Conformational Studies of Polyamides and Model Compounds Derived from Cyclic Dicarboxylic Acids and Spirodiamine

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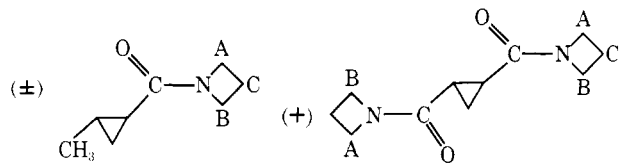
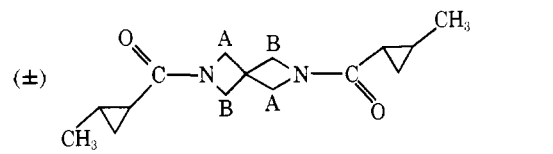
ABSTRACT: Conformations of the polyamides derived from either *trans*-1,2-cyclopropanedicarboxylic acid (C3) or *trans*-1,2-cyclohexanedicarboxylic acid (C6) with 2,6-diazaspiro[3.3]heptane (DSH) were investigated by means of nmr spectroscopy. The nmr spectra of model compounds, (±)-*trans*-2-methylcyclopropanecarboxylic acid azetidide (I), (+)-*trans*-cyclopropanedicarboxylic acid diazetidide (II), 2,6-di[(±)-*trans*-2-methylcyclopropanecarbonyl]-2,6-diazaspiro[3.3]heptane (III), IV, and (±)-*trans*-1,2-cyclohexanedicarboxylic acid diazetidide (V), were measured in various solvents such as $CDCl_3$, 2,2,2-trifluoroethanol-d_3, D_2O, and D_2SO_4. A lanthanide shift reagent, $Eu(fod)_3$, was used for the model compounds in $CDCl_3$. Conformation of the C3 compounds did not vary in the above solvents. In the preferred conformation, both carbonyl groups bisect the cyclopropane ring. This conformation was also suggested by dipole moment measurements of II. However, C6 compounds changed their conformations in the above solvents. In $CDCl_3$ they seem to have a conformation in which two molecules of azetidine or DSH attached to the same C6 ring are rather close to each other; in D_3O the preferred conformation may be the extended D_2O form which has been reported for *trans*-1,2-cyclohexanedicarboxylic acid piperidine diamide, VI.[1]

In a previous paper,[2] we reported the syntheses and optical properties [optical rotatory dispersion (ORD) and circular dichroism (CD)] of asymmetric polyamides and model compounds (I–V) derived from either (+)-(*S*)-*trans*-1,2-cyclopropanedicarboxylic acid [(+)-C3] or (+)-*trans*-1,2-cyclohexanedicarboxylic acid [(+)-C6] with 2,6-diazaspiro[3.3]heptane (DSH). Similar ORD and CD spectra of the polyamides were obtained in a variety of the solvents such as water, 2,2,2-trifluoroethanol (TFE), methanesulfonic acid, and sulfuric acid, suggesting that no significant conformational changes occurred in the above solvents.

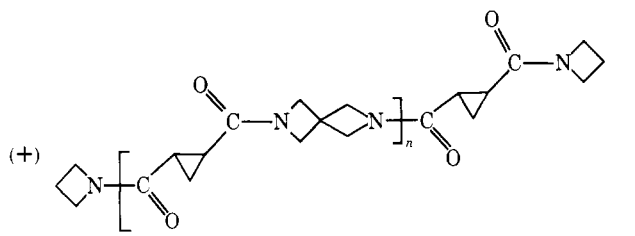


I

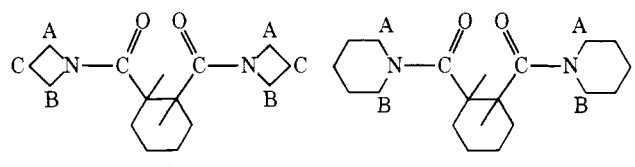
II



III



IV ($n = 3.5$)



V

VI

Since the structure of DSH is very rigid, there is no cis and trans isomerization around the amide bond, except in aqueous acidic solution. The conformation can change only around the bond connecting the carbonyl groups to the cyclopropane ring or in the cyclohexane ring itself, if the direction of the rotation of carbonyl groups by DSH is neglected.[2] However, it is almost impossible to elucidate the preferred conformation from optical data alone. Lanthanide shift reagents in nmr spectroscopy have proved to be very useful to determine configuration and conformation of several amide compounds.[3–5] In the present study, $Eu(fod)_3$[6] in $CDCl_3$ was used for the model compounds. Furthermore, we investigated the effect of solvent on the nmr spectra of the polymers and the model compounds in D_2O, TFE-d_3, $CDCl_3$, and D_2SO_4.

Experimental Section

The syntheses of the polyamides and model compounds were described previously.[1,2] $Eu(fod)_3$ (Ventron Co.) and TFE-d_3 (Merck Co.) were used without further purification.

The nmr spectra were taken with Varian T60 and HA100 spectrometers at 60 and 100 MHz, respectively, using tetramethylsilane or sodium 2,2-dimethyl-2-silapentane-5-sulfonate as the internal standard. The spectra were measured at room temperature, unless otherwise stated. The concentrations of the samples were *ca.* 10% (w/v).

The dipole moment was determined by the method of Guggenheim.[7] The final equation in benzene at 25° was μ^2 (D^2) = $0.009208M(\alpha_\epsilon - \alpha_n)$,[1] where α_ϵ (−4.20) and α_n (0.13) were obtained from $[(\epsilon_{12} - \epsilon_1)/W_2]_{w\to 0}$ and $[(n_{12}^2 - n_1^2)/W_2]_{w\to 0}$, respectively; ϵ_1 and ϵ_{12} are dielectric constants of benzene and the solution, respectively; n_1 and n_{12} are refractive indices; and W_2 is weight fraction of the solute. The dielectric constant at 25° was determined with a WTW Dipolemeter Type DM01 in benzene at 2 MHz. The dielectric constant of benzene was taken to be 2.2725 at 25°.

Results and Discussion

The nmr spectra of II, IV, and (±)-C3-DSH (polyamide derived from (±)-C3 and DSH) were measured in D_2O (Figure 1). Two triplets for II and two singlets for IV and (±)-C3-DSH were observed at around 4.3 ppm because of the restricted rotation around the amide bond. The upfield peaks were assigned to the methylene protons cis to the carbonyl oxygen atom.[8] The peaks at 2.0 and 1.3 ppm were assigned to the methine and methylene protons, respectively, of the cyclopropane ring. The patterns and chemical shifts of the spectra in $CDCl_3$ were quite similar to those in Figure 1, except for slightly poorer resolution of the peaks in $CDCl_3$.[2] This supports the assumption that these compounds do not vary in conformation in solvent. There were no spectral differences between the optically active and the racemic compounds.

Figure 2 is the 100-MHz nmr spectrum of II in D_2SO_4 at 70°. Although the spectrum was not as clear as those mea-

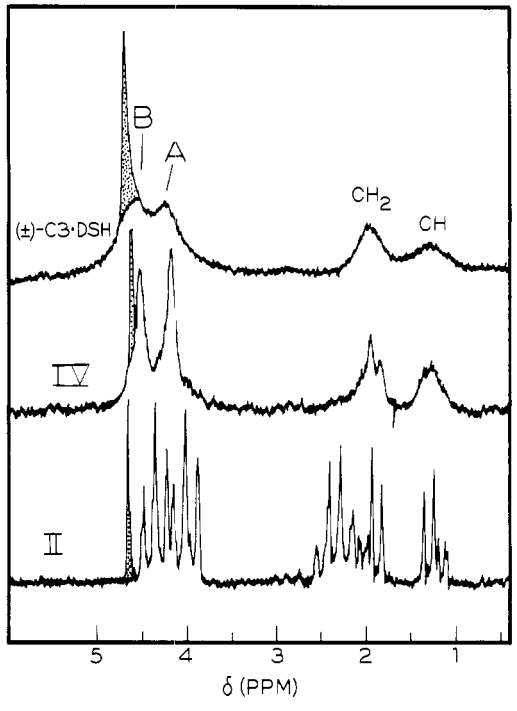


Figure 1. Nmr spectra of II, IV, and (±)-C3·DSH in D_2O (60 MHz).

sured to $CDCl_3$ and D_2O, a broad quintet is recognizable at around 4.3 ppm. This indicates that no rapid rotation occurs around the amide bond. The nmr spectrum of (±)-C3·DSH in D_2SO_4 consisted of unclear, broad peaks. This broadening is possibly due to the rigidity of the polymer molecule in this solvent.

Figure 3 shows the nmr spectra of V and (+)-C6·DSH (polyamide derived from (+)-C6 and DSH) in $CDCl_3$, TFE-d_3, and D_2O. Although the spectra of (+)-C6·DSH were broader than those of V, the methylene peaks of the polymers were analogous to those of V, particularly in the spectra decoupled from C protons in the same solvent. The spectral pattern of the methylene resonances depended very much on the solvent; *i.e.*, the peaks at around 4.2 ppm in $CDCl_3$ and TFE-d_3 were unsymmetric, whereas those in D_2O were symmetric similar to those of the C3 compounds (Figure 1). In $CDCl_3$ one of the methylene groups, probably trans to the carbonyl oxygen, may be affected by the diamagnetic anisotropic effect of another carbonyl group in the conformation as shown in Figure 4, where the two azetidine rings lay close to each other. However, in D_2O the two C=O bonds are possibly eclipsed with respect to the C_1–C_2 bond; in other words two azetidine rings may be situated far from each other as reported for *trans*-1,2-cyclohexanedicarboxylic acid·piperidene diamide.[1] In this conformation the diamagnetic anisotropy effect of the carbonyl groups is unable to influence the methylene groups of the azetidine ring, since the distance between them is too great.

As stated before, the rotation around the amide bond is restricted by partial double bond character. However, rotation was enhanced by the addition of hydrochloric acid. Figure 5 shows the spectral changes of the methylene resonances adjacent to the nitrogen atoms of II and (+)-C6·DSH in D_2O with various concentrations of DCl. Model compound V and (±)-C3·DSH exhibited analogous changes. Based on the spectral changes, the rates of the rotation at the same concentrations of DCl decreased in the order of II > V > (±)-C3·DSH > (+)-C6·DSH, which reflects the order of the rigidity of the molecules. The amide bond was slowly hydrolyzed in D_2O–DCl, while it was stable in D_2SO_4 for a long time. This may be due to the difference in the protonation of the amide bond. Nitrogen atoms may be protonated to a greater extent in D_2O–DCl than in D_2SO_4. The protonation on the nitrogen atom will weaken the amide bond and allow free rotation. However, the protonation on the carbonyl oxygen will strengthen the bond because of the double bond character.[9]

The ORD and CD spectra of II, V, (+)-C3·DSH, and (+)-C6·DSH in 12% HCl were similar to those in water as

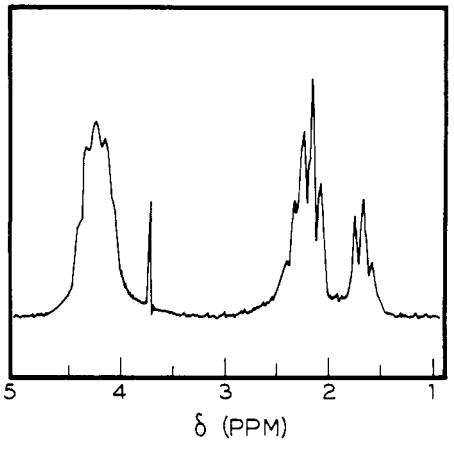


Figure 2. Nmr spectrum of II in D_2SO_4 at 70° (100 MHz).

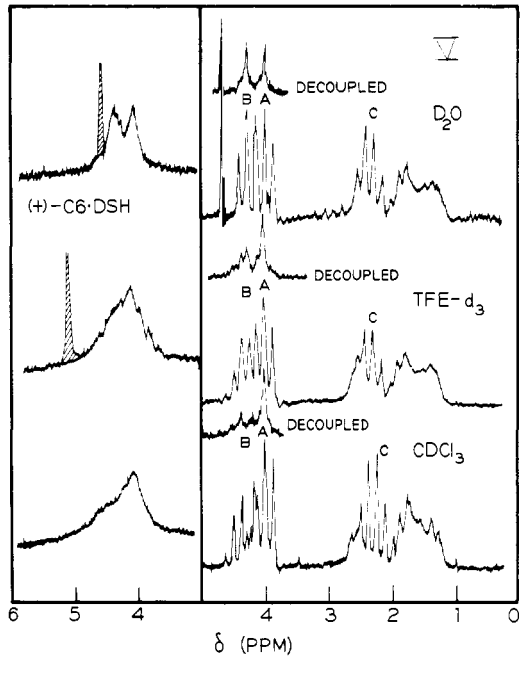


Figure 3. Nmr spectra of V and (+)-C6·DSH in $CDCl_3$, TFE-d_3, and D_2O (60 MHz). Decoupled from C protons.

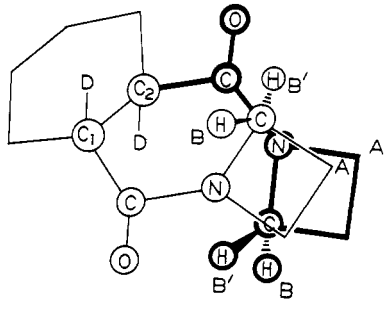


Figure 4. Conformation of V in $CDCl_3$.

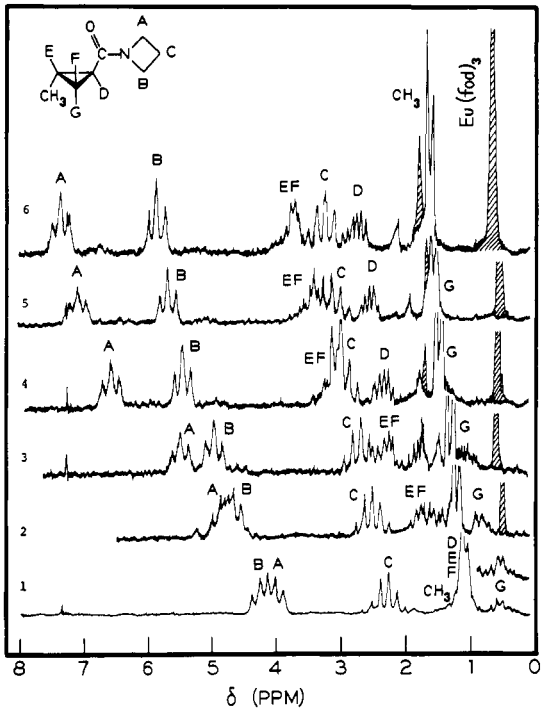


Figure 5. Nmr spectra of II and (+)-C6·DSH in D_2O–DCl (60 MHz).

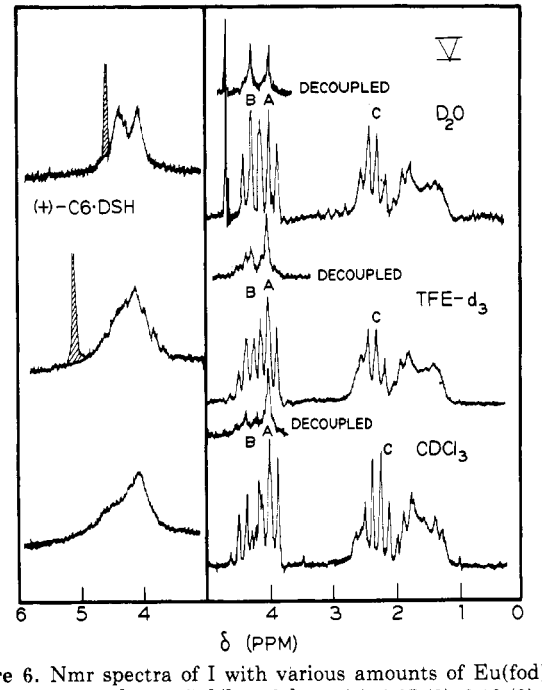


Figure 6. Nmr spectra of I with various amounts of $Eu(fod)_3$ in $CDCl_3$ (60 MHz). [$Eu(fod)_3$]/[amide] = 0 (1), 0.07 (2), 0.13 (3), 0.21 (4), 0.26 (5), 0.32 (6).

reported previously.[2] Hence, the rapid rotation around the bond in the nmr time scale does not significantly affect the ORD and CD spectra. The spectra depend very much on the conformation of the carbonyl groups with the C3 and the C6 rings.

The main purpose of this paper is to determine the conformation of the carbonyl groups with respect to the cyclopropane and the cyclohexane rings. The nmr studies with a lanthanide shift reagent, $Eu(fod)_3$, supply additional data on the conformation. The changes in the nmr spectra of I and III are shown in Figures 6 and 7, respectively. The peaks are shifted downfield with increasing amounts of $Eu(fod)_3$. Induced chemical shifts are plotted against the mole ratios of $Eu(fod)_3$ to the amide residue (Figure 8).

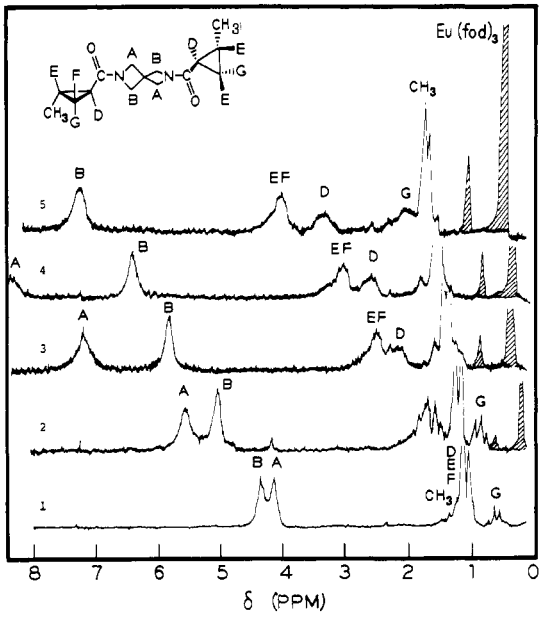


Figure 7. Nmr spectra of III with various amounts of $Eu(fod)_3$ in $CDCl_3$ (60 MHz). [$Eu(fod)_3$]/[amide residue] = 0 (1), 0.05 (2), 0.14 (3), 0.19 (4), 0.30 (5).

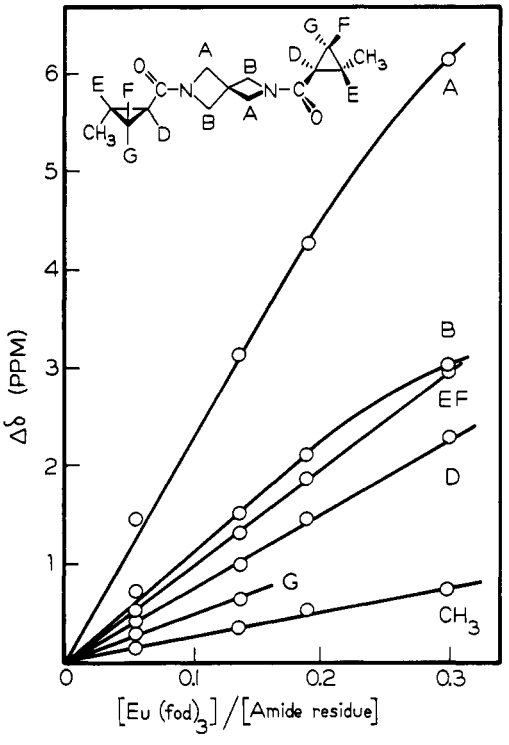


Figure 8. Plots of induced shift *vs.* [$Eu(fod)_3$]/[amide residue] for III.

Straight lines were obtained in the range of [$Eu(fod)_3$]/[amide residue] < 0.2. The slopes of the lines (molar-induced shift, ΔEu) are collected in Table I together with those for other compounds. The assignments of the peaks, A, B, C, E, and Me, were done with the aid of spin-decoupling techniques. It has been reported that the induced shift is mainly due to pseudocontact interaction which can be expressed by the relationship[4,5]

$$\Delta Eu = K(3 \cos^2 \phi - 1)/r^3 \qquad (1)$$

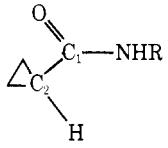
where K is a constant, r is the distance between the Eu

Table I
Molar-Induced Chemical Shift (ΔEu)[a] in $CDCl_3$ at 60 MHz

Compd	A	B	C	D	E	F	G	CH_3
I	12.7	6.0	3.7	5.7	9.4	9.4	4.1	2.1
II	13.2	6.4	3.8	15.4	12.4			
III	23.5	11.6		7.5	9.7	9.7	5.0	2.6
V	5.5	(3.5)[b] (8.6)	2.3	13.8				

[a] Ppm/mol amide residue. [b] The values are not clear.

atom and a proton, and ϕ is the O–Eu–H internuclear angle. The Eu(fod)$_3$·amide complex may be formed through the lone pair of electrons on oxygen.[3c] The assignments for the D, F, and G protons in Figures 6 and 7 were given by assuming that carbonyl oxygen is cis to the cyclopropane ring and the Eu ion is located near the oxygen as reported for tertiary amide compounds.[3-5] An important observation is that the peak assigned to E and F appeared without separation, regardless of the amounts of Eu(fod)$_3$. This implies that the distance of the E and F protons from the Eu ion was the same. Since there is no change in the A and B peaks in Figure 8, even at high Eu(fod)$_3$ content, the most probable time-averaged location of Eu ion is on a plane containing the amide group, the A, and the B carbons. Consequently, the plane containing the amide group probably bisects the cyclopropane ring. Since the E and F peaks moved downfield faster than the D peak, the conformer in which the carbonyl oxygen is cis to cyclopropane ring (see Figures 6 and 7) must be more preferred than that in which the carbonyl group is trans to the cyclopropane ring. The former seems to be more sterically favored than the latter. The bisection of the cyclopropane ring by the amide plane may occur through the maximum overlap of the cyclopropane endo orbitals, the carbonyl π orbitals, and the nitrogen p orbital.[10] Resonance stabilization would overcome the sterically unfavorable interaction which might exist in the conformer. X-Ray analysis of the following cyclopropane derivatives shows that the plane containing the O–C_1–N group bisects the cyclopropane ring with a cis conformation of oxygen to the cyclopropane ring and that the angle $\angle C_1C_2H$ is 116°.[11]



R = H or NH_2

The effect of the shift reagent on II is shown in Figure 9. The complicated peaks, A and B, at high Eu(fod)$_3$ contents are caused by the fact that two protons of each methylene group are located at different distances from the Eu ion coordinating the remote carbonyl group. It is significant that no broadening or further separation was observed on the E and D peaks by the addition of the shift reagent. The two E protons and the two D protons probably are geometrically identical; in other words, the conformations of the two carbonyl groups are the same. If the conformation of the carbonyl groups of II and the time-averaged location of the Eu ion are the same as those of I, the following relationships will be satisfied, assuming a 1:1 stoichiometry

$$\Delta Eu(IID) = \Delta Eu(ID) + \Delta Eu(IE) \quad (2)$$

$$\Delta Eu(IIE) = \Delta Eu(IF) + \Delta Eu(IG) \quad (3)$$

where ΔEu(IID), ΔEu(ID), and ΔEu(IE) represent the corresponding molar induced shifts of the D proton of II and the D and E protons of I. The calculated values for the right-hand sides of eq 2 and 3 were 15.1 and 13.5 ppm/mol amide residue, respectively, which are close to the corresponding observed values of 15.4 and 12.4 ppm/mol amide residue of II (Table I). Consequently, the carbonyl groups of II may bisect the cyclopropane ring in the same manner as in I and III.

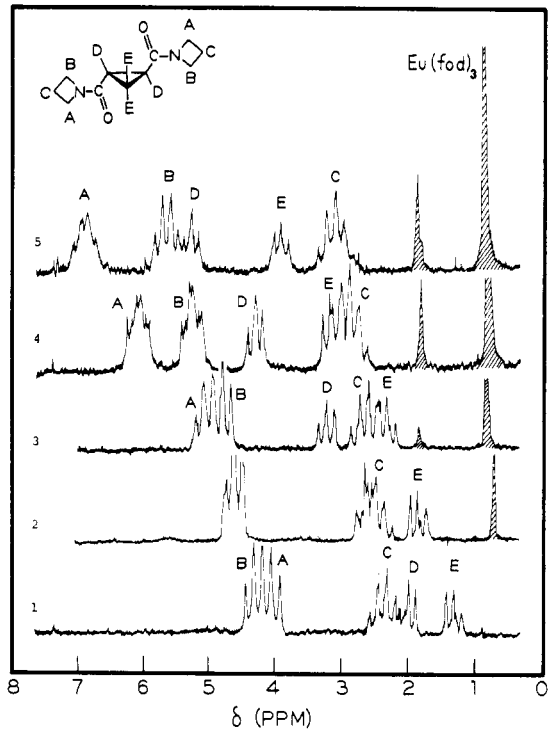


Figure 9. Nmr spectra of II with various amounts of Eu(fod)$_3$ in $CDCl_3$ (60 MHz). [Eu(fod)$_3$]/[amide residue] = 0 (1), 0.04 (2), 0.09 (3), 0.15 (4), 0.22 (5).

The molar-induced shifts for V are also shown in Table I. The values for V are much greater, almost twice as much, than those for VI.[4] The difference may be because V makes a 1:1 complex where each amide group is coordinated to one molecule of Eu(fod)$_3$, while VI forms a 2:1 complex where two amide groups are bound to a Eu(fod)$_3$ molecule.[4] Of course, we must think about the difference in the K value in eq 1. However, the difference of the value between V and VI may not be as great, judging from the previous data,[4,5] and similarity of the structure of V and VI may exist. Since the polymers in $CDCl_3$ precipitated upon addition of Eu(fod)$_3$, the spectrum could not be measured.

The dipole moment of II determined in benzene at 25° was 2.79 D. The value agreed with the calculated value, 2.85 D,[12] for the conformer in which the amide plane bisects the cyclopropane ring.

From the nmr data and the optical data reported in a preceding paper,[2] the following conclusions are obtained on the conformations of C3 and C6 amide compounds.

1. Both the C3 model compounds and the polyamides show no significant conformational change in various solvents such as $CDCl_3$, water, TFE, methanesulfonic acid, and sulfuric acid (from nmr, ORD, CD, and viscosity). In the preferred conformation, the carbonyl groups bisect the cyclopropane ring (from nmr and dipole moment).

2. Both (+)-C6·DSH and V have different conformations in $CDCl_3$ and D_2O (from nmr). (+)-C6·DSH shows no noticeable conformational change in water, TFE, methanesulfonic acid, and sulfuric acid (from ORD, CD, and viscosity). However, the conformation of V varies in the above solvents (from ORD and CD).

Unfortunately, the nmr spectra as well as the ORD and CD spectra did not give us conclusive evidence about the direction of the rotation due to the spirodiamine which rotates the amide bond by 90° either clockwise or counterclockwise.[2] This rotation must occur at random because there seems to be no factor which would determine the direction of the rotation.[2] Therefore, the conformational changes reported here may be due only to the bond connecting the carbonyl groups and the C3 ring or the C6 ring.

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(12) The dipole moment was calculated by assuming that the dipole moment of each amide group was 3.84 D, the angle between the dipole and C–N bond was 39.6°,[1] and the angle C_1C_2H was 115°. The corresponding angles for many cyclopropane derivatives have been shown to be in the range of 110–120°. The calculated dipole moments of II for 110 and 120° are 2.74 and 2.96 D, respectively.

Fluorine Magnetic Resonance Studies of Conformation of Poly(ethylenimines)

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ABSTRACT: The conformation of derivatives of poly(ethylenimine) in aqueous and in organic solvents has been investigated by fluorine magnetic resonance studies of fluorine-labeled polymers and model small molecules. Fluorine chemical shifts, which are sensitive to molecular surroundings, provide a probe of the local environment in derivatives of poly(ethylenimine). In both aqueous and organic solutions the spectra give evidence of interactions among polymer segments. In aqueous solution long apolar pendant groups on the polymer matrix appear to assemble into clusters. The presence of clusters restricts the range of possible conformations of the polymer. A model is presented that encompasses the observations.

Recent work with poly(ethylenimines)[1,2] has demonstrated the possibility of generating derivatives with dramatic binding[3-5] and catalytic abilities.[6-9] For example, derivatives in which about 10% of the amino groups of poly(ethylenimine) (PEI) have been modified by acylation with an ester of dodecanoic acid or alkylation with 1-iodododecane have a high affinity for small molecules in aqueous solution,[3,4] particularly for anions and for molecules with large apolar segments.[5] PEI derivatives with both apolar binding groups and appropriate nucleophilic groups are catalysts for certain hydrolytic reactions,[6-9] presumably by virtue of the ability of the binding group to constrain the substrate in the vicinity of the catalytic group.

Having demonstrated the possibility of making these polymers, we have undertaken studies to elucidate their structure. Thus we have determined the course of reaction of acylating and alkylating agents with the various (primary, secondary, and tertiary) amino groups.[10] In addition we have probed the local environment of the apolar groups on PEI by fluorine nmr studies of derivatives in which fluorine atoms are part of the apolar substituents.[11] That investigation, based on the high sensitivity of fluorine chemical shifts to local environment, showed that in a derivative in which 5.5% of the PEI residues had been acylated with 10,10,10-trifluorodecanoyl substituents, these groups were distributed between classes of environments, one aqueous and the other micelle like. In the present report we have extended the nmr studies to other fluorine-labeled PEI derivatives, one of which is closely related to polymers used in the binding and catalytic studies. Spectra of various derivatives were obtained both in aqueous solution and in organic solvents. From results in organic solvents we have estimated the degree of exposure of the fluorine labels to these solvents. The observations in aqueous solutions reveal directly the nature of the local environment of the label. The delineation of the nature of the surroundings of the probe molecule places severe limits on the range of possible structures for the entire macromolecule. On the basis of these restrictions a conformational model has been built which encompasses a variety of experimental observations