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Studies of α-Phenyl-β-amidoethanols. 1. Solution Conformations and Isomeric Distribution of the *N*-Acylamino Derivatives

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A study of the solution conformations of a series of *p*-substituted α-phenyl-β-(*N*-methylacetamido)ethanols is presented. The ratio between the *E* and Z isomers has been determined under polar and nonpolar conditions using ^{1}H NMR. The *Z* isomer, which is the favoured rotamer in nonpolar solvents, is stabilized by a hydrogen bonded seven-membered ring. Electron-withdrawing substituents in the *para* position and dilute conditions favour the *Z* isomer. A qualitative discussion concerning the isomer distribution is presented.

Amino alcohols have received a lot of attention due to their use as adrenergic agents but also as model compounds for serine enzymes. Especially the multiplicity of NH and OH groups to act as hydrogen bond donors and acceptors has received a considerable interest. However, for studying the dynamic behaviour of peptides, the *N*-acylated derivatives should be more appropriate models, since these derivatives then have similarities to serine residues linked in a peptide chain.

In this paper we report an NMR study of such model compounds, α-phenyl-β-(*N*-acylamino)ethanols. We will especially focus our interest on the complex hydrogen bonding situation by investigating the equilibria between folded and stretched conformations as well as the overall association equilibrium. Besides intermolecular aggregation, one of the stable folded forms of the α-phenyl-β-(*N*-acylamino)ethanols will be intramolecularly hydrogen bonded by a seven-membered ring formed between the OH and the amide carbonyl. Such seven-membered hydrogen bond structures are prevalent in many biological systems[1–3] having an NH as a proton donor (γ-turns). A representative work in this area is the quantitative study of proline containing peptides that recently was reported.[4] Using Ac-Pro-NHMe as a model for proline residues in proteins and peptides, it was concluded that the *cis/trans* (*E/Z*) ratio is highly dependent on the solvent used and that an increased ratio is observed in more polar media. From this ^{1}H NMR study it was also stated that the dominant mode of aggregation is self-aggregation of the *cis* isomer as well as mixed association of the *cis* and *trans* isomers. This latter conclusion has been questioned in a reinvestigation but without conclusive evidence.[5] Unfortunately, such association studies in the Ac-Pro-NHMe system are difficult because of an undetectable *cis* population at low total concentrations. In our system, β-(*N*-acylamino)ethanols, the sensitivity requirement should be less serious since the *cis/trans* conformations are more equally populated in the concentration range studied.

Moreover, by changing *para* substituents of the phenyl ring, we will be able to model the effect of changes in H donating ability and field/inductive effects that could be induced in systems of biological importance.

RESULTS AND DISCUSSION

Since the model compounds contain an amide bond, one expects in an NMR study to find two rotamers within the slow exchange limit, the *E* and *Z* rotamers.

In a nonpolar solvent like chloroform, it is found that the *Z* isomer is favoured due to an intramolecular hydrogen bond developed between the hydroxyl group and the carbonyl oxygen of the amide group. By changing the medium to an aprotic dipolar solvent a shift of the *E/Z* equilibrium towards the

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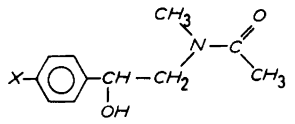
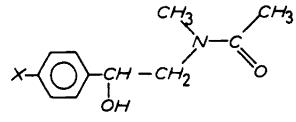


E



Z

E isomer is observed. The medium change also causes an overcrossing of the OH and NCH_3 resonances in ^1H NMR as proven by addition of minute amounts of DMSO to the chloroform solution. This fact facilitates the ^1H chemical shift assignment and a typical ^1H NMR spectrum of α-phenyl-β-(*N*-methylacetamido)ethanol is shown in Fig. 1. The assignment of the hydroxyl, the methine and the methylene resonances has been verified by homospin decoupling experiments.

As shown by the appearance of doublets in the proton spectrum the exchange of the hydroxyl protons is slow on the NMR time scale. This observation suggests that there is no interaction between hydroxyl groups but rather between the hydroxyl and the carbonyl function.

The different forms of molecular aggregates and conformational changes in the β-amidoalcohol system reveal a number of equilibria [eqn. (1)].

$$E_{\text{free, inter}} \leftrightarrows Z_{\text{free, inter, intra}} \quad (1)$$

Thus both conformers can be free or intermolecularly bonded. In addition, the *Z* isomer can maintain a folded, intramolecularly bonded form. By decreasing the concentration it is observed that the hydroxyl doublet of the *Z* isomer undergoes a much smaller high field shift as compared to the *E* isomer (Fig. 1). Moreover, a ^1H chemical shift of $\delta = 4.47$ of the *Z* isomer at 1 mM is a clear indication of the proposed intramolecular chelation. The hydroxyl resonance of the *E* isomer appears at $\delta = 2.05$ at this concentration. This shift value is 1 ppm low field to the infinite dilution shift found for

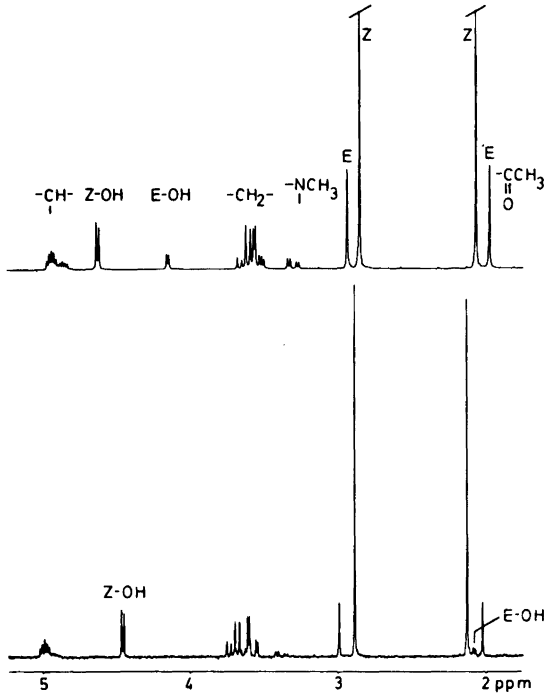


Fig. 1. Portion of a ^1H NMR spectrum of α-phenyl-β-(*N*-methylacetamido)ethanol at two concentrations in $CDCl_3$, 0.32 M (upper) and 0.0032 M.

benzyl alcohol,[6] a difference that could mainly be ascribed to the anisotropy effect of the carbonyl function.

The chemical shift difference in the reported concentration interval is an order of magnitude smaller for the *Z* structures which reflects a stronger tendency of the *Z* rotamer to exist in monomeric forms, either as free or intramolecularly bonded species. This ability is also probed by the observed *E*/*Z* ratio at the two concentrations. At 0.38 M ($CDCl_3$) the fraction of the *Z* isomer is 70 % whereas as at 1 mM the fraction of the *Z* isomer has reached 83 %.

It would also be interesting to know how an induced dipole at the phenyl moiety would affect the *E*/*Z* ratio. One could expect that electron-withdrawing groups would increase the H donating ability of the OH group and consequently favour inter- and intramolecular chelation. Thus a larger fraction of intermolecularly bonded forms would be expected for both isomers, including hybrid *E*−*Z* association. However, within the monomeric fraction of the *Z* rotamer we would also expect a larger share of intramolecularly bonded species. If an induced dipole has an influence on the H accepting ability of the carbonyl group, this polarizing effect will be most obvious for the stretched forms and decrease the H accepting ability. Since folded forms are more likely for the *Z* isomer, one would expect that such a polarizing effect, if existent, would increase the total *Z* fraction. Either of these explanations or both combined would thus account for a larger portion of the *Z* isomer, if electron-withdrawing groups are attached at the *para* position.

Table 1 shows the substituent induced changes on the *E*/*Z* ratio in two solvents and at three different concentrations. In chloroform we observe a decreased *E*/*Z* ratio for all compounds as the concentration is lowered. A few representative compounds were also examined in carbon tetrachloride at the lowest concentration but no significant changes of the *E*/*Z* ratio were observed relative to the chloroform experiments. Thus in this case any influence due to chloroform acting as an H donor can be excluded. In an aprotic polar solvent like dimethyl sulfoxide we observe as expected a large increase of the *E* fraction. The strong hydrogen bond accepting capability of this medium, means that DMSO competes effectively with the carbonyl as a hydrogen bond acceptor. Thus a decreased association of the amidoalcohol is revealed, especially obvious for intermolecular aggregation (*vide infra*). As could be seen from Table 1, the *E*/*Z* ratio is concentration independent in this range. This implies that only solvated monomers are present in DMSO solutions, an assumption in agreement with the results obtained for the Ac-Pro-NHMe system.[4]

Table 1. Substituent induced changes on the *E*/*Z* ratio in different solvents.

p-X	Conc./M	*E*/*Z* ratio	
		DMSO-d_6	$CDCl_3$
H	0.38	1.47	0.42
	0.10	1.48	0.30
	0.002	1.50	0.21
Br	0.38	1.33	0.34
	0.10	1.34	0.22
	0.002	1.42	0.15
Cl	0.38	1.31	0.35
	0.10	1.29	0.22
	0.002	1.38	0.14
F	0.38	1.36	0.37
	0.10	1.38	0.26
	0.002	1.30	0.18
NO_2	0.14[a]	1.11	0.19
	0.10	1.11	0.13
	0.002	1.01	0.07
Ph	0.38	1.40	0.42
	0.10	1.48	0.28
	0.002	1.35	0.20
OMe	0.38	1.53	0.47
	0.10	1.56	0.33
	0.002	1.64	0.21

[a] Saturated solution, 0.14 M ($CDCl_3$).

With the presence of electron-withdrawing *para* substituents, we would expect, by lowering the concentration and thus increasing the monomer population of each isomer, that the fraction of folded, intramolecularly bonded *Z* isomer would increase relative to the situation using the parent *p*-H compound. Hence, the *Z* conformer will be more favoured at low concentrations having *para* substituents like NO_2 attached compared to *p*-H or *p*-OMe. This is also observed. For α-(*p*-nitrophenyl)-β-(*N*-methylacetamido)ethanol (2 mM, $CDCl_3$) we note that almost all molecules exist in the *Z* conformation (93 %) while for α-(*p*-methoxyphenyl)-β-(*N*-methylacetamido)ethanol this portion has shifted to 83 %. Interestingly, this difference is maintained in DMSO-d_6, 50 % of *Z* for the *p*-NO_2 compound and 38 % of *Z* for the *p*-OMe compound. This strongly indicates that the intramolecular hydrogen bonded *Z* structure still exists in this

medium while no intermolecular aggregation can be proven. Similar results have been noted for γ-turns of the Ac-Pro-NHMe molecule in DMSO-d_6.[4]

Further information can be obtained by examining the ^{13}C chemical shifts of the carbonyl carbons in these experiments. The chemical shift difference for the two extremes, $\Delta\delta(\delta_{CO,OMe} - \delta_{CO,NO2})$, is −0.29 for the *E* isomer but −0.63 for the *Z* isomer when measured as 0.1 M solutions in $CDCl_3$. A low field shift is expected by going to the nitro compound for both isomers. This is due to an increased aggregation *i.e.* the fraction of hydrogen bonded carbonyl structures increases. The larger downfield shift noticed for the *Z* isomer is only compatible with a model having an intramolecular bond that is stronger than the intermolecular one or that the fraction of hydrogen bonded carbonyls is larger for the *Z* conformation than for the *E* isomer.

To summarize, the present study shows results that are very similar to those observed for the peptide derivatives[4,5] thus confirming the relevance of β-amidoalcohols as model systems for the study of peptide dynamics. Using α-phenyl-β-(*N*-acylamino)ethanols we observe a change of the overall *E*/*Z* equilibrium towards the *Z* isomer by:

A. Decreasing the amidoalcohol concentration in a nonpolar solvent.

B. Going from polar aprotic solvents to nonpolar media.

C. Having electron-withdrawing *para* substituents attached.

Quantitative variable concentration and variable temperature studies are underway.

EXPERIMENTAL

Measurements. The ^1H and ^{13}C NMR spectra were obtained on a Bruker WM-250 (5.875 T) using 16K input data points and internal ^2H lock ($CDCl_3$, DMSO-d_6). The spectral widths were 2200 Hz for the ^1H experiments and 15000 Hz for the ^{13}C NMR runs. The most dilute ^1H NMR runs required 400 transients using a 90° pulse width. The chemical shifts were measured at 26 °C using TMS as internal standard. The fractions of the *E* and *Z* isomers were measured by integration of the N-methyl and CO-methyl resonances (^1H NMR).

IR spectra were recorded on a Perkin-Elmer Model 681 ratio recording instrument using KBr plates.

Solvents. Chloroform-*d* was washed several times with water and predried over $CaCl_2$. After distillation, $CDCl_3$ was stored over molecular sieves (4A) and stabilized with Ag foil. DMSO-d_6 was dried twice over activated molecular sieves (4A).

Table 2. Melting points and IR bands.

p-X	M.p./°C[a]	IR bands/cm^{-1}
H	81–82[b]	1618, 1634, 3235, 3319, 3458
Br	109–110	1618, 1630, 3300
Cl	104–105	1618, 1631, 3328
F	111–113	1620, 1635, 3329
NO_2	135–136	1600, 1616, 1631, 3300
Ph	144–146	1617, 1632, 3352
OMe	90–92	1583, 1613, 3266

[a] Melting points were determined for *E*/*Z* isomer mixtures (recrystallized from CCl_4 or CCl_4/EtOH). [b] Lit.[10] 83–84 °C, pure *E* isomer.

Compounds. The *para* substituted α-phenyl-β-(*N*-methylamino)ethanols have been prepared according to known synthetic routes[7,8] using *para* substituted ω-bromoacetophenones as starting materials. For the *p*-nitro derivative a somewhat modified procedure has been used. *p*-Nitrostyrene oxide was reacted with an excess of methylamine (40 % solution in H_2O), using dioxane as solvent. The reaction was completed in a sealed ampoule at 120 °C for 1.5 h. The reaction mixture was diluted with chloroform and the product was extracted by dilute HCl. The solution was made basic with 10 M NaOH and finally extracted with chloroform. α-(*p*-Nitrophenyl)-β-(*N*-methylamino)-ethanol was obtained as light yellow crystals.

Acetylation of the *para* substituted α-phenyl-β-(*N*-methylamino)ethanols was achieved by using acetic anhydride.[9] No attempts were made to optimize yields which usually were in the 20–50 % range. Melting points and IR bands are given in Table 2.

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