

Studies of α -Phenyl- β -amidoethanols. 3.* Self-association of Structures with Different Amido Substituents

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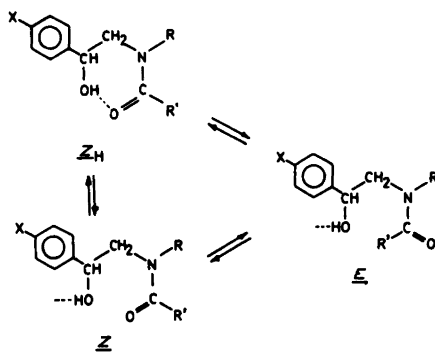
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The state of aggregation of various α -phenyl- β -amidoethanols has been determined by ^1H and ^{13}C NMR in CDCl_3 solution. Hydroxyl chemical shifts have been analyzed by using the Lippert equation and monomer-dimer models are found to fit well for all E , Z conformational isomers. The enthalpy and entropy changes on dimer formation for α -phenyl- β -(N -methylacetamido)ethanol (**1**) are found to be $\Delta H = -22 \pm 1 \text{ kJ mol}^{-1}$ and $\Delta S = -49 \pm 5 \text{ J mol}^{-1} \text{ K}^{-1}$ for E , and $\Delta H = -10 \pm 4 \text{ kJ mol}^{-1}$ and $\Delta S = -27 \pm 13 \text{ J mol}^{-1} \text{ K}^{-1}$ for Z . The smaller enthalpy of dimerization of the Z isomer is attributed to the presence of an intramolecular hydrogen bond in the monomer, the strength of which is lower than that of the intermolecular hydrogen bond in the dimer. ^{13}C T_1 values for C1 (α) and C2 (β) of **1** suggest that the E_2 and Z_2 aggregates are similar in shape.

Earlier studies of the α -phenyl- β -amidoethanol system^{1,2} have shown that these compounds are in equilibrium between folded (Z) and stretched (E) conformations. This is due to the restricted rotation of the amide moiety.³

Using α -phenyl- β -(N -methylacetamido)ethanol it was found that a nonpolar solvent like chloroform favours the Z isomer, especially at high dilution.¹ On the other hand, we observed that in dimethylsulfoxide the $E \rightleftharpoons Z$ equilibrium was shifted towards the E isomer. The E/Z ratio showed no concentration dependence in this solvent. By introducing a *para*

* Part 2. See Ref. 2.



substituent on the phenyl ring an increase of *Z* isomer population is noticed using an electron-withdrawing substituent. This effect might be due to an increased acidity of the OH group, which gives a stronger intramolecular hydrogen bond and thereby alters the position of the equilibrium. Alternatively, the induced *p*-X-phenyl dipole can cause an intramolecular dipole-dipole interaction involving the amido function.

Electric field effects of different *para* substituents in benzyl alcohols⁴ have been found to alter the OH chemical shift although the relation to the hydrogen bonding ability of the hydroxyl group was not explicitly examined. However, certain derivatives of Schiff bases have been studied,⁵ where an electron-demanding substituent remote from the OH strengthens the hydrogen bond.

In our model system the intramolecular hydrogen bond of the *Z* isomer does not raise the free energy of activation, ΔG^\ddagger , for amide rotation $Z \rightarrow E$.² This observation could be interpreted as a hydrogen bonded stabilization of the ground state of *Z* as well as a stabilization of the transition state, or that the amide rotation process involved preferentially $Z \neq Z_H$. A strongly electron-withdrawing group like NO₂ was found to slightly lower ΔG^\ddagger in C₂D₂Cl₄.²

The present report concerns concentration and temperature ¹H NMR studies of some α -phenyl- β -amidoethanols. In addition to ¹H NMR variables, ¹³C spin-lattice relaxation times (*T*₁) were measured to yield complementary information about the self-association processes.

RESULTS AND DISCUSSION

α -Phenyl- β -(*N*-methylacetamido)ethanol. (1). ¹H NMR chemical shifts for the OH groups of the *Z* and *E* isomers have been obtained at different concentrations (0.38–0.0010 M, CDCl₃) and temperatures (223–323 K). Fig. 1 shows the OH chemical shift vs.

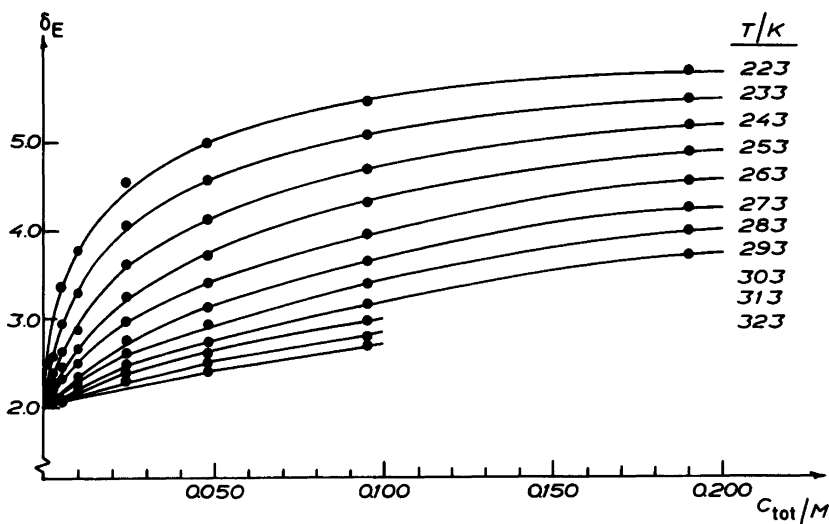


Fig. 1. Variable concentration/temperature data for the OH chemical shift of the *E* isomer of α -phenyl- β -(*N*-methylacetamido)ethanol (1). The use of total *C* or of fractional *C_E* concentration yields the same $\delta_{OH\infty} = 1.99$.

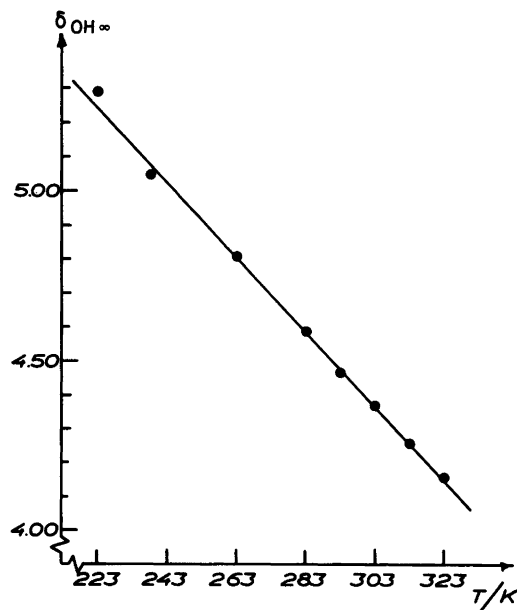


Fig. 2. Temperature dependence of $\delta_{\text{OH}\infty}$ (Z) for 1. The temperature coefficient is 0.011 ppm K^{-1} .

concentration for *E*. By making an infinite dilution extrapolation we estimate the infinite dilution shift for the OH group of *E* to be 1.99 ppm. This value is fairly independent of temperature, an observation which supports a monomeric structure in chloroform. The *Z* monomer chemical shift displays a negative temperature dependence demonstrated in Fig. 2, giving a temperature coefficient of 0.011 ppm K^{-1} . Comparatively, a temperature coefficient of about 0.002 ppm K^{-1} is normally observed for NH protons involved in stable intramolecular hydrogen bonds of biomolecules.⁶ If an increased value is found, as in biomolecules, several molecular conformations are believed to exist. The large temperature coefficient obtained in our system is therefore interpreted analogously, *i.e.* the unfolding of the Z_{H} isomer to a species with a free hydroxyl group.^{6b} Another effect which has to be considered for the observed temperature dependence of the OH shift of the intramolecular hydrogen bond is changes in the effective length of the hydrogen bond.⁷

To extend our knowledge of the association process, we have analyzed our variable concentration/temperature data for possible monomer – *n*-mer equilibria using the Lippert equation⁸ [eqn. (1), see Experimental]. Fig. 3 shows the Lippert plots for $n=2$ and $n=3$ at room temperature (293 K). There is a clear indication of the presence of a monomer-dimer equilibrium in both isomers. The monomer-dimer models are prevalent in the entire temperature range. At very low concentrations (Fig. 3) the experimental values of *E* are observed to deviate from the linear relationship for $n=2$. The most plausible explanation for this deviation is the presence of weak hydrogen bonded complexes involving solvent molecules. Similar deviations have been observed for the phenol system where carbon tetrachloride was used as solvent.⁹ However, traces of water might also cause such a non-linearity at low concentrations.

The OH chemical shift of the associated species, in this case the dimers, can be calculated

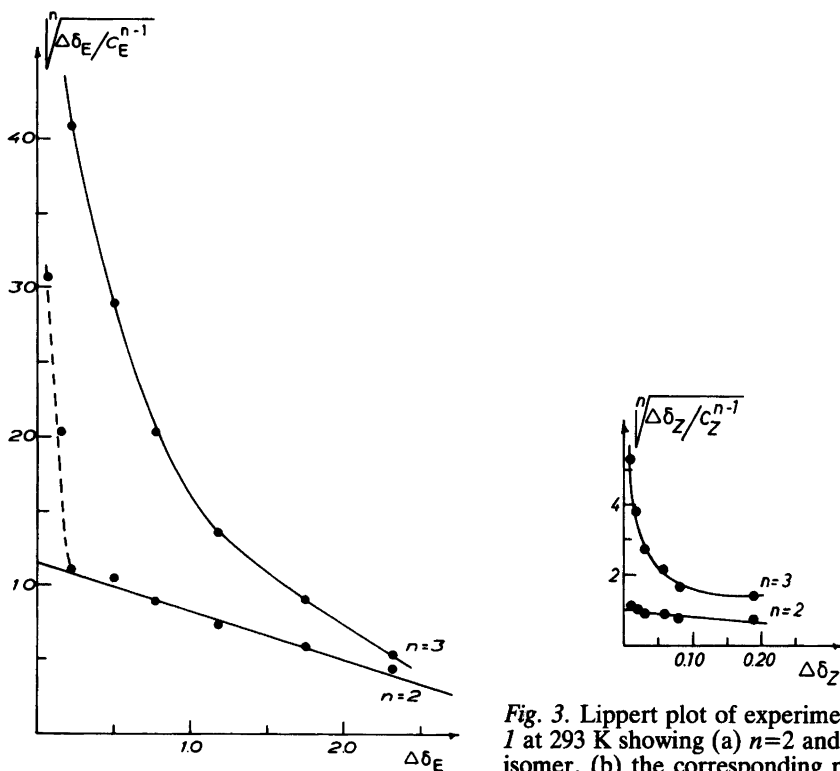
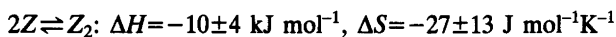
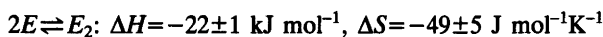


Fig. 3. Lippert plot of experimental data of *I* at 293 K showing (a) $n=2$ and 3 for the *E* isomer, (b) the corresponding plot for *Z*.

[see eqn. (1)] from the intercepts of the linear relationships of the plots in Fig. 3. The slopes of the same curves afford the equilibrium constants at the different temperatures studied. The dimer chemical shifts of the hydroxyl groups of *Z* and *E* are shown in Table 1 together with the equilibrium constants for dimer formation. By making the usual $\ln K$ vs. $1/T$ plot (Fig. 4) the enthalpy and entropy changes for the dimerization process are given as:



The total enthalpy for all hydrogen bonds taking part in the association is larger for the *E* isomer than for the *Z* isomer. This is not surprising as the magnitude of the difference of the observed OH chemical shifts ($\Delta\delta$) at the extreme concentrations is much larger for *E* than for *Z*. In the case of the *E* isomer, the association might either be described as formation of linear dimers of *E* involving one strong hydrogen bond or cyclic dimers, where two weaker hydrogen bonds are formed. This proposal is based on the empirical observation that each hydrogen bond has an energy of about 13–25 kJ/mol.^{10,11} The lower enthalpy for *Z* association reflects the fact that the *Z* isomer is intramolecularly hydrogen bonded. As suggested by the thermodynamic data, the strength of the intermolecular hydrogen bond is greater than that of the intramolecular hydrogen bond. The negative entropy values reflect in part an increased order of the self-associated systems, an effect most obvious for E_2 . For

Table 1. OH_{dimer} chemical shifts and equilibrium constants for dimer formation of compound 1.

T/K	$K_2(E)/\text{M}^{-1}$	$K_2(Z)/\text{M}^{-1}$	$\delta_{\text{OH}}(E_2)$	$\delta_{\text{OH}}(Z_2)$
223	463	7.5	5.57	5.35
233	258	— ^a	5.43	—
243	131	—	5.43	—
253	93	—	5.23	—
263	64	—	5.07	—
273	46	5.8	4.94	4.87
283	38	—	4.74	—
293	25	2.7	4.72	4.65
303	18	1.7	4.76	4.63
313	14	1.6	4.65	4.53
323	10	—	4.54	—

^a A good fit could not be obtained due to scatter of the Lippert plots. The plot in Figure 4 is therefore obtained by using the remaining 5 equilibrium values, giving a less stable model. Thus the thermodynamic parameters for Z are only tentative. However, the comparison of equilibrium constants of different compounds at a given temperature, where fits are obtained, is meaningful.

simplification of the analysis, the association of the Z isomer has been assumed to be a simple dimerization process. In reality, Z aggregation may also involve mixed (or hybrid) association, *i.e.* formation of aggregates consisting of one Z and one E molecule. However, based on the results for *N*-(2-hydroxy-2-phenyl)ethyl-2-pyrrolidone (3) (*vide infra*), it is suggested that such an aggregation does not greatly affect the analysis since the equilibrium constant obtained for Z, 2.7 M^{-1} (293 K), is not very different from the value for 3, 1.2 M^{-1} (294 K). Therefore, the assumption that the Z isomer is represented by Z_2 in its associated

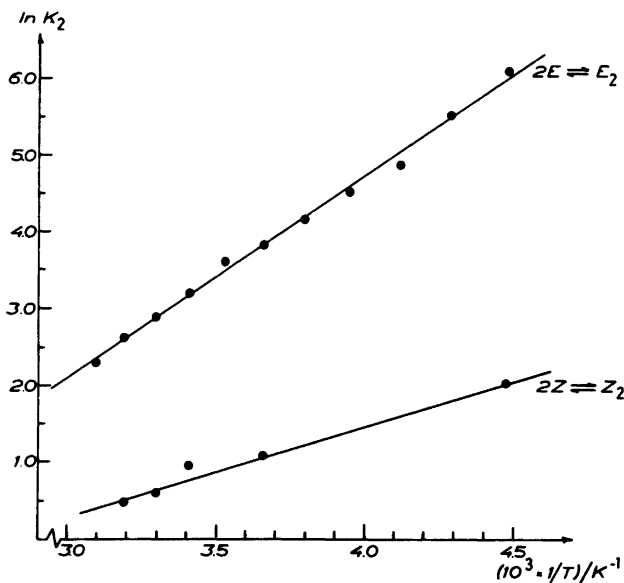


Fig. 4. A plot of $\ln K_2$ versus $1/T$ for the E and Z dimerization processes of α -phenyl- β -(*N*-methylacetamido)ethanol (1). See Table 1 for discussion of significance. Thermodynamic parameters (see text) are determined at the 95 % confidence level.

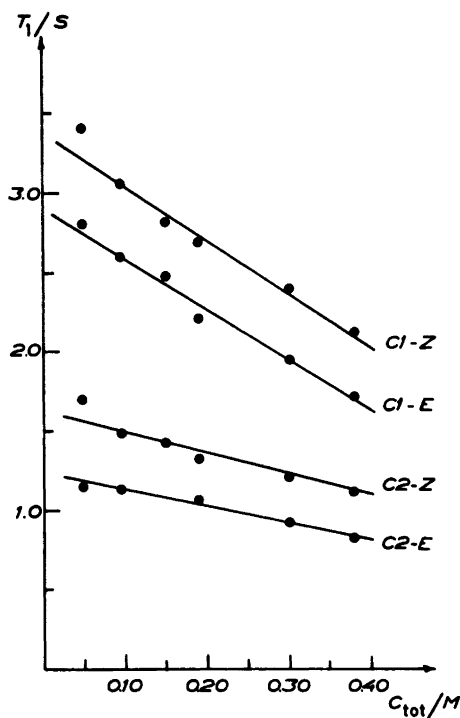


Fig. 5. Spin-lattice relaxation times T_1 for C1 (α) and C2 (β) of 1 as a function of concentration.

state, can be justified in reference to the results for 3, where the only possible association is Z_2 .

Additional information on the monomer-dimer equilibrium was obtained by ^{13}C spin-lattice relaxation times at various concentrations. The T_1 changes of C1 and C2 are reported as a function of concentration (Fig. 5). As can be seen the T_1 values are higher at lower concentrations, which can be rationalized as a cleavage of molecular aggregates. The variation of the relaxation times for C1 (E) and C2 (E) parallels that for C1 (Z) and C2 (Z) as reflected in the T_{1E}/T_{1Z} ratio, which is constant. This indicates that the relaxation of these carbons is governed by nearly the same overall molecular motion. Hence, both the E_2 and Z_2 dimers are of similar shape and accordingly show about the same rotational correlation times.

The preceding discussion of variable 1H shift data and T_1 measurements is equally valid for both cyclic and linear self-associates.

The ^{13}C chemical shifts are slightly affected by dilution. As expected, the most pronounced effects are seen for C1 of both isomers ($\Delta\delta_E = -0.80$, $\Delta\delta_Z = -0.53$).

α -Phenyl- β -(*N*-methylformamido)ethanol (2). For this compound the 1H chemical shifts have been analyzed at one temperature (293 K), thus giving the mode of aggregation, the chemical shift of the monomer and n -mer and the equilibrium constants for monomer – n -mer formation. In Fig. 6 the Lippert plots are presented with $n=2$. The 1H chemical shift for the OH group of the dimer obtained from this plot is 5.04 ppm for the E isomer and 5.22 ppm for the Z isomer. Infinite dilution chemical shifts for the two monomers are: $\delta_{OH\infty}(E) = 2.01$ and $\delta_{OH\infty}(Z) = 3.52$. The OH infinite dilution shift obtained for the E isomer of 1 is almost identical to $\delta_{OH\infty}(E)$ of 2, whereas for the Z isomer a shielding of

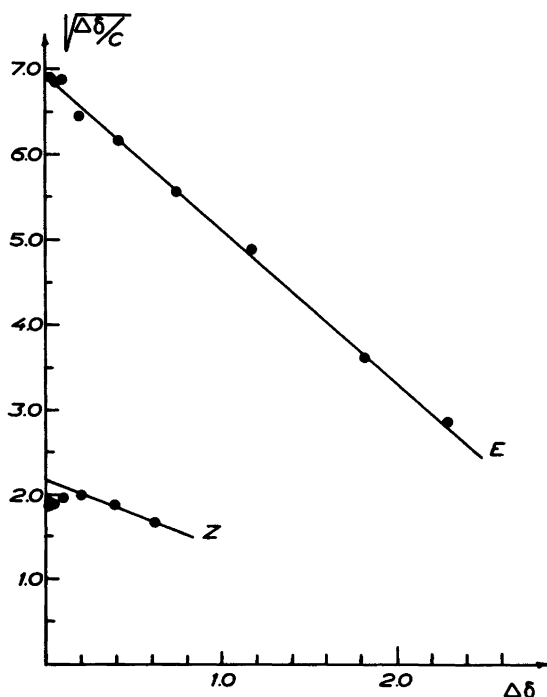


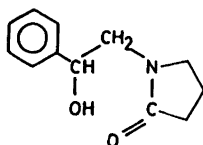
Fig. 6. Lippert plot for α -phenyl- β -(*N*-methylformamido)ethanol (2) showing the curves for $n=2$.

approximately 1 ppm is observed. This value reflects the greater tendency of compound 1 to exist as intramolecularly hydrogen bonded *Z* isomers (Z_H), i.e. 1 has a stronger intramolecular hydrogen bond.¹²

The equilibrium constants for dimer formation are 7.9 and 1.4 M⁻¹ for the $2E \rightleftharpoons E_2$ and $2Z \rightleftharpoons Z_2$ equilibria, respectively. A comparison of these values with K_2 for compound 1 at the same temperature shows that the E_2 as well as the Z_2 dimer formation is slightly favoured for the acetamidoethanol 1.

The population ratio of each β -amidoethanol, $E/Z=0.21$ (1) and $E/Z=0.73$ (2) (obtained from integrated intensities of $N-CH_3$ and $C(O)CH_3$ resonances at 0.0010 M in $CDCl_3$), shows that the *Z* isomers are preferred over the *E* isomers¹ in both compounds. Having a less sterically demanding carbonyl substituent, *E* is favoured in the relative sense.¹³

N-(2-hydroxy-2-phenyl)ethyl-2-pyrrolidone (3). The main reason for studying this compound is that it exists exclusively in the *Z* conformation.



The infinite dilution shift of the hydroxyl group at 294 K is 4.01 ppm, roughly the mean value of the *Z*-shifts of 1 and 2. Hence this condition suggests an intermediate strength of the

intramolecular hydrogen bond. The temperature coefficient is 0.012 ppm K⁻¹, similar to the value of the *Z* isomer of the β -acetamidoethanol 1.

An analysis of the OH chemical shift data as a function of concentration for this compound, using eqn. (1), reveals a monomer – dimer equilibrium with $K_2=1.2 \text{ M}^{-1}$. The OH chemical shift obtained for the dimer is 4.77 ppm. The comparison of infinite dilution shift values of 3 with the *Z* isomers of 1 and 2 suggests that the magnitude reflects the strength of the intramolecular hydrogen bond in the monomers. In conclusion, it has been shown that the association behaviour of the *E* and *Z* conformations of 1 and 2 can be described by 2 monomer \rightleftharpoons dimer equilibria in the low concentration region in CDCl₃ solution. Compound 3, in which the *Z* configuration is enforced by a lactam ring, also shows such an equilibrium.

For the *E* isomer of 1, lacking the possibility of intramolecular hydrogen bonding, the enthalpy of dimer formation is roughly twice that of the *Z* conformation.

EXPERIMENTAL

The synthesis of 1 was performed as reported earlier.¹ The other compounds, 2 and 3, have both been synthesized according to procedures earlier published.^{14,15}

All NMR measurements were performed on a Bruker WM-250 operating at 250 MHz for ¹H and 62.9 MHz for ¹³C. TMS was used as internal reference. Infinite dilution ¹H shifts for the OH group are obtained from chemical shift vs. concentration (or log conc.) plots applying a lowest concentration of 1.0 mM and by extrapolating to infinite dilution. The precision of shift measurements is <0.01 ppm. The instrument is equipped with a temperature unit B-VT1000. The temperatures were checked by the temperature dependent signals of a methanol sample and thus temperatures obtained in this paper are estimated to be accurate to ± 1 °C. Chloroform-*d*, which was used as solvent in all runs, was washed several times with water and predried over MgSO₄. After distillation, CDCl₃ was stored over molecular sieves (4Å) in a dark bottle and stabilized with Ag foil.

The variable concentration ¹H data have been analyzed by using the Lippert equation for self-association⁸

$$\sqrt[n]{\Delta\delta/cn-1} = \sqrt[n]{(\delta_n-\delta_m)nK_n} - \sqrt[n]{(\delta_n-\delta_m)^{1-n}nK_n} \Delta\delta \quad (1)$$

where $\Delta\delta$ is the difference between observed OH chemical shift and δ_m , the monomer chemical shift obtained by extrapolation to infinite dilution ($\delta_{\text{OH}\infty}$). K is the molar equilibrium constant and n is the dimensionality of the aggregates (n -mer or polymer), which have the chemical shift δ_n . A plot on the left-hand side of eqn. (1) vs. $\Delta\delta$ should be linear if the solute associates with aggregate dimension n . By using the linear plot one can test if the conditions are verified and, for a certain n and δ_m , one can obtain K_n and δ_n .

By using this traditional approach we obtain useful equilibrium constants. However, we feel that one has to be very observant of fortuitous results when using plots where the variable of one axis also is contained in the variable of the other axis. We hope to be able to further explore this point in the near future.

¹³C T_1 values were determined at 293 K by using the FIRFT¹⁶ technique with delay times of 3 s between the $-(180-\tau-90)-$ sequences. No viscosity corrections of the T_1 values are made and inaccuracies due to viscosity changes are estimated to about 10 %. The T_1 values derived from Fig. 5 were obtained by using the three parameter exponential fit supplied by the Bruker NMR software. NOE measurements for some of the solutions showed full enhancement for protonated carbons, confirming the dominance of dipolar relaxation at these sites.

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