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Formic Acid Reduction. XXIII.[1] Kinetic Studies on the Formic Acid Reduction of Carbon-Carbon Double Bond Adjacent to Carbonyl

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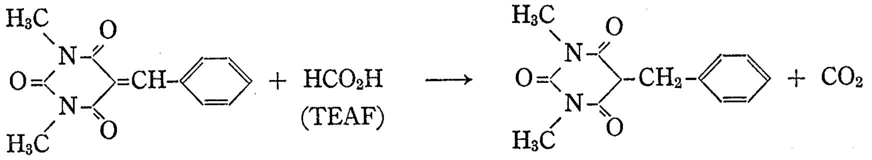
Kinetic manner was introduced into mechanistic studies on the formic acid reduction of carbon-carbon double bond adjacent to carbonyl induced by the formate reagent, TEAF, $5HCO_2H \cdot 2NEt_3$. Kinetic data obtained by the use of 1,3-dimethyl-5-benzylidenebarbituric acid as a representative, the second order kinetics, the large negative entropy of activation, the isotope effect (2.79) and the positive ρ-value (+1.00) of the Hammett equation, suggest one step path, which proceeds by the attack of $HCO_2^- \cdot H\overset{+}{N}Et_3$ involving the push-pull mechanism of ring system of a transition state.

Scattered papers have dealt with formic acid reduction in mechanistic aspect, but only in limited fields.[3-5] In our previous works[6-8] in the field the high selective formic acid reduction of conjugated carbon-carbon double bond adjacent to carbonyl, which is effected by the constant boiling liquid formate composed of formic acid and trialkylamine, appeared to merit a mechanistic investigation because of its synthetic significance. It is an investigation by kinetic manner that the present paper describes.

Results

Rate of the Reduction

For rate measurement the formic acid reduction[6] of 1,3-dimethyl-5-benzylidenebarbituric acid (DBBA) into 1,3-dimethyl-5-benzylbarbituric acid was adopted as a representative reaction with the formate reagent, TEAF,[3,9] bp 98° (18 mmHg), corresponding to $5HCO_2H \cdot 2NEt_3$.



Rate measurement was made by means of trapping CO_2 emitted in the reaction. First, comparative effects of several solvents on the reaction were examined under the selected conditions resulting as shown in Fig. 1. With every solvent nearly quantitative conversion was checked. Remarkable solvent effect was seen with N,N-dimethylformamide (DMF), in which the reaction was 136 and 7 times as rapid as in anisole and in TEAF, respectively.

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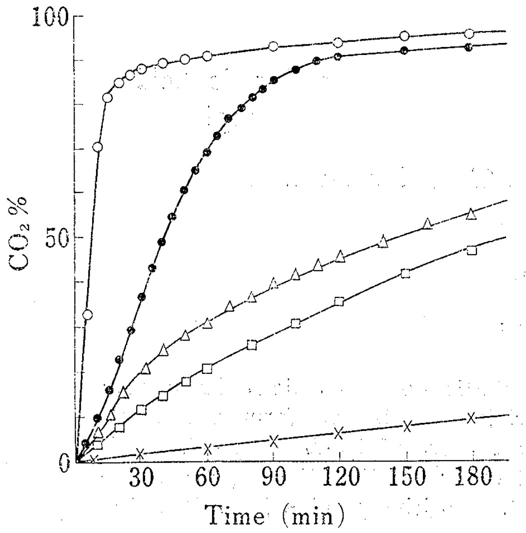


Fig. 1. Effect of Solvent

○—○: DMF, ●—●: TEAF, △—△: methyl cellosolve, □—□: nitrobenzene, ×—×: anisole
reaction conditions:
reaction temperature, 55±0.1°
[DBBA]=0.0125 (mole·1^{-1})
[TEAF]=0.0250 (mole·1^{-1})
relative rate (calculated from the initial 10% conversion):
anisole (1), nitrobenzene (8), methyl cellosolve (13), TEAF (19), DMF (136)

For determination of kinetic rate equation anisole was selected as a solvent appropriate to the rate measurement preventing solvent effect, and rate was measured at 55±0.1° by initial rate method. It was demonstrated that the reaction is of first order with respect to each DBBA and TEAF by measurement of effect of their concentrations on the rate, as shown in Tables I and II. Values of the rate constants k_{DBBA} and k_{TEAF}, which should be equal under the given conditions, were calculated to be $(3.16 \pm 0.01) \times 10^{-5}\,\mathrm{sec}^{-1}$ and $(3.17 \pm 0.01) \times 10^{-5}\,\mathrm{sec}^{-1}$, respectively. Rate equation is then expressed by

$$v = k[\mathrm{DBBA}][\mathrm{TEAF}] \qquad (1)$$

Concentration of TEAF can be replaced by concentration of formic acid or of triethylamine. It was then needed to determine independent effect of concentration of formic acid and triethylamine on the rate. In order to carry out the reaction with fairly small change of basicity or acidity of the reaction medium, effects of concentration of formic acid and of triethylamine were examined by the use of the constant boiling liquid composed of acetic acid and triethylamine[3] (TEAA) in place of triethylamine. Previously, analysis[3] by potentiometric titration has determined the composition of TEAA as $7CH_3CO_2H \cdot 2NEt_3$. Measurement of effects of concentrations of formic acid and triethylamine resulted as shown in Tables III and IV, respectively. As can be seen, rate of the reduction is proportional to each concentration of formic acid and triethylamine. Values of the rate constants, $k_{\mathrm{HCO_2H}}$ and $k_{\mathrm{NEt_3}}$ are calculated to be $(0.953 \pm 0.012) \times 10^{-5}\,\mathrm{sec}^{-1}$ and $(1.27 \pm 0.01) \times 10^{-5}\,\mathrm{sec}^{-1}$, respectively. Consequently the rate equation can be described as follows.

TABLE I. Effect of the Concentration of DBBA

[DBBA] (mole·1^{-1})	$v \times 10^6$ (mole·1^{-1}·sec^{-1})
0.068	2.081
0.135	3.811
0.169	5.738
0.203	6.388

[TEAF]=0.135 (mole·1^{-1})
$v = k_{\mathrm{DBBA}}[\mathrm{DBBA}]$, $k_{\mathrm{DBBA}} = (3.16 \pm 0.01) \times 10^{-5}\,\mathrm{sec}^{-1}$

TABLE II. Effect of the Concentration of TEAF

[TEAF] (mole·1^{-1})	$v \times 10^6$ (mole·1^{-1}·sec^{-1})
0.034	0.917
0.068	1.794
0.135	3.811
0.203	6.895
0.270	9.128

[DBBA]=0.135 (mole·1^{-1})
$v = k_{\mathrm{TEAF}}[\mathrm{TEAF}]$, $k_{\mathrm{TEAF}} = (3.17 \pm 0.01) \times 10^{-5}\,\mathrm{sec}^{-1}$

$$v = k'[\mathrm{DBBA}][\mathrm{HCO_2H}][\mathrm{NEt_3}] \qquad (2)$$

In consideration of equilibration in TEAF, $[HCO_2H][NEt_3] = 1/K[HCO_2^- \cdot H\overset{+}{N}Et_3] \propto [\mathrm{TEAF}]$ should be valid, where K is equilibrium constant. Therefore Eq. 1 agrees with Eq. 2, disclosing a reacting species, $HCO_2^- \cdot H\overset{+}{N}Et_3$.

Rate measurement at varied temperatures (see Table V) allowed us to give the following activation energy and entropy.

$$\Delta E = 20.1\,\mathrm{kcal \cdot mole^{-1}}, \quad \Delta S = -15.9\,\mathrm{cal \cdot deg^{-1} \cdot mole^{-1}}$$

Table III. Effect of the Concentration of Formic Acid

[TEAF] $(\text{mole}\cdot\text{l}^{-1})$	[TEAA] $(\text{mole}\cdot\text{l}^{-1})$	$[HCO_2H]$ $(\text{mole}\cdot\text{l}^{-1})$	$v\times10^6$ $(\text{mole}\cdot\text{l}^{-1}\cdot\text{sec}^{-1})$
0.068	0.202	0.340	3.856
0.101	0.169	0.505	4.268
0.135	0.135	0.675	6.469
0.169	0.101	0.845	7.853
0.202	0.068	1.015	9.851

[DBBA]=0.135 $(\text{mole}\cdot\text{l}^{-1})$; $[NEt_3]=0.540$ $(\text{mole}\cdot\text{l}^{-1})$
$v=k_{HCO_2H}[HCO_2H]$, $k_{HCO_2H}=(0.953\pm0.012)\times10^{-5}\text{sec}^{-1}$

Table IV. Effect of the Concentration of Triethylamine

[TEAA] $(\text{mole}\cdot\text{l}^{-1})$	$[NEt_3]$ $(\text{mole}\cdot\text{l}^{-1})$	$v\times10^6$ $(\text{mole}\cdot\text{l}^{-1}\cdot\text{sec}^{-1})$
0	0.270	3.811
0.068	0.405	5.449
0.135	0.540	6.469
0.200	0.670	8.418
0.270	0.810	10.43

[DBBA]=0.135 $(\text{mole}\cdot\text{l}^{-1})$; [TEAF]=0.135 $(\text{mole}\cdot\text{l}^{-1})$
$v=k_{NEt_3}[NEt_3]$, $k_{NEt_3}=(1.27\pm0.01)\times10^{-5}\text{sec}^{-1}$

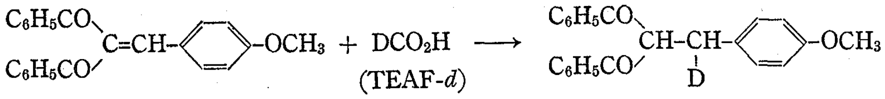
Table V. Effect of Temperature

Reaction temperature (°C)	$k\times10^4$
40	0.502
50	1.56
55	2.34
60	3.93

$\Delta E=20.1$ $(\text{kcal}\cdot\text{mole}^{-1})$; $\Delta S=-15.9$ $(\text{cal}\cdot\text{deg}^{-1}\cdot\text{mole}^{-1})$

Reduction Mode and Isotope Effect

In the formate reduction of the conjugated carbon-carbon double bond, incorporation mode of the two different hydrogens of the formic acid into the reduction product was then examined. We selected a method of carrying out the reduction with a TEAF reagent composed of formic-*d* acid (DCO_2H) in order to see deuterated position and deuterium content in the product by means of nuclear magnetic resonance (NMR) measurement. Use of DBBA did not give satisfaction to this purpose, because of close proximity of proton signals desired for the measurement. For the determination of the reduction mode *p*-methoxybenzylidenedibenzoylmethane[7] was selected instead and was allowed to react with the deuterated TEAF reagent. The observed NMR spectrum of *p*-methoxybenzyldibenzoylmethane in $CDCl_3$ exhibited a triplet at $\delta=5.55$ ($J=7$ Hz) for the methine proton and a doublet at $\delta=3.40$ ($J=7$ Hz) for the methylene protons, while in the NMR spectrum of the reduction product, the peak corresponding to methine proton appeared as a doublet and that corresponding to the methylene protons showed decrease in intensity. Calculation of proton contents of these two signals in comparison with that of the methoxy proton signal ($\delta=3.70$, singlet, 3H) showed one proton content in each disclosing one deuterium possession at β-carbon of the product. From this result, mode of the reduction with deuterated TEAF can be expressed by the following scheme.



It is then concluded that in the formate reduction of conjugated carbon-carbon double bond adjacent to carbonyl, the formyl hydrogen of formic acid is transferred to the β-carbon.

Taking account of this reduction mode, isotope effect in the formate reduction of DBBA with the deuterated TEAF, $5DCO_2H \cdot 2NEt_3$, was then examined. By the same manner as for the measurement of k_{HCO_2H}, rate constant k_{DCO_2H} was obtained from the data shown in Table VI and compared to k_{HCO_2H} to give the following isotope effect.

$$k_{HCO_2H}/k_{DCO_2H} = 0.953/0.341 = 2.79$$

Table VI. Deuterium Isotope Effect

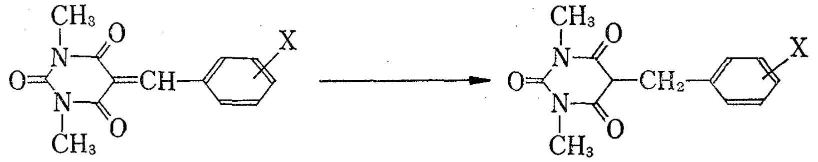
[TEAF-d] (mole·l^{-1})	[TEAA] (mole·l^{-1})	[DCO_2H] (mole·l^{-1})	$v \times 10^6$ (mole·l^{-1}·sec^{-1})
0.068	0.202	0.340	1.287
0.101	0.169	0.505	2.136
0.135	0.135	0.675	2.299
0.169	0.101	0.845	2.575

[DBBA]=0.135 (mole·l^{-1}); [NEt_3]=0.540 (mole·l^{-1})
$v = k_{DCO_2H}[DCO_2H]$, $k_{DCO_2H} = (0.341 \pm 0.014) \times 10^{5-}$ sec^{-1}
$k_{HCO_2H}/k_{DCO_2H} = 0.953/0.341 \fallingdotseq 2.79$

Substituent Effect

Kinetic substituent effect on the TEAF reduction of DBBA was examined. Six 1,3-dimethyl-5-benzylidenebarbituric acids possessing *p*-OCH_3, *m*-OCH_3, *p*-CH_3, *p*-Cl, *m*-Cl and *m*-NO_2 substituents on the benzene rings were prepared and the rate measurements with these in their varying concentrations were examined by the initial rate method. The obtained rate constants kx are listed in Table VII with the previously obtained k_{DBBA}. Fig. 2 shows plots of log (kx/k_{DBBA}) *vs* Hammett's σ-value for the substituents. Adherence of these plots to the Hammett equation was excellent giving a positive ρ-value. By the least square method the ρ-value was calculated to be +1.00. Therefore the reduction is facilitated by introduction of electron withdrawing substituent on the benzene ring.

Table VII. Substituent Effect for the TEAF Reduction of 1,3-Dimethyl-5-benzylidenebarbituric Acids



Substituent X	$k_X \times 10^5$	log (k_X/k_{DBBA})
p-OCH_3	1.47	−0.358
p-CH_3	1.86	−0.256
H (DBBA)	3.16	0
m-OCH_3	3.76	+0.051
p-Cl	3.91	+0.068
m-Cl	7.94	+0.375
m-NO_2	13.9	+0.619

Discussion

The results obtained in the foregoing sections are summarized as follows.

1. The obtained rate equation is $v=k$[DBBA][TEAF]. [TEAF] can be replaced by [HCO_2H][NEt_3] from the following equation.

$$[\mathrm{TEAF}] \propto \frac{1}{K}[\mathrm{HCO_2^-}\cdot\mathrm{H\overset{+}{N}Et_3}] = [\mathrm{HCO_2H}][\mathrm{NEt_3}]$$

2. Activation energy and entropy in the reduction are

$$\Delta E = 20.1\ \mathrm{kcal\cdot mole^{-1}},$$
$$\Delta S = -15.9\ \mathrm{cal\cdot deg^{-1}\cdot mole^{-1}}.$$

3. Formyl hydrogen of formic acid is transferred to β-carbon of the carbon-carbon double bond adjacent to carbonyl.
4. The isotope effect: $k_{HCO_2H}/k_{DCO_2H}=2.79$.
5. The obtained ρ-value of the Hammett equation is $+1.00$.

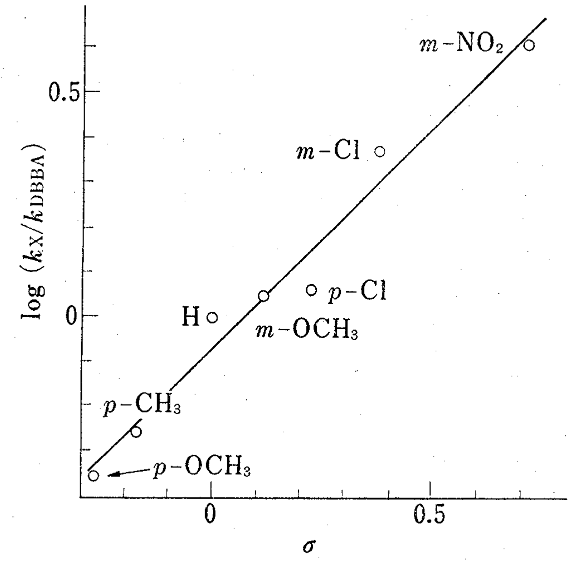


Fig. 2. The Hammett Plot for the TEAF Reduction of 1,3-Dimethyl-5-benzylidenebarbituric Acids

A possible mechanism which is comprehensible for the above results is drawn as shown in Chart 1.

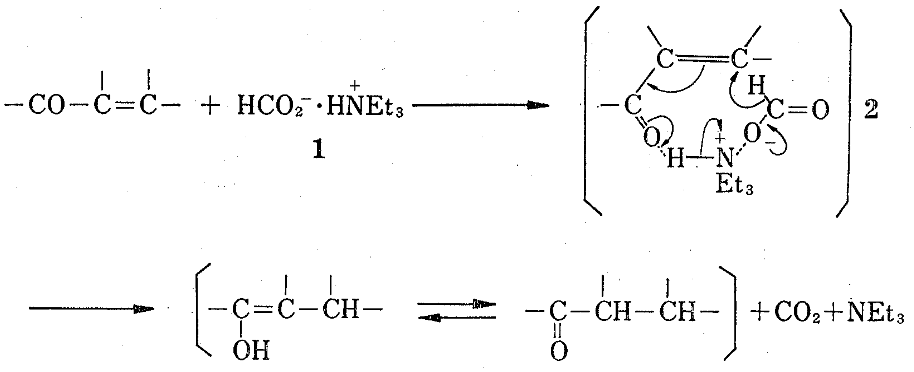


Chart 1

The reaction is considered to consist of an attack of the reacting species, $HCO_2^-\cdot H\overset{+}{N}Et_3$ (**1**), which was disclosed in terms of the rate equation, on the conjugated site of the substrate. The observed isotope effect indicates that breaking of formyl hydrogen of formic acid as hydride is rate determining step. The value, 2.79, suggests a transition state in which the carbon-hydrogen bond of the formate **1** appears not to be broken but somewhat weakened as previously stated by Grinter, *et al.*[5] in the formic acid reduction of tris-arylcarbinol, which exhibits the isotope effect value (2.5[4]) resembling the above value. When compared with the reduction of tris-arylcarbinol ($\Delta S=-7.5$[4] cal·mole^{-1}·deg^{-1}; $\Delta E=18.3$[4] kcal·mole^{-1}), the larger negative entropy of activation obtained suggests more complex configuration in transition state.

A probable transition state may be given by the configuration incorporating $HCO_2^-\cdot H\overset{+}{N}Et_3$ as shown by **2** in Chart 1. It is very likely that the process of the decarboxylation is induced by the push-pull mechanism of the ring system as in **2**. The described route is also in agreement with the observed positive ρ-value in the Hammett equation, in which electron withdrawing substituent on the benzene ring would accelerate the reaction by decreasing electron density at the β-carbon attracting the formyl hydrogen of the formate **1**.

Experimental[10]

Materials——The following seven 1,3-dimethyl-5-benzylidenebarbituric acids including four new compounds were prepared from the corresponding benzaldehydes and 1,3-dimethylbarbituric acid on referring to the previously reported method.[6] 1,3-Dimethyl-5-benzylidenebarbituric acid, mp 157—158° (lit,[6,11] mp 159—160°); 1,3-dimethyl-5-(*p*-methoxybenzylidene)barbituric acid, mp 144—145° (lit.[11] mp 148.5—149°); 1,3-dimethyl-5-(*p*-methylbenzylidene)barbituric acid, mp 140—141° (lit.[11] mp 142—142.5°); 1,3-dimethyl-5-(*p*-chlorobenzylidene)barbituric acid, yellow needles (from EtOH), mp 154—155°. *Anal.* Calcd. for $C_{13}H_{11}O_3N_2Cl$: C, 56.03; H, 3.98; Cl, 12.72; N, 10.05. Found: C, 56.27; H, 4.01; Cl, 12.74; N, 9.82. UV $\lambda_{\max}^{\text{EtOH}}$ nm (ε): 333 (16500), 256$^{\text{sh}}$ (7600), 239 (10700), 235 (10600); 1,3-dimethyl-5-(*m*-chlorobenzylidene)barbituric acid, light yellow needles (from EtOH), mp 141—142°. *Anal.* Calcd. for $C_{13}H_{11}O_3N_2Cl$: C, 56.03; H, 3.98; Cl, 12.72; N, 10.05. Found: C, 55.82; H, 3.97; Cl, 12.49; N, 10.02. UV $\lambda_{\max}^{\text{EtOH}}$ nm (ε): 318 (11000), 236 (9300); 1,3-dimethyl-5-(*m*-nitrobenzylidene)barbituric acid, light yellow prisms (from toluene), mp 150—151°. *Anal.* Calcd. for $C_{13}H_{11}O_5N_3$: C, 53.98; H, 3.83; N, 14.53. Found: C, 54.06; H, 3.71; N, 14.70. UV $\lambda_{\max}^{\text{EtOH}}$ nm (ε): 300$^{\text{sh}}$ (19300), 260 (62500); 1,3-dimethyl-5-(*m*-methoxybenzylidene)barbituric acid, light yellow prisms (from EtOH), mp 133—134°. *Anal.* Calcd. for $C_{14}H_{14}O_4N_2$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.44; H, 5.19; N, 10.30. UV $\lambda_{\max}^{\text{EtOH}}$ nm (ε): 324 (12300), 252 (10500), 218.5 (15500).

The formate reagents, TEAF,[3,9] $5HCO_2H \cdot 2NEt_3$, bp 98° (18 mmHg), and that[3,12] composed of formic-*d* acid, $5DCO_2H \cdot 2NEt_3$, bp 98° (18 mmHg) and the acetate,[3] $7CH_3CO_2H \cdot 2NEt_3$, bp 74° (16 mmHg) were prepared and purified by the previously reported methods.

Anisole was washed with 5% NaOH solution, dried over $CaCl_2$ and by refluxing over metal sodium, and then distilled so as to give a liquid of bp 155.0—155.5°. DMF (bp 152.5—153.0°), methyl cellosolve (bp 124.0°) and nitrobenzene (bp 210.0—210.5°) were rectified repeatedly so as to show their boiling points given in parentheses.

Kinetic Measurement——Rates of the TEAF reduction of DBBA were determined by measurement of the emitted CO_2 at $55 \pm 0.1°$. For determination of activation energy and entropy, rate measurement at $40 \pm 0.1°$, $50 \pm 0.1°$ and $60 \pm 0.1°$ were also conducted by the same manner.

A stream of CO_2 free, dried and prewarmed N_2 of constant flow rate (50 ml/min) was bubbled through the reaction vessel (3 × 10 cm). The N_2 containing CO_2 from the reaction vessel was passed through a tube packed with H_2SO_4–silica gel, granular P_2O_5 and anhyd. magnesium perchlorate to remove a trace of NEt_3 and water, and then CO_2 was absorbed in soda asbestos and analyzed by weighing to a precision of 1 μg. The amount of the emitted CO_2 was analyzed at appropriate intervals of time.

In the use of not only anisole but also, for the solvent effect measurement, methyl cellosolve and nitrobenzene, kinetic runs were generally started by the following procedures. An appropriate amount of DBBA weighed precisely and was dissolved in 30—40 ml of a solvent in a volumetric flask. After addition of a requisite amount of TEAF and, if necessary, TEAA, the whole was diluted to 50 ml with the solvent and transferred to the reaction vessel.

In the use of DMF and TEAF for the kinetic solvent effect measurement, rapid progress of the reaction even at lower temperature did not permit the above procedures. So as to have the reaction started at 55°, the requisite amount of DBBA, TEAF and a solvent, prewarmed nearly at the same temperature, were transferred as rapid as possible into the reaction vessel.

Rate measurements with the 1,3-dimethyl-5-benzylidenebarbituric acids possessing substituent on the benzene ring for the work on kinetic substituent effect were made using anisole as a solvent by the same manner as described above.

Reaction of *p*-Methoxybenzylidenedibenzoylmethane with $5DCO_2H \cdot 2NEt_3$——A mixture of 1.71 g (0.005 mole) of *p*-methoxybenzylidenedibenzoylmethane and 4.37 g (0.05 mole based on DCO_2H) of TEAF composed of formic-*d* acid was heated at 145—150° for 4.5 hr with stirring. The reaction solution was concentrated under reduced pressure so as to remove NEt_3 and excess TEAF. Recrystallization of the resulting crystalline residue from dry acetonitrile gave colorless prisms of *p*-methoxybenzyldibenzoylmethane-β-*d*, mp 94—95°. In a NMR spectrum of this product, the signal corresponding to the methylene protons appeared as a doublet at $\delta = 3.40$ ($J = 7$ Hz) and peak area of this showed one proton content by comparison with that of methoxy proton signal ($\delta = 3.70$, singlet, 3H) owing to deuterium substitution. Appearance of a doublet signal at $\delta = 5.55$ ($J = 7$ Hz) for the methine proton in contrast to a triplet of the same of non-deuterated one was consistent with one deuterium substitution of the adjacent methylene.

Acknowledgement We wish to thank Mr. K. Narita, Analytical Center of Shizuoka College of Pharmacy, for analytical measurement.

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10) All melting points are uncorrected. Ultraviolet (UV) spectra were recorded with a Hitachi EPS-2U spectrophotometer. NMR spectra were taken with a JEOL-C-60-H spectrophotometer (at 60 MHz).

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