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Substituent Effects of Potassium Phenoxides on the Carboxylation of Indene by Carbon Dioxide

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The carboxylation of indene by carbon dioxide was investigated in the presence of substituted phenoxides in DMF. The reaction took place rapidly at 0 °C and was apparently completed within about ten minutes. Indene-3-carboxylic acid was found to be formed in 42—98% yields from indene, depending on the substituents (p-OC_4H_9, p-OCH_3, p-CH_3, H, p-Cl, m-Cl, p-CN, and m-NO_2) of the phenoxides. The substituent effect upon the interaction of carbon dioxide with the substituted phenoxides was observed. It was found that the yield of indene-3-carboxylic acid increased with substituents of negative σ values, giving rise to a linear relation between the logarithm of the equilibrium constants of carboxylation of indene and the σ values. Relative rates of reaction were compared with the various substituted phenoxides mentioned above. The mechanism of the reaction is briefly discussed.

Keywords——potassium phenoxide; carbon dioxide; indene; indene-3-carboxylic acid; substituent effect; carboxylation; Hammett substituent constant

Carbon dioxide fixation into organic compounds to form new carbon–carbon bonds is a basic and useful process not only from an industrial point of view but also from a biological standpoint (for example, the carboxylation–decarboxylation process effected by vitamin H). The history of carbon dioxide fixation goes back to the Kolbe–Schmitt reaction or the synthesis of salicylic acid in the pharmaceutical industry. It must be remembered, however, that the above reaction proceeds under rather severe conditions in the semi-solid state, while biological carboxylation occurs under mild conditions in living cells.

In recent years, the use of aprotic solvents has enabled us to achieve carbon dioxide fixation under milder conditions. Carbon dioxide fixation into a number of organic pseudo acids has been reported to occur in the presence of alkali phenoxide in aprotic solvents.1,2) A similar carboxylation reaction was found to take place with the use of potassium pyrrolidone (a model of vitamin H) in dimethyl sulfoxide or hexamethylphosphoric triamide.3) The synthesis using alkali phenoxide may be regarded as a simple but useful technique.

Little work has been carried out, however, on the role of the substituent of phenoxide derivatives. It is expected that the introduction of substituents on the phenoxides would modify the extent of the interaction with carbon dioxide and consequently the carboxylation of organic pseudo acids. In the present paper, we describe the carboxylation of indene by carbon dioxide in the presence of various substituted phenoxides in *N,N*-dimethylformamide (DMF).

Experimental

Materials and Procedure——It is known that slight water contamination of the reagents can affect the nature of the reaction, so extreme care was taken to exclude moisture or humidity from any source during the experiment.

DMF was used as an aprotic solvent. It was distilled over P_2O_5 under reduced pressure. Indene (Ind-H) was distilled in an atmosphere of N_2. Potassium phenoxide derivatives (RPhOK) were prepared as follows. A methanol solution of a substituted phenol derivative of the highest grade commercially available was mixed with an aqueous solution of potassium hydroxide (equimolar). The solvent was evaporated off on a water bath under reduced pressure. The residue was further dried over an oil bath (140 °C) for 4 h *in vacuo*. The purity of the potassium phenoxide derivatives thus prepared was confirmed by the sodium tetraphenylboron method.[4] The substituents investigated were *p*-OC_4H_9, *p*-OCH_3, *p*-CH_3, H, *p*-Cl, *m*-Cl, *p*-CN, and *m*-NO_2.

A potassium phenoxide derivative was dissolved in DMF to give a concentration of 0.1 M. Gaseous carbon dioxide, passed through molecular sieves, was then bubbled into the DMF solution kept at 0 °C for about 30 min, then equimolar Ind-H with RPhOK was introduced into the reaction vessel with the CO_2 flow.

Analysis and Identification——The reaction solution was sampled with the use of a syringe at appropriate intervals. Each sample was acidified with dilute hydrochloric acid and then extracted with ether. The ethereal layer was dried over anhydrous sodium sulfate and analyzed by gas chromatography (15% OV-17 Chromosorb W, 2.5 m, hydrogen flame ionization detector (FID)) to determine the quantity of Ind-H. On the other hand, the ethereal solution of the sample was trimethylsilylated and subjected to gas chromatographic analysis to determine the quantity of carboxylate. In order to separate the carboxylic acid, aqueous $NaHCO_3$ solution was added to the ethereal solution, extracting the carboxylate into the aqueous layer and leaving the phenol derivative in the ethereal layer. The aqueous carboxylate solution was again acidified with dilute hydrochloric acid to extract the carboxylate into the ethereal layer. After the evaporation of the ether solution, the residue was recrystallized from acetone. Colorless needles were obtained. *Anal.* Calcd for $C_{10}H_8O_2$: C, 74.99; H, 5.03. Found: C, 74.77; H, 5.04. The crystalline sample was mixed with an authentic sample of indene-3-carboxylic acid, and there was no depression of mp (159—160 °C). The product was esterified and subjected to nuclear magnetic resonance (NMR) measurements. The spectra showed signals (δ values) at 3.48 and 7.40 due to olefinic and methylenic protons, respectively in accordance with the values of 3.43 and 7.40 in the literature.[5] Thus, it is clear that carbon dioxide fixation does occur with Ind-H and yields indene-3-carboxylic acid. Furthermore, thin layer chromatography showed that no products were present other than that identified above.

Results

Interaction of Substituted Phenoxides with Carbon Dioxide

As already described,[2] the carboxylation of organic pseudo acids by carbon dioxide in the presence of potassium phenoxide (unsubstituted) may be preceded by the formation of a complex between phenoxide and CO_2. Therefore, the absorption of CO_2 by substituted

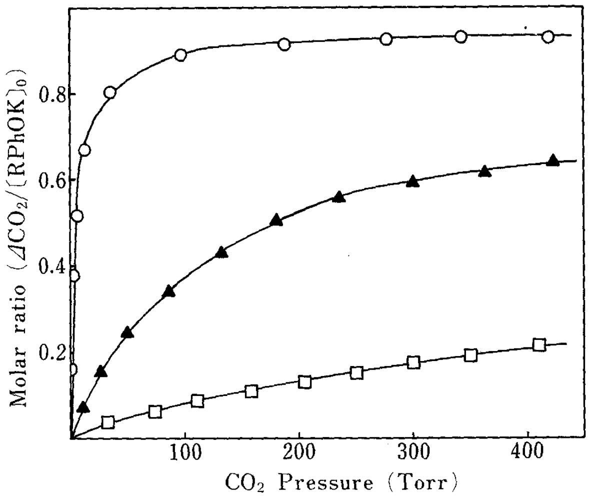

Fig. 1. The Uptake of Carbon Dioxide by Some Potassium Phenoxide Derivatives at 0 °C

—○—, H; —▲—, *p*-Cl; —□—, *m*-Cl.

The ordinate indicates the molar ratio of the absorbed carbon dioxide to the potassium phenoxide derivative added.

The reaction was done in 0.4 M DMF solution of the potassium phenoxide derivative.

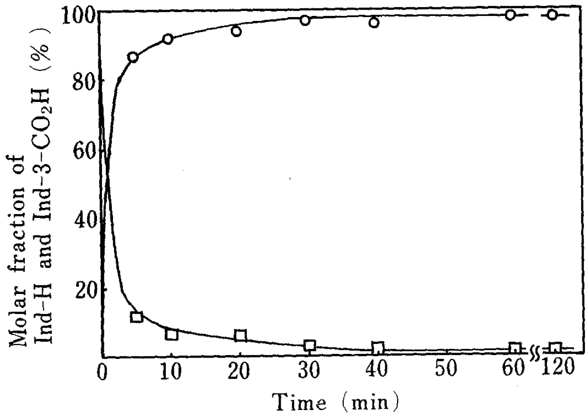

Fig. 2. The Material Balance for Ind-H and Ind-3-CO_2H during the Carboxylation Reaction

—○—, Ind-3-CO_2H; —□—, Ind-H.

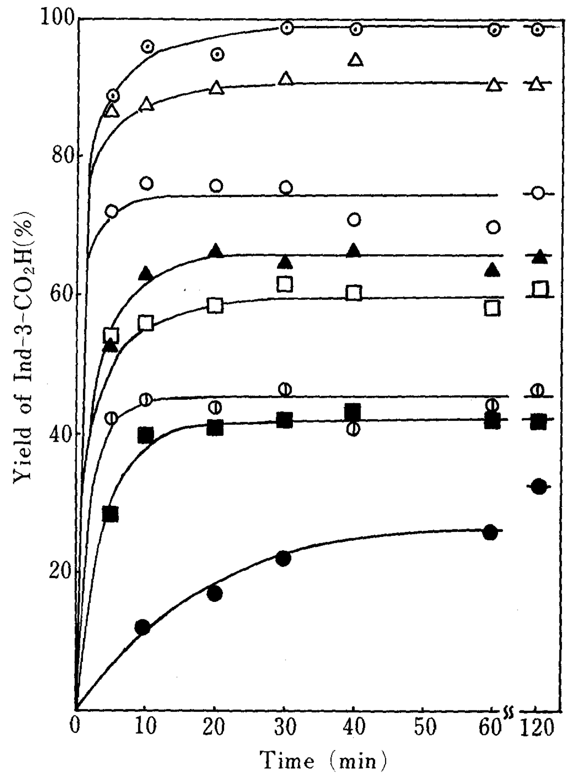

Fig. 3. Substituent Effects upon the Yield of Ind-3-CO_2H

—⊙—, *p*-OCH_3; —△—, *p*-CH_3; —○—, H; —▲—, *p*-Cl; —□—, *m*-Cl; —■—, *p*-CN; —⦶—, *m*-NO_2.

—●—, carboxylation of cyclohexanone by potassium phenoxide.

Table I. Substituent Constants, Yields of Ind-3-CO_2H and Equilibrium Constants of the Carboxylation of Ind-H (0 °C)

R	σ Value	Yield (%)	*K*
p-OC_4H_9	−0.32	89	6.7×10
p-OCH_3	−0.27	98	2.4×10^3
p-CH_3	−0.17	88	5.4×10
H	0	79	1.4×10
p-Cl	0.23	62	2.7
m-Cl	0.37	57	1.8
p-CN	0.66	40	4.0×10^{-1}
m-NO_2	0.71	45	7.0×10^{-1}

phenoxide was investigated statically at 0 °C. The CO_2 uptake by RPhOK in DMF was determined by subtracting the amount of CO_2 taken up by DMF alone from the total uptake by the solution.

Figure 1 shows the molar ratios of CO_2 to RPhOK added, as determined with *p*-Cl, *m*-Cl, and unsubstituted phenoxide. The CO_2 uptake by other phenoxides with substituents having negative σ values is not shown in Fig. 1 because it appeared to be nearly the same as that of unsubstituted phenoxide. It is suggested that phenoxides with substituents having negative σ values, as well as the unsubstituted compound, interact strongly with CO_2 and consequently complex formation between CO_2 and the phenoxide may reach saturation under the experimental conditions used. On the other hand, the uptake of CO_2 by phenoxides with substituents having positive σ values was rather weak, suggesting that complex formation is far from saturation. Since the extent of CO_2 uptake by phenoxides was found to depend on the sort of substituent, the differences would probably be reflected in the carboxylation of indene by CO_2.

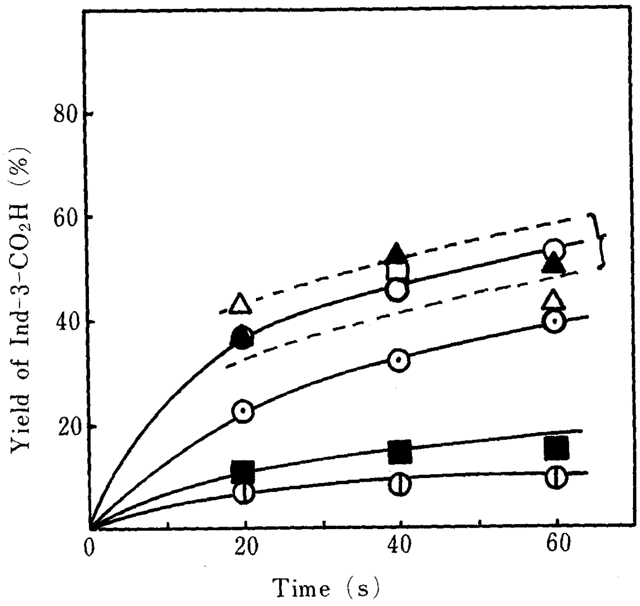

Fig. 4. Rates of Carboxylation of Ind-H by CO_2 with RPhOK

—⊙—, p-OCH_3; —△—, p-CH_3; —○—, H; —▲—, p-Cl; —□—, m-Cl; —■—, p-CN; —⦶—, m-NO_2.

The reaction curves lie between the two dotted lines in the cases of p-CH_3, H, p-Cl, and m-Cl.

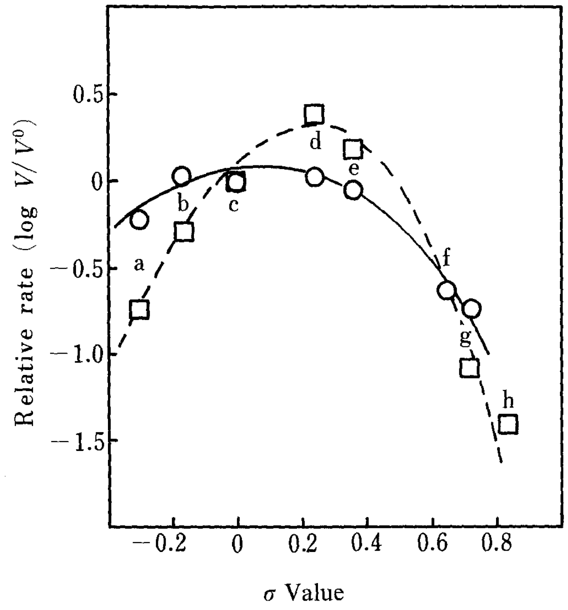

Fig. 5. Relationship between σ Values and Relative Rates of Carboxylation by RPhOK

—○—, Ind-H; ---□---, cyclohexanone.

a, p-OCH_3; b, p-CH_3; c, H; d, p-Cl; e, m-Cl; f, p-CN; g, m-NO_2; h, p-$COCH_3$.

V^0 indicates the rate in the carboxylation using potassium phenoxide.

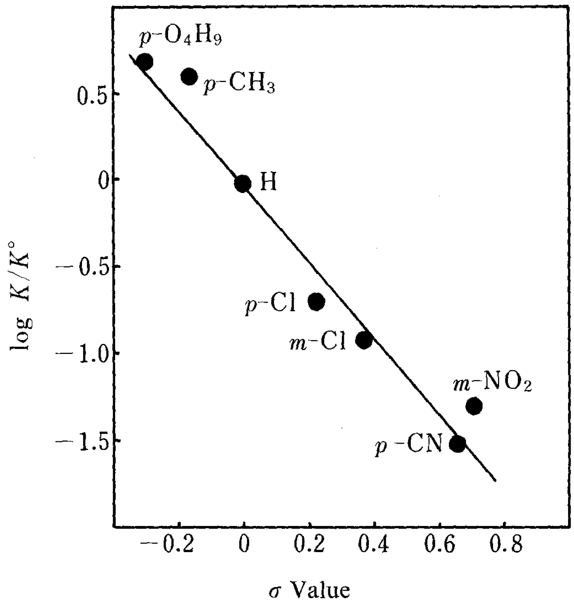

Fig. 6. Relationship between σ Value and $\log K/K^0$

Substituent Effects on the Yields of Carboxylate

The carboxylation of indene (Ind-H) by CO_2 was investigated in the presence of various substituted phenoxide derivatives. As already mentioned, the sole product was identified as indene-3-carboxylic acid (Ind-3-CO_2H). The time course of the reaction is illustrated in Fig. 2 for the p-OC_4H_9 substituted phenoxide. As is apparent in Fig. 2, the material balance for the reactant (Ind-H) and the product (Ind-3-CO_2H) was satisfactory. Accordingly, the carboxylation of Ind-H by CO_2 may be expressed by

$$CO_2 + RPhOK + Ind\text{-}H = RPhOH + Ind\text{-}3\text{-}CO_2K \qquad (1)$$

The carboxylation of Ind-H by CO_2 was then investigated with the other phenoxide derivatives. The results are shown in Fig. 3, where the yield (%) of Ind-3-CO_2H based on the initial amount of Ind-H is shown during the course of the reaction.

The carboxylation of Ind-H took place rapidly with any substituted phenoxide, as shown in Fig. 3, and was complete within about 10 min. No appreciable changes were seen in the yield of Ind-3-CO_2H during the later period of the reaction. It should be noted, however, that the yield of Ind-3-CO_2H (at 60 min) depended distinctly on the substituents, as expected. The yield of Ind-3-CO_2H was lowest with *p*-CN (42%) and highest with *p*-OCH_3 (98%). The yields as well as Hammett substituent constants[6)] are listed in Table I. One can see from Table I that the carboxylation of Ind-H by CO_2 occurs in better yield with the use of a substituent of negative σ value as compared with one having a positive value. The order of yield was as follows:

$$p\text{-OCH}_3 > p\text{-OC}_4\text{H}_9\text{–}p\text{-CH}_3 > \text{H} > p\text{-Cl} > m\text{-Cl} > p\text{-CN–}m\text{-NO}_2 .$$

Kinetic Aspects of Carboxylation

As shown in Fig. 3, the kinetic runs were rather indistinguishable with the substituted phenoxides investigated, due to the rapidity of the reaction. Figure 4 shows kinetic data obtained within one minute, but the rates of carboxylation were still too fast to yield reliable data. Nevertheless, the relative rates of carboxylation of Ind-H were in the following order:

$$p\text{-CH}_3\text{–H–}p\text{-Cl–}m\text{-Cl} > p\text{-OCH}_3 > p\text{-CN} > m\text{-NO}_2 .$$

Figure 5 shows the relationship between the σ values of the substituents and the relative rates. As shown in Fig. 4, there were considerable experimental errors, and the reactions may be limited by diffusion of CO_2 in the solution in some cases.

An additional investigation was made on the carboxylation of cyclohexanone, where the yield of carboxylate when it reached a roughly constant value was less than half of that of Ind-H carboxylation under similar conditions (Fig. 3). Relative rates in the case of cyclohexanone conventionally determined from the kinetic runs were as follows:

$$p\text{-Cl} > m\text{-Cl–H} > p\text{-CH}_3 > p\text{-OCH}_3 > m\text{-NO}_2 > p\text{-COCH}_3 .$$

The relationship with the σ values is shown in Fig. 5.

While the kinetic data are only qualitative, it should be noted that the highest rate can be found with some phenoxides whose σ value is neither highly negative nor highly positive. With cyclohexanone, the highest rate was found with *p*-Cl, though this did not appear to be the case with Ind-H.

Discussion

The overall reaction of Ind-H with carbon dioxide in the presence of potassium phenoxide can be expressed, in general, by Eq. (1). The reaction may proceed *via* two or more consecutive steps. As suggested elsewhere,[2)] the reaction may be preceded by the formation of a complex between CO_2 and RPhOK;

$$\text{RPhOK} + \text{CO}_2 = \text{RPhOK} \cdot \text{CO}_2 \qquad (2)$$

On addition of Ind-H, the transfer of the activated CO_2 from the complex to the substrate may take place, yielding Ind-3-CO_2H.

$$\text{RPhOK} \cdot \text{CO}_2 + \text{Ind-H} = \text{RPhOH} + \text{Ind-3-CO}_2\text{K} \qquad (3)$$

Now, the concentration of CO_2 complex in the solution depends on the nature of the substituent (Fig. 1). The fraction of the CO_2 complex, θ, over total phenoxide

(phenoxide + CO_2 complex) in the solution is approximately given by

$$\theta = \frac{bP}{1+bP} \tag{4}$$

where b is the binding constant of phenoxide toward CO_2, and P is the ambient CO_2 pressure. For larger b or P, θ may tend to unity. Such a situation seems to apply to p-OCH_3, p-CH_3 and H, but not to substituents with a positive σ value, at least under the present experimental conditions.

It is assumed[7)] that the yields given in Table I correspond to the equilibrium concentrations of Ind-3-CO_2H. Now we define the equilibrium constant, K, which represents the extent of carboxylation, as follows:

$$K = \frac{X^2}{(1-X)^2} \tag{5}$$

where X is the molar fraction of Ind-3-CO_2H, based on the initial amount of Ind-H. Under the present experimental conditions ($P = 1$ atm), K can be readily obtained from the data in Table I. Figure 6 shows a plot of log K/K^0 against σ, where K^0 is the equilibrium constant for the unsubstituted phenoxide.

An approximately linear relation was obtained for log K/K^0 against σ value. The relation might be useful to predict the yield of Ind-3-CO_2H for a given phenoxide derivative. The relationship suggests that the use of substituents with very negative σ values may give better yields.

Since the Hammett substituent constants have been interpreted in terms of electron-repelling or -withdrawing character of substituents, it is conceivable that substituents modify the basicities of the phenoxides, and hence may control the binding strength toward CO_2, which is acidic. Therefore, the transfer of CO_2 from the complex to Ind-H would be dependent on the σ values of the substituents. The relation shown in Fig. 6 implies that the carboxylation of organic pseudo acids by CO_2 in the presence of potassium phenoxide derivatives or other basic media[8-10)] as represented by magnesium methoxide is associated with the basicities of the media.

Let us discuss some kinetic aspects of the carboxylation. In this reaction, CO_2 was passed into the RPhOK solution for about 30 min before the addition of the substrate, so that reaction (2) is in pre-equilibrium, forming RPhOK·CO_2 in the amount of θ $[\mathrm{RPhOK}]_0$. If reaction (2) is followed by reaction (3), the initial rate of carboxylation may be expressed by

$$V = k\theta[\mathrm{RPhOK}]_0[\mathrm{AH}]_0 \tag{6}$$

where k is the rate constant of step (3) and AH represents the organic pseudo acid. As already mentioned, θ may reach nearly unity with the phenoxides having substituents with negative σ values. Therefore, k would decrease for these phenoxides to an extent related to the binding strength between CO_2 and phenoxide. This may be the case for the carboxylation of cyclohexanone with phenoxides having substituents of negative σ value (Fig. 5). On the other hand, the kinetic sequence was partly parallel to the equilibrium one in the region of σ values more positive than that of p-Cl; the rate of carboxylation was found to increase with decrease of σ value. This result can be simply explained by Eq. (6) where θ should increase with decrease of σ value.

The kinetics do not, however, exclude the possibility that the complexed CO_2 attacks A^- instead of AH, because CO_2 is well known to react readily with carbanions. Also, step (3) may involve an isomerization of the type:

$$\text{Ind-1-}CO_2H = \text{Ind-3-}CO_2H \tag{7}$$

Ind-1-CO_2H can rapidly tautomerize[11] to Ind-3-CO_2H in the presence of base.

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