-4} mmol $Torr^{-1}$ cm^{-3}, 1 Torr= 133.322 Pa) from that dissolved in the DMSO solution of DBU. The ordinate indicates the M.R.: that is, the molar ratio of CO_2 adduct to the total amount of DBU. The value of M.R. was less than 0.1, even at a CO_2 pressure of about 400 Torr. On the contrary, the uptake by PhOK was extensive and the M.R. value amounted to more than 0.5 at 10 Torr.[3]

In Fig. 3, the time courses of the carboxylation with varying amounts of DBU are shown. The yields of carboxylate were calculated on the basis of the amount of cyclohexanone initially added (10 mmol). The yield of carboxylate increased almost linearly with the reaction time. The initial rates of carboxylate formation were calculated from the results. A plot of the initial rates of carboxylate formation against the initial concentration of DBU gave a straight line with a slope of 1.71 ± 0.07 (% min^{-1} M^{-1}). Thus, it was shown that the rate of carboxylation depended upon the concentration of DBU in the first order.

The dependence of the reaction rate upon the concentration of cyclohexanone was also studied. In this case, the yield of carboxylate was calculated on the basis of the amount of DBU initially added. The rate of the carboxylation increased almost linearly with the increase in the concentration of cyclohexanone, with a slope of 1.67 ± 0.15 (% min^{-1} M^{-1}). Thus, the relationship between the reaction rate and the concentration of cyclohexanone showed a first-order dependence; the obtained slope was almost the same magnitude as that obtained in the study of the dependence upon the concentration of DBU. Thus, the slopes give a pseudo second-order rate constant of about 1.7 (% min^{-1} M^{-1}).

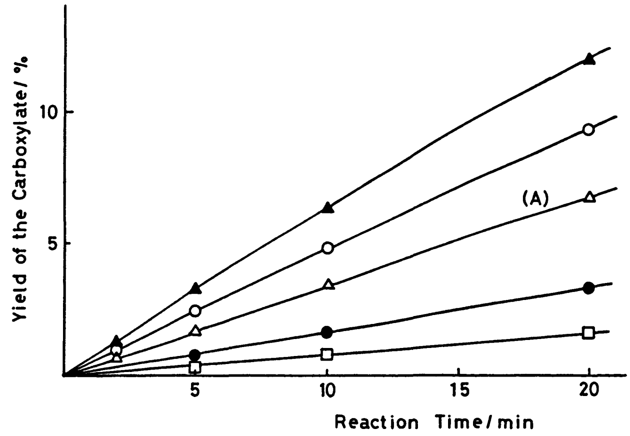

Fig. 3. The carboxylation with various amounts of DBU. —□—, 5 mmol; —●—, 10 mmol; —△—, 20 mmol; —○—, 30 mmol; —▲—, 40 mmol.

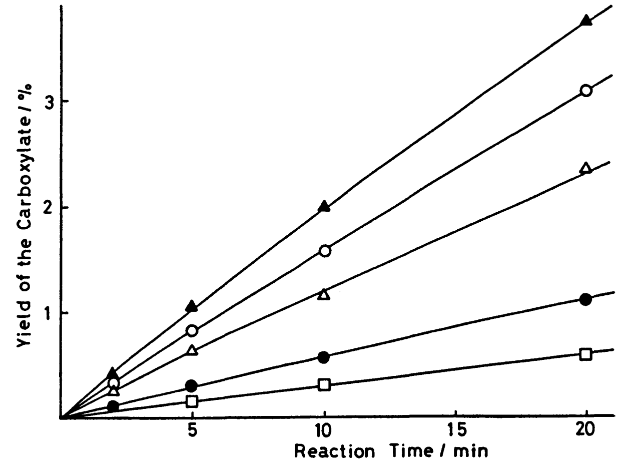

Fig. 4. The carboxylation with various CO_2 pressure. —□—, 47.5 Torr; —●—, 95 Torr; —△—, 190 Torr; —○—, 285 Torr; —▲—, 380 Torr.

In Fig. 4, the time courses of carboxylation under various CO_2 pressures are shown. The yield of the carboxylate increased almost linearly with the reaction time. The initial rates of the carboxylate formation were obtained from the results. A plot of the initial rate against the CO_2 pressure gave a curve with a slight deviation from a straight line (Fig. 5).

With respect to carboxylation, two species can be considered as the possible CO_2 source of the carboxylate. They are the CO_2 adduct with DBU and CO_2

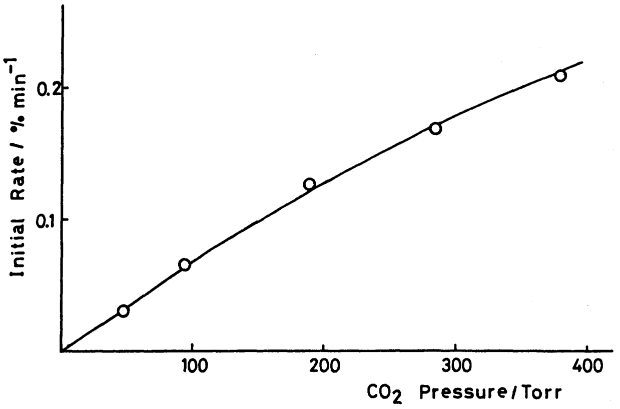

Fig. 5. The relationship between the initial rate of the carboxylation and CO_2 pressure.

dissolved in DMSO. We now discuss the reaction mechanisms corresponding to the respective CO_2 species. The mechanism including CO_2 adduct with DBU is shown below, as is proposed by Iwatani et al.[10] Here,

$$\text{(A)}\quad \begin{cases} \text{DBU} + \text{CO}_2 \rightarrow \text{DBU}\cdot\text{CO}_2 & (1) \\ \text{DBU}\cdot\text{CO}_2 + \text{ChH} \rightarrow \text{ChCO}_2^-\cdot\text{DBUH}^+ & (2) \end{cases}$$

ChH designates cyclohexanone. In this mechanism, a CO_2 transfer occurs from the adduct to cyclohexanone to form the carboxylate (step (2)). Since the DMSO solution of DBU was preequilibrated with CO_2, step (1) might be in equilibrium. In such a case, the concentration of the adduct can be expressed by

$$c = aPK/(1+PK), \qquad (3)$$

where P is the pressure of CO_2, K is the equilibrium constant of step (1), and a is the total concentration of DBU. This equation indicates that the concentration of the adduct increases proportionately with the initial concentration of DBU under a constant CO_2 pressure. In the carboxylation reaction, cyclohexanone was added to a CO_2 saturated DMSO solution of DBU. Therefore, the initial rate of carboxylation would be that of step (2). The rate of step (2) would show a first-order dependence upon the concentrations of both cyclohexanone and the adduct and, consequently, upon the concentration of DBU (as shown in Eq. 3). Experimental results were in accordance with the above discussion. The dependency of the rate upon the CO_2 pressure was assumed to be analogous to the curve shown in Fig. 1, since this curve indicates the dependence of the concentration of the adduct upon the CO_2 pressure. However, the experimental results (Fig. 5) were not in agreement with this assumption.

Another possible mechanism (B) is shown below:

$$\text{(B)}\quad \begin{cases} \text{ChH} + \text{DBU} \rightarrow \text{Ch}^-\cdot\text{DBUH}^+ & (4) \\ \text{Ch}^-\cdot\text{DBUH}^+ + \text{CO}_2 \rightarrow \text{ChCO}_2^-\cdot\text{DBUH}^+ & (5) \end{cases}$$

Cyclohexanone anion (Ch^-) is formed by the reaction between cyclohexanone and DBU (step (4)) and reacts with CO_2 dissolved in DMSO to form the carboxylate (step (5)). If step (5) was the rate-limiting step, the reaction rate would depend upon the respective concentrations of the anion and CO_2 to the first order. Cyclohexanone is a very weak acid (pK_a=16.9[11]), and DBU is a strong base with a pK_a of 11.5.[12] Thus, a small amount of cyclohexanone anion might be formed in step (4), and during the initial stage of carboxylation, the amount of formed cyclohexanone anion would be proportional to the amounts of the respective substrates. Though a part of DBU forms the adduct with CO_2 (as indicated in Eq. 3), the resultant concentration of DBU increases along with an increase in the initial concentration of DBU. Thus, the rate of carboxylation would show a first-order dependence upon the initial concentrations of both DBU and cyclohexanone. As shown in Fig. 2, the solubility of CO_2 in DMSO increased linearly in accordance with the increase in CO_2 pressure. Therefore, the rate of the reaction would increase linearly with an increase in the CO_2 pressure. Experimental results described previously seem to be consistent with this mechanism (B).

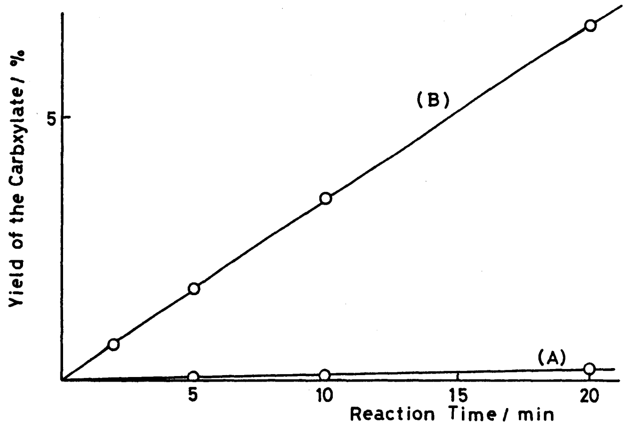

Fig. 6. The time courses of the carboxylation. (A) in the case of using CO_2 adduct with DBU, (B) in the case of using CO_2 dissolved in DMSO.

As discussed above, it is suggested that carboxylation proceeds via the reaction mechanism (B) rather than mechanism (A). In order to obtain further support for this mechanism, we studied carboxylation using only one CO_2 species. In the absence of the solvent, DBU (neat) was reacted with CO_2 at atmospheric pressure. It absorbed CO_2 in the molar ratio of 0.08. The carboxylation reaction was carried out with this mixture of the adduct and unreacted DBU.[13] The time course of the reaction is shown in Fig. 6 (curve (A)). A separate experiment[14] showed that CO_2 was scarcely transferred from the adduct to the solvent. If carboxylation proceeded via reaction mechanism (A), the initial rate of carboxylation with this adduct sample should have been the same as that of carboxylation for the case[15] in which atmospheric CO_2 was passed through about a 0.2-M DMSO solution of DBU (Fig. 3 curve (A)). However, the initial rate of the former was considerably smaller than that of the latter (in the ratio of about 1 : 30). This result shows that the contribution of the adduct to the carboxylation was very small. As shown in Fig. 1, the concentration of the adduct, the low active species, increases with an increase in the CO_2 pressure, reducing the concentration of DBU. Thus, with respect to the curve shown in Fig. 5, the deviation from a straight line could be ascribed to the reduced amount of DBU at the starting point of carboxylation with the increased CO_2 pressure.

Carboxylation using CO_2 dissolved in DMSO was also carried out.[16] The time course of this carboxylation is given in Fig. 6 (curve (B)). This curve for carboxylate formation is very similar to that shown in Fig. 3 (curve (A)). It can therefore be pointed out that CO_2 dissolved in DMSO plays an important role in carboxylation by DBU.

The reaction between DBU and cyclohexanone was studied spectrophotometrically. Figure 7 shows the electronic absorption spectrum of a DMSO solution containing both 1 M DBU and 1 M cyclohexanone (spectrum (A)), which was measured with a 1-M DMSO solution of DBU as a reference. Since cyclohexanone does not have an absorption in this region of the spectrum, a new absorption with a maximum between 360 and 370 nm can be ascribed to the formation of the cyclohexanone anion. The spectrum of potassium salt of cyclohexanone (enolate)[17] in DMSO has a maximum at 362 nm (spectrum (B)). The results confirmed the reaction between cyclohexanone and DBU to form the cyclohexanone anion (step (4)).

The experimental results described above support the idea that carboxylation catalyzed by DBU proceeds via reaction mechanism (B). On the contrary, Iwatani et al. suggested[10] mechanism (A) for carboxylation under a higher CO_2 pressure and higher concentrations of DBU and cyclohexanone than ours. However, upon inspecting their data, it seems that mechanism (B) could not always be excluded as a possible mechanism. A further investigation may be necessary before the results of the two groups can be understood with consistency, considering the difference in the reaction conditions.

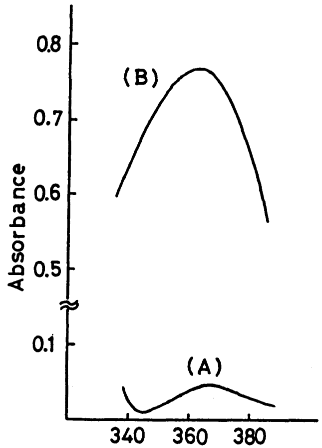

Fig. 7. Electronic absorption spectra. (A) DMSO solution containing both 1 M DBU and 1 M cyclohexanone, (B) DMSO solution of potassium salts of cyclohexanone.

Anyhow, the results obtained in our present work strongly suggest that the reaction proceeds mainly via reaction mechanism (B). This mechanism is in contrast with that of carboxylation catalyzed by PhOK, in which the CO_2 source of the carboxylate was considered to be CO_2 complexed with PhOK.[3] In the two reactions, the rate of the latter is, generally, much larger than that of the former, especially at a low CO_2 pressure. The dependence of the rate upon the CO_2 pressure is fairly different among the two reactions. It is noted that PhOK binds with CO_2 more strongly than DBU, in spite of its low pK_a (pK_a of phenol is 10.0). The formation of CO_2 species other than $CO_2 \cdot PhOK$ is suggested (data are not shown). Thus, the difference of the reactivity in carboxylation between PhOK and DBU may result from the unique reactivity of PhOK toward CO_2.

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13) Twenty mmol of DBU(neat) was reacted with CO_2 of atmospheric pressure for 1 h, absorbing 1.6 mmol of CO_2

(gravimetrically determined). This sample was dissolved in 100 cm^3 of DMSO and reacted with 10 mmol of cyclohexanone.

14) The variation of the concentration of CO_2 adduct with DBU was observed in the IR spectra after the sample was dissolved in DMSO. The relative intensity of the absorption at 1642 cm^{-1} to that at 1610 cm^{-1} due to DBU was followed for 1 h. And no marked variation of the relative intensity was observed. It was also shown, by comparison with the spectrum of the DBU solution (in DMSO) which was saturated with CO_2 of atmospheric pressure, that most parts of the dissolved adduct retained the form of adduct in solution.

15) With respect to this solution, it was estimated by the gravimetric method that 100 cm^3 of DMSO dissolves 15.0 mmol of CO_2 and 20 mmol of DBU uptakes 1.8 mmol of CO_2, respectively.

16) CO_2 of atmospheric pressure was passed through the solution containing 100 cm^3 of DMSO and 10 mmol of cyclohexanone for 1 h. Then 20 mmol of DBU was added. In connection with this carboxylation reaction, the experiment as shown below was carried out. DBU was added to the CO_2 saturated DMSO solution and the IR spectrum of the solution was measured. The spectrum showed that only a small portion of CO_2 was present in the adduct form in the solution.

17) Potassium salt of cyclohexanone was prepared in THF by the reaction of cyclohexanone with potassium hydride (Ref. 18), and this solution was diluted with DMSO.

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