HINDERED ROTATION AROUND AMIDE OC-N BONDS.
ITS ENERGY DEPENDENCE ON C-N-C BOND ANGLE[1]

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Compounds 1-5 exhibit the presence of rotamers in their PMR spectra measured at room temperature. After assignment of signals to each rotamer, temperature dependent change of the signal shape was simulated for 3-5 using line-shape method. Activation parameters deduced therefrom contain usually large free energy of activation for all of these compounds compared with the corresponding dimethylamides. This abnormality was ascribed to the additional destabilization in rotational transition states because of the unusually wide C-N-C angle in the cage system.

To support the large free energy of activations, pure rotamer 5A and nearly pure rotamer 5B were isolated by preparative TLC.

In the study of cycloaddition reaction of tropone and N-ethoxycarbonyl-1H-azepin, we have found that both of the two cycloadducts 1 and 2 showed at ordinary temperature two sets of signals in their PMR spectra which collapsed to one set when measured at elevated temperatures. Rough estimation of the free energy of activation

based on the coalescence temperature gave a value of $\Delta Gc^{\neq}=18.3$ kcal/mol $(Tc=83^{\circ}C)$ for $\underset{\sim}{1}$. Since the value is very large for N-alkoxycarbonyl,[2] we have carried out more detailed analysis on the analogs of $\underset{\sim}{1}$ in order to clarify the origin of the abnormal rotational barrier in this particular type of amide.
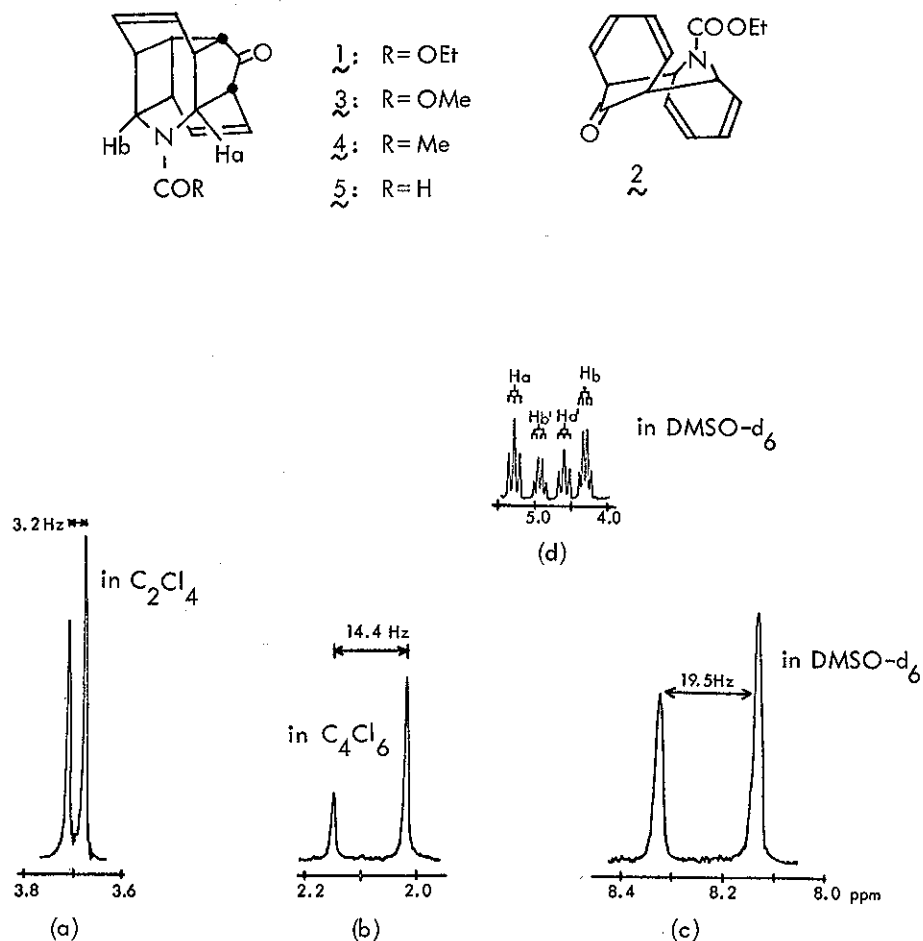

$\underset{\sim}{1}$: R= OEt
$\underset{\sim}{3}$: R= OMe
$\underset{\sim}{4}$: R= Me
$\underset{\sim}{5}$: R= H

Fig. 1   PMR Spectra of R.   (a) O$\underline{Me}$ of $\underset{\sim}{3}$ (b) CO$\underline{Me}$ of $\underset{\sim}{4}$
(c) C$\underline{H}$O of $\underset{\sim}{5}$ (d) amide NC$\underline{H}$ of $\underset{\sim}{5}$

Compounds used in the present study are 3, 4, and 5, which were derived from 1.[3] PMR spectra of these compounds at 20° also exhibit two signals due to R group (R and R') with different intensities (Fig. 1a-1c). Similar intensity ratio was observed in the signals due to Ha (Ha:Ha') and Hb (Hb:Hb') which appear as two triplets and two double doublets, respectively, at δ 4-6 ppm (e.g. Fig. 1d). The compounds derived from tropone-2,7-d_2 should have two deuterium atoms at two α positions to the carbonyl group as shown by ● in the formula and exhibit in their PMR spectra two doublets and two double doublets, allowing the unequivocal assignment of Ha and Hb for 3-5.

Stereochemical relationship between Ha and Hb, and R was secured by NOE measurements; e.g. irradiation at Ha' and Hb in 4 caused the enhancement in intensity of lower- and higher field methyl signals by 13% and 9%, respectively, while in 5 aldehydic proton signals showed NOEs (20% and 25%, respectively) with Ha' and Hb. These experiments clarified that the R' and R groups are oriented towards Ha' and Hb as shown below and that, from their intensity ratios, the rotamer A is thermodynamically more stable than B.[4]
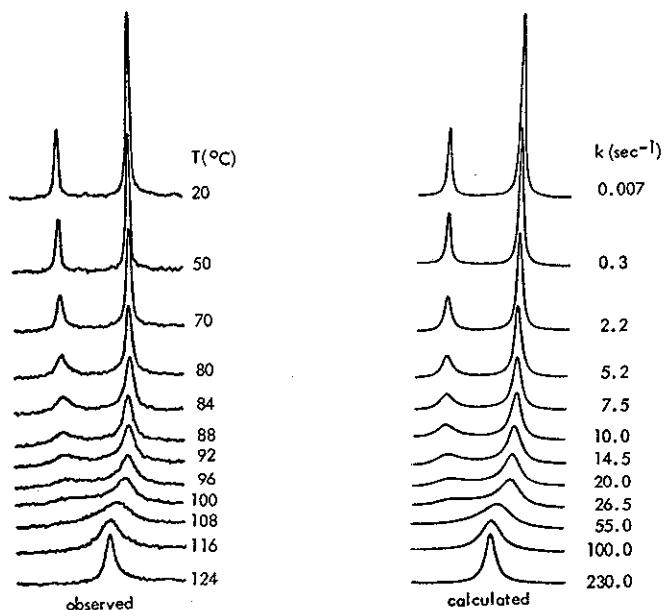

(A)   (B)
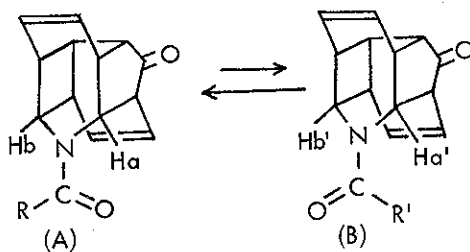
Fig. 2 Temperature dependence of methyl signals
in PMR spectrum of 4. The rate constant k
calculated corresponds to the change B⟶ A.

In order to estimate the energy barrier between these rotamers, computer simula-
tion was carried out on the change of R signals with temperature using the total line-
shape method.[5] The result for 4 is shown in Fig. 2 as an example. From these data,
activation parameters at $20°C$ were obtained and listed in Table[6] together with those
for the corresponding N, N-dimethyl amides. It is clear from the Table that the
present systems always have a larger free energy of activation compared with the open
chain analogs. The difference can be ascribed as is explained below to the conforma-
tional rigidity of the cage system.

The X-ray diffraction data for dimethyl formamide disclosed the coplanarity of
formyl and dimethylamide groups and the Me-N-Me angle of $120.4°$.[9] However, in
the rotational transition state where two groups are perpendicular to each other, the

Table   Activation parameters of amides (B→A)

Compounds	3		4	5	R=OCH$_3$ 2a	CH$_3$ 7	H 8
Temperature	20°	-13°	20°	20°	-13°	20°	20°
Solvent	C$_2$Cl$_4$		C$_4$Cl$_6$	DMSO-d$_6$	CHCl$_3$	neat	neat
ΔG° (kcal/mol)	0.2±0.1		0.5±0.1	0.2±0.0			
ΔG‡ (kcal/mol)	18.9±0.0	19.4±0.1	20.0±0.1	23.0±0.0	14.8	18.7	20.6
ΔH‡ (kcal/mol)	22.8±0.3		22.0±0.3	22.8±0.1		22.4	19.9
ΔS‡ (eu)	11.6±1.0		6.8±1.0	-0.7±0.3		12.6	-2.39
Ea (kcal/mol)	23.4±0.3		22.6±0.3	23.3±0.1		23.0	20.5
log Ao	16.1±0.2		14.7±0.2	13.0±0.1		16.0	12.7
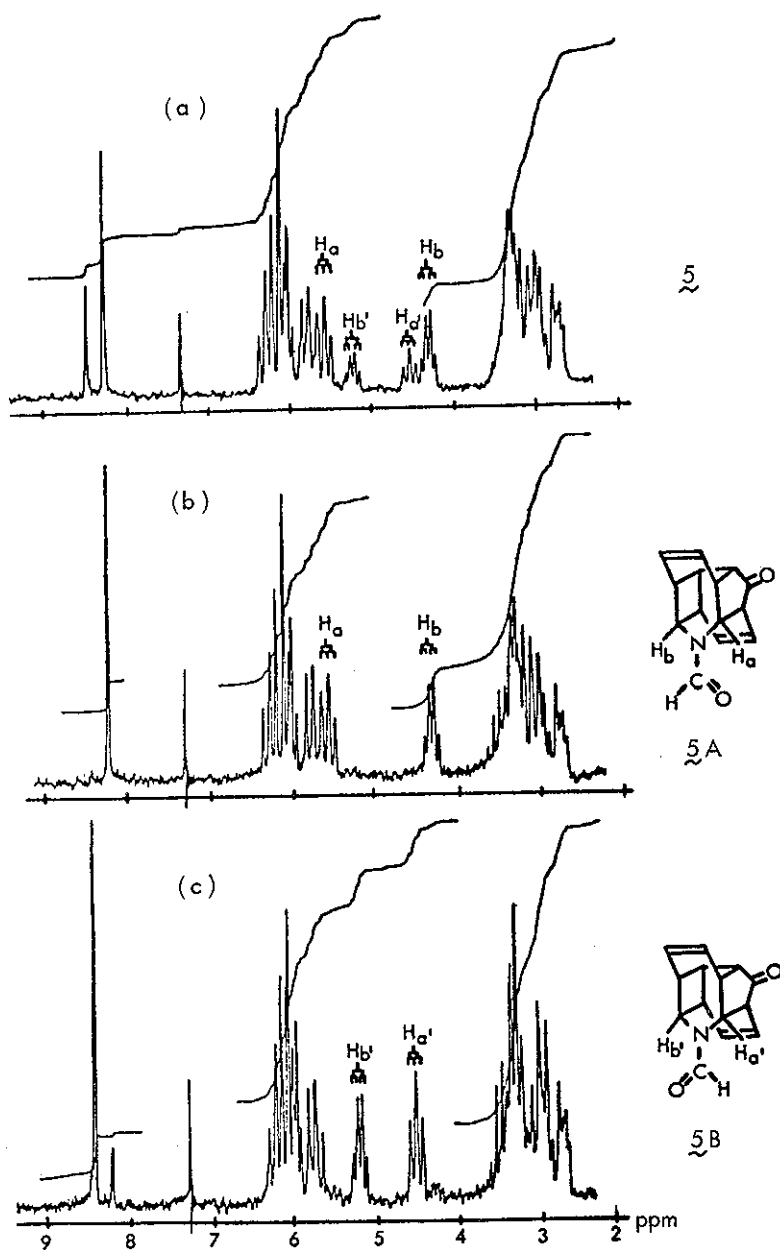
Fig. 3 PMR Spectra of $\underset{\sim}{5}$, $\underset{\sim}{5}$A, and $\underset{\sim}{5}$B in CDCl$_3$

bond angle Me-N-Me would come close to $109°$ (sp^3N) because of the loss of conjugation. Therefore, the rotation around N-CO bond would accompany a scissoring motion of the Me-N-Me angle.[10]

X-ray analysis of the similar cage compound 7 in which >NCOR group is replaced by >CH_2 disclosed that the angle in question is unusually wide ($119°$) for tetragonal carbon.[11] Since replacement of >CH_2 by >NCOR would not cause much change in the bond angle of this rigid molecules, 3, 4, and 5 would have similar stabilization with open chain analogs in rotational ground state. However, the scissoring motion discussed above would be impossible and thus the rotational transition state would be destabilized, giving a larger free energy of activation.
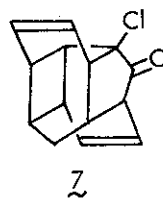
The free energy of activation obtained for 5 exceeds the energy barrier required for isolation of conformers at room temperature.[2a] Since TLC of 5 (PMR, Fig. 3a) always showed two spots with very similar R_f values, separation was attempted by preparative TLC on SiO_2. PMR spectra (Fig. 3) of the separated products, measured at 4 hrs after the start of isolation, clearly indicate that 5A was obtained in pure form (Cf. Fig. 3b) and 5B was contaminated by a small amount of 5A (fig. 3c).[12] PMR spectra of 5A and 5B taken 24 hrs later are both identical with that of 5.

This, as far as we know, is the first isolation of such isomeric formamide derivatives.

REFERENCES

1 The paper is dedicated to Professor R.B. Woodward on the occasion of his 60th birthday.

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3 For the derivation of these compounds, 1 was hydrolyzed with KOt-Bu in DMSO after ketalization of the carbonyl group. Acid hydrolysis produced the ketone 6, with -NH- group, colorless needles, mp 101-102°, ν 3340, 1725 cm^{-1}. Methyl chlorocarbonate in the presence of triethylamine converted 6 to 3, colorless plates, mp 124-126°, ν 1740, 1680 cm^{-1}, while acetic anhydride in pyridine afforded 4, colorless granules, mp 132-133°, ν 1735, 1640 cm^{-1}, and acetyl formate in formic acid gave 5, colorless prisms, mp 223-225°, ν 1735, 1645 cm^{-1}.

4 Such a difference in the stability may have stemed from the difference in the N-C-H angle. Apparently, the angle involving the cyclobutane carbon (Hb-C-N) is larger than the one (Ha-C-N) with cyclopentane carbon, so that, when an R-C=O group with an R larger than O assumes the most stable coplanar conformation with Hb-C-N-C-Ha plane, Ha rather than Hb would have larger van der Waals repulsion with R, thus destabilizing the conformation B. In the case of R=H, however, the explanation above is not valid since O is larger than H. (L.A. LaPlanche and M.T. Rogers, J. Amer. Chem. Soc., 1963, 85, 3728). *This is reminiscent of the confor-mation in aliphatic aldehydes. (Cf. R.W. Kilb, C.C. Lin and E.B. Wilson, Jr., J. Chem. Phys., 1957, 26, 1695; R.J. Abraham and J.A. Pople, Mol Phys., 1960, 3, 609.*

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12 Kinetic parameters at 20°C (B → A) obtained by the rate of isomerization using PMR technique are as follows. $\Delta G^{\circ} = 0.5 \pm 0.1$ kcal/mol, $\Delta G^{\ddagger} = 23.5 \pm 0.1$ kcal/mol, $\Delta H^{\ddagger} = 23.8 \pm 1.2$ kcal/mol, $\Delta S^{\ddagger} = 0.7 \pm 4.1$ eu., $E_a = 24.4 \pm 1.2$ kcal/mol, log $A_o = 13.4 \pm 0.9$ (in $CDCl_3$).