CHEMICAL & PHARMACEUTICAL BULLETIN

Vol. 29, No. 9 September 1981

Regular Articles

Chem. Pharm. Bull.
29(9)2397—2402(1981)

Nuclear Magnetic Resonance Studies of Acid-Base Association in Solution. II.[1] Association between Ketones and Tris(dipivaloylmethanato)europium

HIDEKO KAWAKI,* TATSUYA TAKAGI, HIDEAKI FUJIWARA, and YOSHIO SASAKI*

Faculty of Pharmacy, Kinki University, Kowakae 3-4-1, Higashi-Osaka, Osaka 577, Japan and Faculty of Pharmaceutical Sciences, Osaka University, Yamadaoka 1-6, Suita, Osaka 565, Japan

(Received January 21, 1981)

Association between Eu(dpm)$_3$ and 4-substituted acetophenones or aliphatic ketones has been investigated by measurement of the concentration dependence of ^{1}H chemical shifts.

The stoichiometry was found to be 1: 1 by the Job method, and both the equilibrium constant K_1 and the bound chemical shift Δ_1 were estimated.

K_1 values of 4-substituted acetophenones were found to be governed predominantly by the electronic effect, whereas those of symmetrical ketones are controlled by the difference of the standard entropy $\Delta S°$ but those of nonsymmetrical ketones are not.

These results can be interpreted in terms of the coordination populations of Eu(dpm)$_3$ on the two sites of the carbonyl oxygen.

The populations were obtained independently from the ratio of the geometrical factor $(3\cos^2\theta-1)/r^3$ and from $\Delta S°$, and the results were consistent with each other.

Keywords——^{1}H NMR, acid-base association, equilibrium constant, bound chemical shift, enthalpy, entropy, ketones, shift reagent

In our previous report,[1] a 1: 1 association between the shift reagent tris(dipivaloylmethanato)europium—Eu(dpm)$_3$—and pyridine bases as well as aliphatic alcohols was confirmed.

Shapiro *et al.*[2] had previously examined the association between aliphatic ketones and tris-(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate)europium—Eu(fod)$_3$—and concluded that both 1: 1 and 1: 2 associations occurred.

In this work, the stoichiometry of association between ketones and Eu(dpm)$_3$ was determined to be 1: 1, and both the equilibrium constant K_1 and the bound chemical shift Δ_1 were estimated by the curve fitting method. The two parameters thus obtained are discussed in terms of the substituent constants.

The coordination population of Eu(dpm)$_3$ on the two sites of carbonyl oxygen were given by the ratio of the geometrical factor $(3\cos^2\theta-1)/r^3$ of the two kinds of ^{1}H nuclei.

The results were consistent with the values estimated from the difference of the standard entropy $\Delta S°$.[3]

Experimental

Ketones used in this study were of the J.I.S.S.R. grade. Liquid samples were dried over Linde molecular sieves 4A, whereas solids were stored over silica gel in a desiccator for several days before use. The shift reagent Eu(dpm)$_3$ (purchased from Dojin Chemical Laboratories) was sublimed under reduced pressure and stored over silica gel in a desiccator. Sample preparations were carried out in a dry box. All nuclear magnetic resonance (NMR) spectra were taken on a Hitachi R-20A high resolution NMR spectrometer at 35°C in cyclohexane containing 0.3% Me$_4$Si as an internal reference, and the signal position was determined with a frequency counter to within ±1.0 Hz. Variable temperature experiments were carried out with a temperature control unit and the measurement temperature was calibrated by using ethyleneglycol to within ±1°C. Experimental conditions are described in the figures and tables.

Results and Discussion

The existence of 1: 2 association between Eu(dpm)$_3$ and pyridine has been confirmed in the solid state by X-ray crystallography and by NMR spectroscopy at low temperatures.[4]

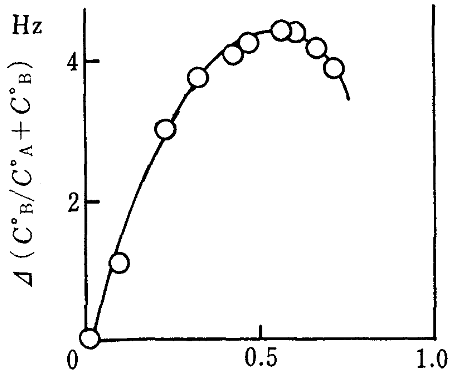

Fig. 1. Job Plots of Methyl ^{1}H Shift of *tert*-C_4H_9COMe + Eu(dpm)$_3$ in Cyclohexane at 35°C

$C_A°$, $C_B°$ = ~0.04 mol/l.

As a first step in the present work, we tried to determined the stoichiometry of association between Eu(dpm)$_3$ and ketones by the Job method (*cf.* Fig. 1). In the Job plots, the maximum appeared at mole fractions of Eu(dpm)$_3$ over 0.5, supporting the occurrence of 1: 1 association.

The K_1 and Δ_1 values were determined by curve fitting[5] of the concentration-shift curve, and the calculated K_1 and Δ_1 values were reproducible to within ±5% (*cf.* Table I and Fig. 2).

Plots of lnK_1 *vs.* $1/T$ in the variable temperature experiment were linear, as shown in Fig. 3, and the thermodynamic parameters were determined (*cf.* Table II).

4-Substituted Acetophenones

Plots of lnK_1 *vs.* σ_i or σ_π indicate that lnK_1

TABLE I. Equilibrium Constants K_1 and Bound Chemical Shifts Δ_1 of Ketones + Eu(dpm)$_3$ at 35°C in Cyclohexane

	Δ_1 (ppm)[a]				
	β-H[c]	β'-H[d]	γ-H	δ-H	K_1 (1/mol)[b]
C_6H_5COMe	15.3				210
4-$CH_3C_6H_4COMe$	15.4		13.0	3.5	250
4-$C_2H_5C_6H_4COMe$	15.4		12.9	3.4	248
4-$CH_3OC_6H_4COMe$	15.5		13.0	3.5	337
4-ClC_6H_4COMe	15.4				159
4-BrC_6H_4COMe	15.3				143
4-$NO_2C_6H_4COMe$	15.1		12.5	3.5	47
CH_3COMe	15.0				218
C_2H_5COMe	15.1	15.3	11.5		205
n-C_3H_7COMe	14.6	14.9			209
iso-C_3H_7COMe	14.2	14.6			206
n-C_4H_9COMe	14.3		10.0		185
iso-C_4H_9COMe	14.9	15.4		6.7	186
tert-C_4H_9COMe	15.0		10.1		205
$(C_2H_5)_2CO$	14.4		10.2		177
(*n*-$C_3H_7)_2CO$	13.9		10.8	4.5	182
(*n*-$C_4H_9)_2CO$	14.2				172
(iso-$C_4H_9)_2CO$	14.3			5.3	161
(*tert*-$C_4H_9)_2CO$			9.7		175
$(C_6H_5)_2CO$			11.5		195

a) Error within ±5%.
b) Error within ±10%.
c) β=CH_3 or CH_2 group at β-position relative to carbonyl oxygen.
d) β'=CH_2 group at β-position relative to carbonyl oxygen.

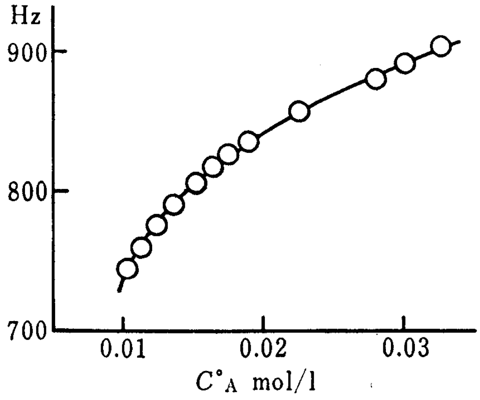

Fig. 2. Concentration Dependence of the Methyl ^{1}H Signal of $CH_3OC_6H_4COMe$ $+Eu(dpm)_3$ in Cyclohexane

$C^{\circ}_A=\sim0.01$—0.04 mol/l. $C^{\circ}_B=\sim0.02$—0.04 mol/l.
○; experimental points, —; calculated curve.

Table II. $\varDelta H$ and $\varDelta S$ of Association between Ketones and $Eu(dpm)_3$ in Cyclohexane

	$-\varDelta H$ (kJ/mol)[a]	$-\varDelta S$ (J/mol deg)[b]
$4\text{-}CH_3C_6H_4COMe$	34.3	68.2
$4\text{-}CH_3OC_6H_4COMe$	33.7	63.0
$4\text{-}BrC_6H_4COMe$	33.5	71.1
CH_3COMe	30.0	57.7
$(n\text{-}C_3H_7)_2CO$	34.3	72.8
$(n\text{-}C_4H_9)_2CO$	36.4	77.4
$(\text{iso-}C_4H_9)_2CO$	34.7	76.6
$(tert\text{-}C_4H_9)_2CO$	35.2	79.2

a) Error within ± 5%.
b) Error within ± 10%.

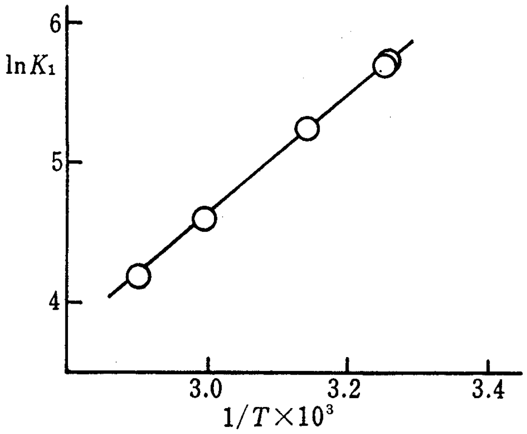

Fig. 3. Correlation between $\ln K_1$ and $1/T$ of $CH_3OC_6H_4COMe+Eu(dpm)_3$ in Cyclohexane

$C^{\circ}_A=\sim0.02$—0.04 mol/l. $C^{\circ}_B=\sim0.02$—0.04 mol/l.

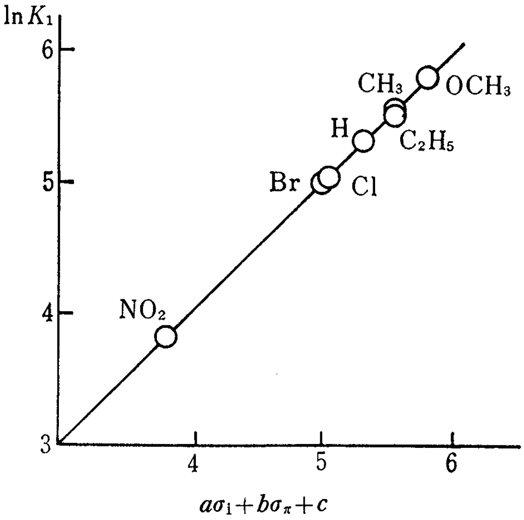

Fig. 4. Two Parameter Analysis of $\ln K_1$ of $RC_6H_4COMe+Eu(dpm)_3$ in Cyclohexane

$a=-1.31$, $b=-2.59$, $c=5.31$, fitting parameter= 0.03.

decreases with increases of the two kinds of substituent constants σ_i and σ_π,[6] and K_1's are given by Eq. 1;

$$\ln K_1 = -1.31\,\sigma_I - 2.59\,\sigma_\pi + 5.31 \qquad (1)$$

The fitting parameter of this treatment is 0.03 (*cf.* Fig. 4).

As shown in Table II, $\varDelta H$'s and $\varDelta S$'s of the complex formation between 4-substituted acetophenones and $Eu(dpm)_3$ are nearly equal, so we examined the correlation between total charge density of the carbonyl oxygen as estimated by the CNDO/2 method[7] and $\ln K_1$ (*cf.* Fig. 5).

The results support the view that the complex formation between seven kinds of 4-substituted acetophenones and $Eu(dpm)_3$ depends on the enthalpy effect.

Next, determination of the population by use of the geometric factor was carried out as follows. The induced chemical shift δ of a paramagnetic complex is given by Eq. 2;[8]

$$\delta = k(3\cos^2\theta - 1)/r^3 \qquad (2)$$

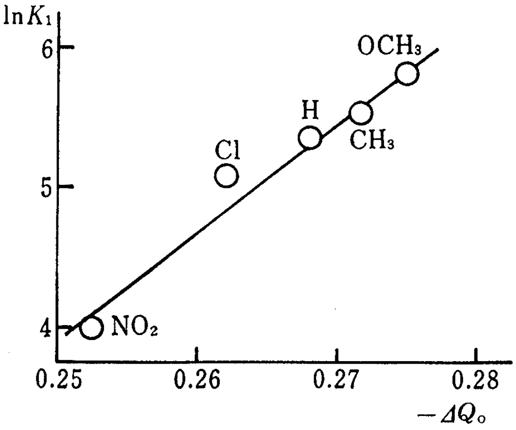

Fig. 5. Correlation between $\ln K_1$ and the Difference of Total Charge Density of Carbonyl Oxygen, $-\Delta Q_o$ of RC_6H_4-COMe

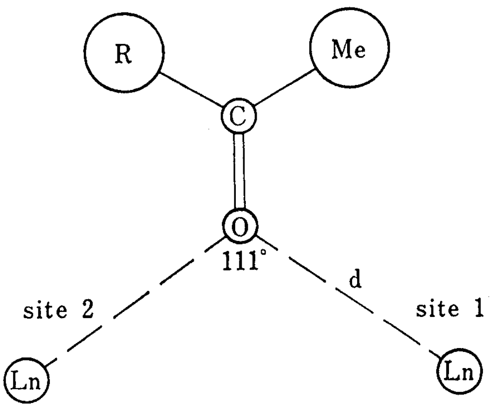

Fig. 6. Two-Site Model of RCOMe+ $Eu(dpm)_3$ for Computation

where k is a constant related to the central lanthanide atom, r is a distance between the lanthanide atom and the nucleus being observed, and θ is the angle between vector r and the O-Ln bond. A binding model of the shift reagent on the two lone-pair sites of carbonyl oxygen is shown in Fig. 6.

The values of $(3\cos^2\theta-1)/r^3$ can be estimated separately at the two sites of carbonyl oxygen and expressed as a function of the O-Ln distance, d. When the coordination population on site 1 is defined as P_1, that of site 2 is given by $1-P_1$.⁹⁾

$$R=\frac{P_1\delta_{\mathrm{Me},1}+(1-P_1)\delta_{\mathrm{Me},2}}{P_1\delta_{\mathrm{H}_i,1}+(1-P_1)\delta_{\mathrm{H}_i,2}} \tag{3}$$

where R means the ratio (methyl to i-th H) for the experimentally observed shift, and $\delta_{\mathrm{Me},1}$, $\delta_{\mathrm{Me},2}$, $\delta_{\mathrm{H}_i,1}$ and $\delta_{\mathrm{H}_i,2}$ are the calculated values of $(3\cos^2\theta-1)/r^3$ for methyl and i-th H of sites 1 and 2.

Table III. Values of $(3\cos^2\theta-1)/r^3$ obtained on the Basis of Free Rotation of the Functional Group for RCOMe

	$[(3\cos^2\theta-1)/r^3]\times10^3$		
	CH_3	C_2H_5 a)	
Site 1	0.23	9.33	
Site 2	13.31	−16.79	
	CH_3	iso-C_3H_7 b)	
Site 1	7.51	7.26	
Site 2	9.81	0.24	
	CH_3	*tert*-C_4H_9 c)	
Site 1	8.63	6.70	
Site 2	8.91	3.31	
	CH_3	C_6H_5 d)	
		2-H	3-H
Site 1	6.83	12.79	5.13
Site 2	16.25	−17.41	−9.07

a) d=0.24 nm, <EuOEu=111°. *b*) d=0.30 nm, <EuOEu=111°.
c) d=0.32 nm, <EuOEu=111°. *d*) d=0.26 nm, <EuOEu=111°.
The calculated values of CH_3 and C_6H_5 groups were estimated as follows;

$$\delta_{\text{calcd.}}\propto\frac{1}{2\pi}\int_0^{2\pi}(3\cos^2\theta-1)/r^3 d\phi$$

and those of C_2H_5, iso-C_3H_7 and *tert*-C_4H_9 groups were obtained as follows;

$$\delta_{\text{calcd.}}\propto\left(\frac{1}{2\pi}\right)^2\int_0^{2\pi}\int_0^{2\pi}(3\cos^2\theta-1)/r^3 d_1\phi d\phi_2.$$

TABLE IV. Coordination Populations of Eu(dpm)$_3$ at the Methyl Site of the Carbonyl Group of RCOMe determined from $(3\cos^2\theta-1)/r^3$ for the Two-Site Model and from the Difference of the Standard Entropy $\Delta S°$

R	P_1[a]	P_1[b]	$\Delta S°$[c]
CH_3	0.50	0.50	7.34
C_2H_5	0.71	0.75	17.64
n-C_3H_7	0.79		28.02
n-C_4H_9	0.84		38.39
iso-C_3H_7	0.78	0.77	25.30
iso-C_4H_9	0.83		35.44
tert-C_4H_9	0.79	0.80	28.4
C_6H_4R'[d]	0.78	0.80	26.17

a) P_1 estimated from $\Delta S°$.
b) P_1 estimated from $(3\cos^2\theta-1)/r^3$.
c) $\Delta S° = S°_R - S°_H$, where $S°_R$ and $S°_H$ are the standard entropies of substituted and parent compounds. Dimension of $S°$ = gibbs/mol (4.184 J/mol deg).
d) $R' = OCH_3$, CH_3, C_2H_5 and NO_2.

The values of $(3\cos^2\theta-1)/r^3$···geometrical factor of ^{1}H shift of methyl and phenyl group··· are evaluated on the basis of free rotation around the carbon-carbonyl bond (*cf.* Table III), and the values of P_1 are all estimated from Eq. 3 (*cf.* Table IV). 4-Substituted acetophenones (R=OMe, Me, Et and NO_2) gave the same populations.

Aliphatic Ketones

Symmetrical and Nonsymmetrical Ketones

As the ΔH values summarized in Table II are nearly the same in magnitude, $\ln K_1$ should be correlated with ΔS (*cf.* Fig. 7).

In this work, the ligand could be considered to exist as an unperturbed molecule in solution, because K_1 and ΔH are much smaller than in the alkyl pyridine+Eu(dpm)$_3$ series, where K_1 values were related to ΔS. In the present case, ΔS values were found to be linearly related to $\Delta S°$, the difference of the standard entropy $S^\circ_R - S^\circ_H$, where S°_R and S°_H are the standard entropies of the substituted and parent compounds. For symmetrical ketones, it is evident that the two sites are equivalent and the population is 0.5.

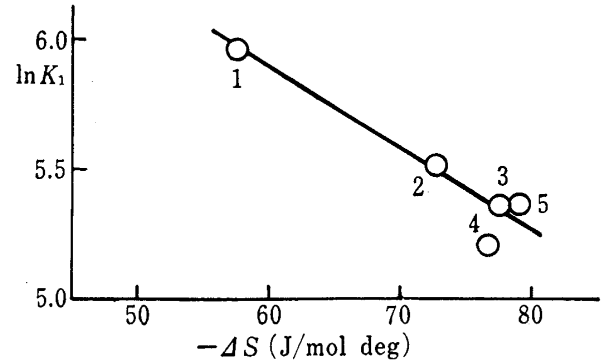

Fig. 7. Correlation between $\ln K_1$ and ΔS of RCOR+Eu(dpm)$_3$ in Cyclohexane

1: CH_3, 2: n-C_3H_7, 3: n-C_4H_9, 4: iso-C_4H_9, 5: *tert*-C_4H_9.

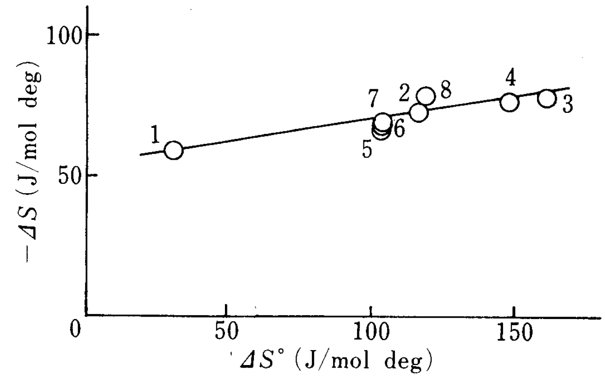

Fig. 8. Correlation between $-\Delta S$ of R_1COR_2+Eu(dpm)$_3$ and the Difference of the Standard Entropy, $\Delta S°$

1: $R_1=R_2=CH_3$, 2: $R_1=R_2=n$-C_3H_7, 3: $R_1=R_2=n$-C_4H_9, 4: $R_1=R_2=$iso-C_4H_9, 5: $R_1=4$-BrC_6H_4, $R_2=CH_3$, 6: $R_1=4$-$CH_3C_6H_4$, $R_2=CH_3$, 7: $R_1=4$-$CH_3OC_6H_4$, $R_2=CH_3$, 8: $R_1=R_2=$*tert*-C_4H_9.

For nonsymmetrical ketones, P_1 can be estimated from the ratio···methyl to alkyl group··· of $\Delta S°$ (*cf.* Table IV); in other words, K_1 values could be expressed by the following equation;

$$K_1 = P_1K_1^{\mathrm{Me}} + (1-P_1)K_1^{\mathrm{R}} \qquad (4)$$

where K_1^{Me} and K_1^{R} are the equilibrium constants of MeCOMe and RCOR, respectively. For instance, the values of K_1 given by Eq. 4 were 206, 210, 209 and 213 for ethyl-, *n*-C_3H_7-, *tert*-C_4H_9- and C_6H_5-COMe (*cf.* Table I), respectively, which are comparable with the experimental values.

References and Notes

1) Part 1: H. Kawaki, Y. Okazaki, H. Fujiwara and Y. Sasaki, *Chem. Pharm. Bull.*, **28**, 871 (1980).
2) M.D. Johnston, Jr., B.L. Shapiro, M.J. Shapiro, T.M. Proulex, A.D. Godwin and H.L. Pearce, *J. Am. Chem. Soc.*, **97**, 542 (1975).
3) *a*) S.W. Benson, "Thermochemical Kinetics", John Wiley and Sons, Inc., New York, 1968; *b*) S.W. Benson, F.R. Cruickshank, D.M. Golden, G.R. Haugen, H.E.O, Neal, A.S. Rodger, R. Shaw and R. Walsh, *Chem. Rev.*, **69**, 279 (1969).
4) *a*) D.F. Evans and N. Wyatt, *J. C.S. Chem. Commun.*, **1972**, 312; *b*) R.E. Cramer and K. Seff, *ibid.*, **1972**, 400; *Idem.*, *Acta Cryst.*, **B28**, 3281 (1972); *c*) R.E. Cramer, R. Dubois and K. Seff, *J. Am. Chem. Soc.*, **96**, 4125 (1974).
5) K_1 and Δ_1 values were estimated by the following method.

$$A + B = AB \qquad (1)$$

$$\Delta_{\mathrm{calcd.}} = \frac{1+K_1(C_A+C_B)-\sqrt{[1+K_1(C_A+C_B)]^2-4K_1^2C_AC_B}}{2K_1C_B}\Delta_1 \qquad (2)$$

In Eq. 2, $\Delta_{\mathrm{calcd}} = \delta_{\mathrm{calcd}} - \delta_B$, where δ_{calcd} and δ_B are the calculated chemical shift of B and that of the free state, $\Delta_1 = \delta_{AB} - \delta_B$, where δ_{AB} is the shift of B in an associated state, C_A and C_B are initial concentrations of A and B, and K_1 is an equilibrium constant. Based on the equilibrium of Eq. 1, root-mean-square deviations of the values calculated by Eq. 2 and observed shifts were minimized by the curve-fitting method. Calculations were performed with an IBM 370 model 138 computer at Kinki University Computer Center. Program DAVID for function minimization was used.
6) Y. Yukawa and Y. Tsuno, *Nippon Kagaku Zasshi*, **86**, 873 (1965).
7) Y. Tanimoto, H. Kobayashi, S. Nagakura and Y. Saito, *Acta Cryst.*, **B29**, 1822 (1973). Calculation by the CNDO/2 method was performed with a NEAC ACOS 900 computer system at Osaka University Computer Center.
8) *a*) H.M. McConnell and R.E. Robertson, *J. Chem. Phys.*, **29**, 1361 (1958); *b*) B. Bleaney, *J. Mag. Reson.*, **8**, 91 (1972); *c*) W. Dew. Horrocks, Jr., *J. Am. Chem. Soc.*, **96**, 3022 (1974).
9) R.E. Lenkinski and J. Reuben, *J. Am. Chem. Soc.*, **98**, 4065 (1976).