Conformations of *cis*- and *trans*-4-Fluoro-L-proline in Aqueous Solution

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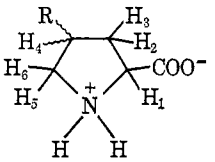
Abstract: High-resolution proton and fluorine magnetic resonance spectra of the two α-imino acids, *cis*- and *trans*-4-fluoro-L-proline, have been analyzed. The vicinal coupling constants are used in conjunction with a Karplus-type equation to ascertain the conformational properties of the proline ring in each system. Both molecules are found to be in envelope conformations; the existence of a single, strongly dominant conformational isomer with the fluorine atom in an axial orientation is indicated for each compound by the data.

The only cyclic α-imino acids which commonly appear in protein structures are L-proline (Ia) and 4-hydroxy-L-proline (Ib), and as a result the conformational properties of these molecules are of particular interest. Previous studies of the five-membered proline ring have largely been crystallographic determinations,[1-8] although the cis and trans isomers of 4-hydroxy-L-proline have been examined in solution by pmr spectroscopy.[9] These investigations show the general tendency of the unsubstituted and 4-monosubstituted proline ring to be puckered, with carbon C_γ 0.4–0.6 Å out of the plane occupied by the C_δ, N, C_α, and C_β atoms. This puckered atom may be below the plane, and thereby oriented trans to the carbonyl group, as found in copper proline dihydrate[5] and *trans*-hydroxy-L-proline[1,9] or may lie above the plane, cis to the carboxyl group. Examples of this latter ring conformation are afforded by L-proline[2] and *cis*-4-hydroxy-L-proline. A number of proline-containing peptides have also been found to be puckered at C_γ[10-12] although in several substituted prolines and in some peptides, atoms other than C_γ take up the out-of-plane position.[4,6,7,13]



Ia, R = H
b, R = OH
c, R = F

We have employed fluorine-substituted prolines (Ic) in an effort to define the solution state conformational properties of the proline ring system more precisely; the presence of the fluorine atom spreads out the proton spectrum of these molecules to the extent that a complete spectral analysis is possible. Fluorine substitution has generally proven to be of great value in conformational studies for several reasons including the observation that covalently bound fluorine is nearly isosteric with covalently bound hydrogen.[14] However, fluorine is highly electronegative and thus may participate in hydrogen bonding. The conformations of the molecules which are the subject of the present paper could therefore resemble either those of the parent proline ring or the structures found for 4-hydroxy-L-proline.

Experimental Section

cis-**4-Fluoro-L-proline** was prepared by the method of Gottlieb, *et al.*,[15] and had mp 271° (lit.[15] mp 271°) and $[\alpha]^{20}D$ −54.9° (*c* 1, H_2O) (lit.[15] $[\alpha]^{20}D$ −40.2).

trans-**4-Fluoro-L-proline** was also synthesized by the procedure of Gottlieb, *et al.*,[15] and showed mp 264° (lit.[15] mp 243–246°) and $[\alpha]^{20}D$ −79.2° (*c* 1, H_2O) (lit.[15] $[\alpha]^{20}D$ −87.6°).

Additional recrystallizations of these materials produced no change in the melting point or optical rotation. The fluorine-19 magnetic resonance spectrum of each isomer was quite distinctive (see below), and by this technique, no impurities were detected in either compound. Proton magnetic resonance spectra were recorded at ambient temperature on a Varian HA-100 spectrometer operating at 100 MHz while fluorine-19 magnetic resonance spectra were recorded on the same instrument operating at 94.1 MHz. External capillaries containing hexamethyldisiloxane or hexafluorobenzene were used to provide lock-reference signals. Spectra were calibrated by counting the manual and sweep oscillator frequency with the Varian V-4315 counter. The linearity of each sweep range was checked and the appropriate corrections were applied. Deuterium oxide was employed as the solvent with the solute being about 1 *M*; the apparent pH of the samples was about 6.

Computer calculations were done with a local version of the LAOCN3 program[16] on an IBM 360/75. About 100 lines were

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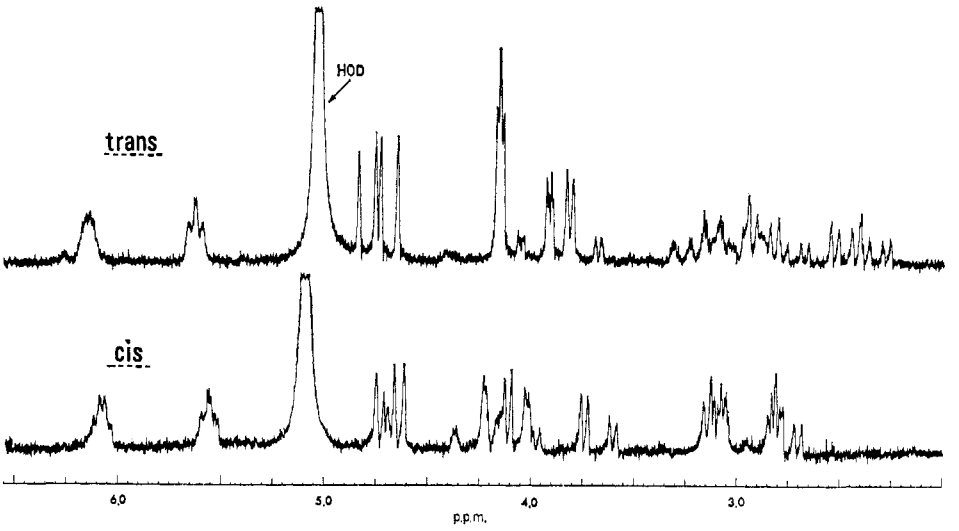

Figure 1. The pmr spectra of *cis*- and *trans*-4-fluoro-L-proline.

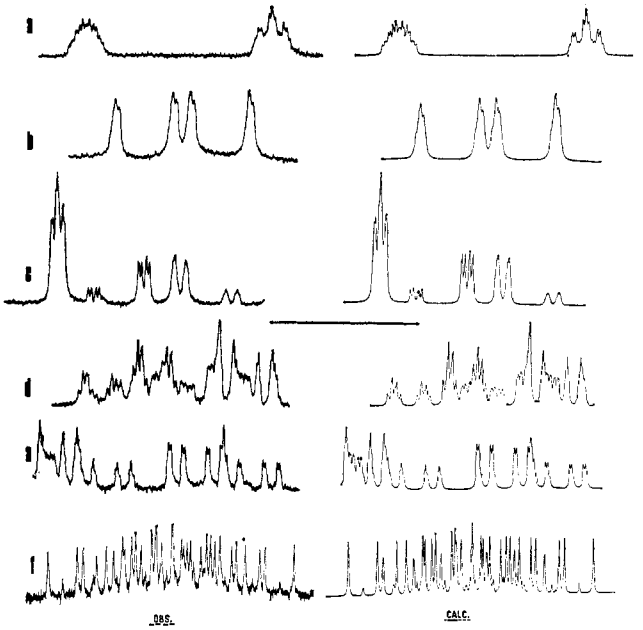

Figure 2. A comparison of the observed and calculated proton and fluorine-19 spectra of *trans*-4-fluoro-L-proline. The calibration bar represents 50 Hz in spectrum f and 10 Hz in the others. Scans a–e are portions of the proton spectrum and f is the fluorine spectrum.

assigned in each case; the quoted chemical shifts and coupling constants reproduced these lines to within an error of 0.1 Hz or less.

Results

Figure 1 shows in broad perspective the pmr spectra of the cis and trans isomers of Ic. Since the N–H and carboxyl protons exchange rapidly with the solvent (D_2O), their corresponding signals will be coalesced with the residual water peak, and no coupling of these protons with the other nuclei in these molecules is expected or observed. The remaining seven spin $^1/_2$ nuclei attached to the proline ring define an ABCDEFX spectrum in each case. Spectra with the narrowest possible sweep widths were collected for each multiplet in the pmr spectra at a resolution of 0.4–0.5 Hz. The fluorine spectrum, in each case, was a single collection of lines spanning nearly 200 Hz. The detailed spectra were then analyzed by the iterative procedure of Castellano and Bothner-By[17] until computed theoretical spectra agreed with the experimental observations (Figure 2). This tedious process was aided by homonuclear and heteronuclear double resonance experiments. As is indicated in Figure 2, the agreement between experimental and computed spectra is good in the case of the trans compound. The quality of the agreement with the cis isomer was very slightly lower but still acceptable. The chemical shifts and coupling constants determined in this way are recorded in Table I.

Table I. Nmr Spectral Parameters of *cis*- and *trans*-4-Fluoro-L-proline[a]

δ, ppm[b]	J, Hz[c]	
	Trans Isomer	
$\delta_1 = 4.7530$	$J_{12} = 8.10$	$J_{34} = 3.82$
$\delta_2 = 3.0982$	$J_{13} = 10.36$	$J_{35} = 0.12$
$\delta_3 = 2.6257$	$J_{14} = 0.60$	$J_{36} = 0.72$
$\delta_4 = 5.8723$	$J_{15} = -0.10$	$J_{3F} = 40.48$
$\delta_5 = 4.0730$	$J_{16} = 0.40$	$J_{45} = 0.62$
$\delta_6 = 3.9682$	$J_{1F} = -0.43$	$J_{46} = 3.26$
$\delta_F = 10.287$	$J_{23} = -15.19$	$J_{4F} = 51.27$
	$J_{24} = 0.93$	$J_{56} = -13.86$
	$J_{25} = 2.36$	$J_{5F} = 20.06$
	$J_{26} = 0.17$	$J_{6F} = 37.41$
	$J_{2F} = 19.61$	
	Cis Isomer	
$\delta_1 = 4.6802$	$J_{12} = 10.50$	$J_{34} = 1.10$
$\delta_2 = 2.9278$	$J_{13} = 2.80$	$J_{35} = 0.33$
$\delta_3 = 2.9663$	$J_{14} = -0.17$	$J_{36} = 2.20$
$\delta_4 = 5.8060$	$J_{15} = 0.10$	$J_{3F} = 20.45$
$\delta_5 = 3.8849$	$J_{16} = -0.55$	$J_{45} = 3.42$
$\delta_6 = 4.1814$	$J_{1F} = -0.75$	$J_{46} = 0.51$
$\delta_F = 8.2656$	$J_{23} = -15.28$	$J_{4F} = 50.84$
	$J_{24} = 3.85$	$J_{56} = -13.93$
	$J_{25} = 0.40$	$J_{5F} = 37.62$
	$J_{26} = 0.42$	$J_{6F} = 19.43$
	$J_{2F} = 41.93$	

[a] Samples were 0.97 and 0.95 M, respectively, in D_2O at apparent pH 5.88 for the trans compound and pH 6.00 for the cis isomer. [b] Proton shifts are downfield relative to external hexamethyldisiloxane; the average rms error of the shifts as estimated by the computer program was ± 0.0003 ppm. Fluorine shifts are ppm upfield from external hexafluorobenzene. [c] The rms error of the coupling constants estimated by the program was ± 0.03 Hz.

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An important aspect of such analyses is the relative signs of the spin coupling constants. We have assumed that the signs of the geminal coupling constants are negative (except for geminal HF coupling[18]) and that the vicinal H–H coupling constants are positive.[19,20] Various sign combinations for the remaining coupling constants were tried; the signs recorded in Table I are those which gave the optimum agreement between the theoretical line intensities and positions and the observed spectra. We found that the sign of J_{25}, a four-bond proton–proton coupling constant, could strongly affect the appearance of the computed fluorine spectrum as well as the theoretical pmr spectrum. All coupling interactions did not have equivalently potent effects on the nature of the theoretical spectra, however, and the signs of some of the very small coupling constants are not as firmly established as this one. The coupling constants particularly important for the present work are those for the various vicinal H–H and H–F interactions and we believe these to be well determined by our analyses, probably to an accuracy somewhat better than 0.1 Hz.

Discussion

Although the spectral analyses described above can be carried out to reasonable accuracy, the results do not necessarily indicate which resonances may be assigned to a given nucleus in the spin system. The assignment of the appropriate resonances to H_1 and H_4 can confidently be made because of the expected effects of the adjacent ring substituents. However, there can be some ambiguity in deciding which of the pair of signals assignable to H_2 and H_3 corresponds to the proper proton of this pair. A similar problem could be present in the case of H_5 and H_6. In order to make the assignments presented in Table I, we assumed at this stage the qualitative validity of the Karplus equation for vicinal H–H and H–F spin coupling constants.[21–23] In *trans*-4-fluoro-L-proline, the larger of the two coupling constants J_{12} and J_{13} was assumed to arise from a trans orientation of nuclei 1 and 3 with its concomitantly large dihedral angle. A corresponding assignment of the resonances from protons H_5 and H_6 follows directly from this assumption since, as one progresses around the ring from H_2 and H_3, each set of vicinal coupling constants contains one member that is large and one that is small so that a qualitative estimate of the dihedral angle between a given pair of protons is possible. For example, in the trans compound, J_{3F} and J_{6F} are both much larger than J_{2F} or J_{5F}, indicating that both nuclei 3 and 6 are likely trans to the fluorine atom.

Two observations indicate the correctness of the assignments made. First of all, conformational analyses of the two systems based on quantitative application of Karplus-like equations can be carried out smoothly with the assignments reported. These results will be described below. Secondly, molecular models of the conformations so determined clearly show that certain pairs of nuclei, for example H_2 and H_5 in the trans isomer, lie in the planar W or M configuration that has been found to be especially conducive to large, long-range (four-bond) coupling constants.[24] The coupling constants for these pairs of nuclei in our molecules are found to be substantially larger than other four-bond couplings.

The dependence of vicinal coupling constants on dihedral angle has been a powerful tool in conformational analysis. This dependence is commonly expressed as some form of the Karplus equation

$$J_{vic} = A \cos^2 \phi + B \cos \phi + C \qquad (1)$$

where ϕ is the dihedral angle between the covalent bonds which hold the coupling nuclei to the molecule of interest.[19] The coefficients A, B, and C are usually determined empirically by fitting experimental data to eq 1. A number of considerations limit the slavish application of the Karplus function to widely diverse systems,[20] but within a set of closely related structures, it has at least semiquantitative validity in the determination of molecular conformations. We have utilized eq 1 in an attempt to define more precisely the conformations of the fluoroprolines examined in this work.

The three-dimensional structure of an arbitrary five-membered ring can be specified by the five bond lengths and by four angles which can be any combination of bond angles or dihedral angles.[25] For our purposes we assumed all bond lengths in the proline ring to be fixed at 1.52 Å, the average of bond lengths found in a number of crystal structures.[1–6] A given conformation of this ring system was then specified by three contiguous interior bond angles and a dihedral angle; the remaining four dihedral angles were computed from the set of Cartesian coordinates for the five atoms in the ring that can be generated from these data. The five dihedral angles obtained in this way are the "interior" angles formed by the atoms in the ring. In order to obtain the "exterior" dihedral angles between the atoms attached to the ring skeleton, we assumed that perfect tetrahedral angles obtained in the bonds exterior to the ring in all conformations. A computer program was then developed which searches through a range of values for each of the conformation-specifying angles; at each step a new conformation is defined and a least-squares fit of the vicinal coupling constant data to eq 1 is performed. (Separate fits were made for the H–H and H–F data.) For each isomer, the three bond angles were varied from 90 to 108° and the dihedral angle from −50 to 50°. A large number of conformations for each isomer was explored in this way and wider search ranges for these parameters were not deemed necessary since the fit was bad at the extremes of the ranges indicated and because most values for the corresponding angles in the various crystal structures mentioned previously lie within these ranges.

For *trans*-4-fluoro-L-proline the procedure described above converged cleanly upon one conformation of the proline ring. The parameter set A = 13.1 Hz, B = −1.2 Hz, and C = −0.6 Hz when the ring takes the conformation reported in Table II gave the best fit of the H–H coupling constant data to eq 1. In this con-

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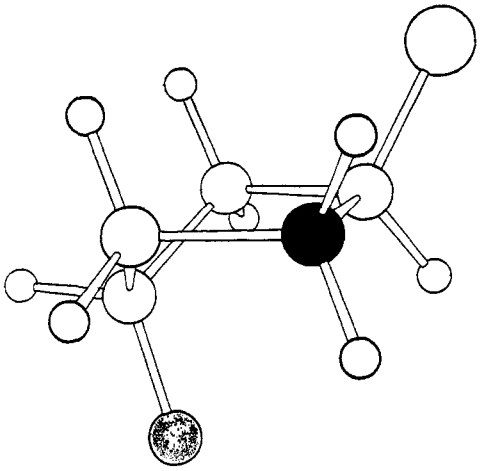

Figure 3. The dominant (best fit) conformation of *trans*-4-fluoro-L-proline located by the coupling constant fitting procedure described in the text.

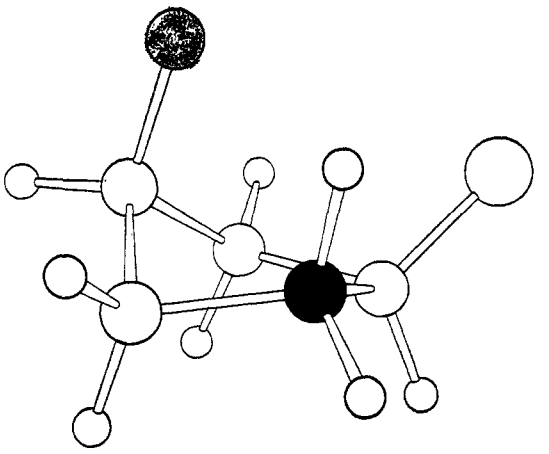

Figure 4. The dominant conformation of *cis*-4-fluoro-L-proline implied by the calculations described in the text.

Table II. Parameters Resulting from Conformational Analysis of 4-Fluoroprolines

	Trans	Cis
	a. Bond Angles, deg	
$NC_\alpha C_\beta$	102.0	92.0
$C_\alpha C_\beta C_\gamma$	105.0	108.0
$C_\beta C_\gamma C_\delta$	94.6	102.0
$C_\gamma C_\delta N$	101.8	86.9
$C_\delta NC_\alpha$	105.0	118.4
	b. Dihedral angles,[a] deg	
ϕ_N	30.3	−17.0
ϕ_{C_α}	−51.5	49.4
ϕ_{C_β}	52.7	−51.5
ϕ_{C_γ}	−36.6	48.1
ϕ_{C_δ}	4.0	−21.1
	c. H–H Vicinal Coupling Constants,[b] Hz	
J_{12}	8.08 (8.10)	10.40 (10.50)
J_{13}	10.35 (10.36)	2.84 (2.80)
J_{24}	0.68 (0.93)	3.98 (3.85)
J_{34}	3.66 (3.82)	0.61 (1.10)
J_{45}	0.84 (0.62)	3.54 (3.42)
J_{46}	3.43 (3.26)	0.81 (0.51)
	d. H–F Vicinal Coupling Constants,[b] Hz	
$J_{2,F}$	21.26 (19.61)	38.95 (41.93)
$J_{3,F}$	39.64 (40.48)	20.43 (20.45)
$J_{5,F}$	20.68 (20.06)	39.36 (37.62)
$J_{6,F}$	39.80 (37.41)	19.19 (19.43)

[a] The dihedral angles are defined according to Hendrickson's notation.[25] [b] The experimental values for these coupling constants are given in parentheses.

formation the H–F constants were described by eq 1 with A = 31 Hz, B = 0, and C = 9.3 Hz. A comparison of the observed vicinal coupling constants and those computed by these formulas is given in Table II.

Bothner-By suggests that with cyclohexanes a reasonable set of parameters for eq 1 is A = 10 Hz, B = −1 Hz, and C = 5 Hz.[19] Moreover, Williamson, *et al.*, show that eq 1 with A = 31 Hz, B = 0, and C = 0 describes vicinal H–F coupling constants when $0° < \phi < 90°$.[22b] The coefficients found for the trans isomer by our procedure are thus quite reasonable ones, and the fact that this approach is successful strongly indicates that the single conformation of the proline ring elucidated by this procedure is the one strongly preferred by the trans compound. A drawing of this structure is presented in Figure 3; it is essentially the expected envelope conformation with C_γ projecting below the mean plane of the ring, trans relative to the carboxyl group. The solution conformation of the trans isomer indicated by the coupling constant data is thus nearly identical with that found for *trans*-4-hydroxy-L-proline in aqueous solution by a similar analysis.[9]

Efforts to determine the conformation of *cis*-4-fluoro-L-proline followed the same procedure and afforded the parameters A = 16.7, B = −5.8, and C = 0.7 for eq 1. For the H–F coupling constants the values A = 34.1, B = 0, and C = 6.0 gave the best agreement for this conformation. Table II gives the angles which describe the best-fit conformation and compares the observed and calculated vicinal coupling constants. While not totally unreasonable, the values for A, B, and C in this system are somewhat different from those found with the trans isomer. This situation could be the result of a breakdown in one or more of the assumptions made in the fitting procedure. In particular, the fluorine atom, especially if it is solvated,[26] may interact with the carboxyl function in such a way that the bond lengths and exterior dehedral angles of the cis compound deviate substantially from the ideal behavior presumed by the computer program. Irregardless, the coupling constant data qualitatively indicate that the conformation of *cis*-4-fluoro-L-proline in solution is predominantly the one defined in Table II and sketched in Figure 4.

The conformations for both the cis and trans isomers of 4-fluoroproline that are suggested by the nuclear magnetic resonance data described here are thus found to be strongly related to the structures of the corresponding hydroxy-substituted compounds. At first glance this result may imply that in these cases fluorine is behaving more like hydroxyl than like a proton. However, we note that in the dominant conformation of each isomer the fluorine atom takes up an axial position. In six-membered rings it is often found that

(26) The possibility of a cross-ring hydrogen-bonded interaction between fluorine and carboxyl in the cis isomer exists. Such an interaction could account not only for the preference of the molecule for the conformation indicated but would also be consistent with the 2.1-ppm deshielding of the fluorine nucleus in the cis compound relative to the trans isomer.

fluorine strongly prefers to be axial rather than equatorial[27-29] and whatever factors are responsible for this preference may also be at work in the five-membered rings discussed here.

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Nucleoside Conformations. XI. Solvent Effects on Optical Properties of Guanosine and Its Derivatives in Dilute Solutions[1a]

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Abstract: Precise attributions of the B_{2u}, B_{1u}, and E_{1ua} bands of guanosine and several derivatives by MCD in water, propanol, and dioxane in conjunction with CD spectra have demonstrated that for a given compound the bands B_{2u} and B_{1u} are differently influenced by solvent changes or by substitutions. An attempt was made to correlate the sign of the Cotton effect with a simple sectional rule (octant rule) taking into account the flexibility of the molecules. It was concluded that small conformational changes of Guo and its analogs could be the source for relatively large changes in the Cotton effects (band inversions).

Many conformational problems of nucleic acids cannot be solved without information about all the allowed states of the monomers. This explains the many studies[2-10] on their optical properties which are supposedly linked to their conformation. Crystallographic studies[11] have demonstrated the presence of two conformations in the single crystal of guanosine and many others in its derivatives.[12,13] Nmr studies and particularly those by nuclear Overhauser effect[14-17] have shown that there is a multitude of populations with different angles Φ_{CN} for a given nucleoside in solution, which for unhindered compounds is never all *syn* or all *anti*.

We report here the effects of substituents and solvents on the CD spectra of guanosine and its derivatives. We have assigned precisely the transitions of the bands of the CD spectra with the help of MCD and absorption spectra. B_{1u} and B_{2u} transitions are sensitive to the environment of the molecule but not in the same way; their variations and the weakness of the signals indicate that the CD spectra are an average of different conformations in solution. It appears that either of the two bands B_{2u} and B_{1u} can, but need not to be, more sensitive to solvent effects and conformational changes than the other.

Methods and Materials

Guanosine and compounds A, B, C, and M (Figure 1) were purchased from P. L. Laboratories, Milwaukee, Wis.; m^7Guo (L)[18] was purchased from Cyclo-Chemicals, Los Angeles, Calif.

Compounds D, E, F, G, H, and K were gifts of Dr. A. Holy (Praha). Compound J was given by Dr.

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(18) Abbreviations used: nucleosides are abbreviated according to IUB-IUPAC convention [(*Progr. Nucl. Acid Res.*, **11** (1971) IX; nmr, nuclear magnetic resonance; CD, circular dichroism; MCD, magnetic circular dichroism.