Studies of α-Phenyl-β-amidoethanols. 2.* Internal Rotational Barriers of Some Phenyl Substituted Derivatives

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Recently we reported on the α-phenyl-β-(*N*-methylacetamido)ethanol system[1]. The amide equilibrium position was governed by (a) the choice of solvent, (b) the concentration and (c) the *para* substituent on the phenyl ring. The *E* and *Z* isomer populations are approximatively equal in a polar aprotic solvent like dimethylsulfoxide-d_6 (DMSO-d_6), while the *Z* isomer is favoured in chloroform-*d* ($CDCl_3$). The overall *E*/*Z* equilibrium is changed towards the intramolecular hydrogen bonded *Z* isomer by decreasing the substrate concentration in a nonpolar solvent. This isomer is also preferred when electron-withdrawing *para* substituents are attached, an observation valid in both DMSO-d_6 and $CDCl_3$.

Hence, in the present system it could be of interest to investigate to what extent the intramolecular hydrogen bond of the *Z* isomer influences the rotation barrier about the amide bond.

Intramolecular hydrogen bonds have been found to lower $\Delta G^{\neq}$ in *o*-hydroxy and *o*-amino-*N*,*N*-dimethylbenzamides.[2] In these systems it is assumed that the intramolecular hydrogen bond maintains the coplanarity of the $C(O)NMe_2$ moiety and the aromatic ring. Consequently there is an enhanced conjugative stabilization of the transition state. This has also been claimed for *o*-hydroxy-*N*,*N*-dimethylthiobenzamides.[3]

Since the −OH and $-CH_3$ groups occupy roughly the same van der Waals volume,[4] a substitution of −OH for $-CH_3$ could serve as a tool for probing the hydrogen bonding contribution to the rotational process without changing the steric influence.

Also, it would be of interest to observe whether a change of *para* phenyl substituent has any pronounced effect on the dynamic behaviour. For example a *para* substituent might modify the −OH proton donating ability and also change a field induced stabilization of the ground state and/or the transition state.

Experimental. α-Phenyl-β-(*N*-methylacetamido)ethanols were prepared as reported earlier.[1] These compounds show IR absorptions (Perkin Elmer 681, 0.010 M in $C_2D_2Cl_4$) due to free, intramolecular hydrogen bonded and intermolecular hydrogen bonded hydroxyl groups at ~3610, ~3586 and ~3340 cm^{-1}, respectively.[5]

N-methyl-*N*-(2-phenyl)propylacetamide was obtained by reaction of 2-phenylpropyl bromide (10 mmol) with a tenfold excess of methylamine (40 % H_2O solution) at 115 °C in a sealed ampoule using ethanol as solvent. The reaction proceeded overnight and the obtained amine was then extracted with chloroform. The chloroform solution was extracted with 6 M HCl, the solution made basic with NaOH and finally extracted with chloroform. After drying with $MgSO_4$ and evaporation, 47 mmole of *N*-methyl-*N*-(2-phenyl) propylamine were obtained. The amine was treated with acetic anhydride to give the desired product, which was purified by column chromatography (silica gel-60, $CHCl_3$).

^{1}H NMR (Bruker WM-250, 250 MHz, $CDCl_3$): 1.26, *J*=7 Hz (*E*-CH_3), 1.33, *J*=7 Hz (*Z*-CH_3), 1.84 (*E*-$C(O)CH_3$), 2.03 (*Z*-$C(O)CH_3$), 2.72 (*Z*-NCH_3), 2.87 (*E*-NCH_3), 2.99–3.47 (*E*, *Z*-CH_2, m), 3.78–3.89 (*E*, *Z*-CH, m), 7.17–7.37 (*E*, *Z*-aromatic region). IR (Perkin-Elmer 681, $CDCl_3$, cm^{-1}): 3035, 3070, 3091 (sp^2 C–H); 2880, 2938, 2974 (sp^3 C–H); 1666 (broad, carbonyls). MS (Finnigan 4000, 70 eV): *m/e* 191 (% rel. int. 33), 176 (2, M−CH_3), 148 (1, M−$C(O)CH_3$), 105 (14, M−C_4H_8NO).

Variable temperature measurements, by monitoring the $C(O)CH_3$ resonances, were performed on a Bruker WM-250 operating at 250 MHz and equipped with a temperature unit B–VT1000. The concentrations of the test solutions were held

* Part 1. See Ref. 1.

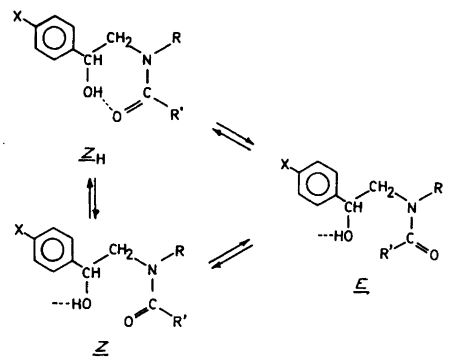

Fig. 1. The α-phenyl-β-(*N*-alkylamido)ethanol system where the hydroxyl groups of the *E* and *Z* isomers are either free or intermolecularly hydrogen bonded and Z_H is intramolecularly hydrogen bonded.

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Table 1. Free energies of activation[a] for the amide rotation in α-(*p*-X)phenyl-β-(*N*-methylacetamido)ethanol and *N*-methyl-*N*-(2-phenyl)propylacetamide (B) at 0.010 M.

Compound	$C_2D_2Cl_4$ $\Delta G^{\ddagger}_{Z\rightarrow E}$	$\Delta G°$	DMSO-d_6 $\Delta G^{\ddagger}_{Z\rightarrow E}$	$\Delta G°$
p-H	78.78 (0.46)	4.09 (0.026)	78.44 (0.43)	−0.78 (0.34)
p-Br	77.63 (0.34)	4.52 (0.046)	−[b]	−[b]
p-NO_2	77.20 (0.26)	5.42 (0.039)	78.30 (0.26)	0.02 (0.025)
B	78.83 (0.15)	0.07 (0.035)	78.05 (0.30)	0.02 (0.034)

[a] In kJ/mol with standard deviation in parenthesis. [b] Not obtained.

constant at 0.010 M. Temperatures were measured immediately before and after each experiment (by a thermocouple inside an NMR tube containing heat exchange paste) and are considered accurate to within 0.5 °C. The solvents used in this study, tetrachloroethane-d_2 and dimethylsulfoxide-d_6, were dried over 4Å molecular sieves.

The evaluation of T_2 was performed as described in the literature, using TMS as internal reference.[6]

The populations and rate constants were evaluated by superposition of the calculated and experimental spectra. The free energies of activation were calculated using the Eyring equation,[7] assuming a transmission coefficient of unity.

The NMR lineshape calculations were computed using the McConnell equation for an uncoupled two-site exchange,[8] and they were performed at the Computer Graphics Laboratory at the Chemical Center of Lund.

Results and discussion. The free energy of activation for the amides investigated are shown in Table 1. $\Delta G^{\ddagger}_{Z\rightarrow E}$ has the same magnitude for all compounds in DMSO-d_6. In this context it is important to consider the slightly different isomer distribution when comparing the *para* NO_2 substituted β-amidoethanol with the parent unsubstituted compound. The population of the *Z* isomer (for *p*-H) is 0.43 compared to the *Z* population (for *p*-NO_2) of 0.50 (T=341 K).

Based on the *E* and *Z* isomer distribution for *para* substituted α- phenyl-β-amidoethanols,[1] and results in similar systems,[9] the population difference in DMSO-d_6 was interpreted as if an intramolecular hydrogen bond in the *Z* isomer still exists. However, the free energies of activation for the listed compounds (Table 1) suggest that the intramolecular hydrogen bond of the *Z* isomer is not present in that medium. Thus the observed barrier heights are comparable to ordinary *N*,*N*-disubstituted amide barriers.[10]

In the absence of an intramolecular hydrogen bond, the dipole–dipole type, ground state stabilization of the *p*-NO_2 *Z* isomer relative to the *p*-H *Z* isomer is quite likely. Moreover, our obtained values for $\Delta G^{\ddagger}_{Z\rightarrow E}$ (78.44 and 78.30 kJ/mol for the *p*-H and *p*-NO_2 β-amidoethanol respectively) suggest that the *Z* isomer transition state receives a similar stabilization. Alternatively, the *p*-NO_2 *E* isomer is less stable relative to the *p*-H *E* isomer.

An inspection of the data in the nonpolar solvent $C_2D_2Cl_4$ reveals that $\Delta G^{\ddagger}_{Z\rightarrow E}$ is lowest for the nitrosubstituted compound. This derivative shows the largest fraction of the thermodynamically more stable *Z* isomer. The intramolecular hydrogen bond in this medium can, however, stabilize the ground state as well as the transition state.

Interestingly, *N*-methyl-*N*-(2-phenyl)propylacetamide has the same barrier to rotation as the parent unsubstituted β-amidoethanol. A plausible explanation for this observed trend is an equal stabilization of the ground state and transition state in the case of *p*-H, while on the other hand, stabilization of transition state relative to ground state increases in the order *p*-H<*p*-Br<*p*-NO_2.

An alternative explanation would be a total lack of influence of the intramolecular hydrogen bond on the barrier height. In this case the dipole in the phenyl moiety (for *p*-Br and *p*-NO_2) would interact with the amide function, thus lowering $\Delta G^{\ddagger}_{Z\rightarrow E}$.

N-methyl-*N*-(2-phenyl)propylacetamide shows a slightly larger (0.78 kJ/mole) free energy of activation in $C_2D_2Cl_4$ compared to DMSO-d_6. At least two types of solvation phenomena can be operative in amide systems in these solvents. $C_2D_2Cl_4$ can act as a proton (deuteron) donor, thus interacting with amide oxygen function (in a similar fashion as has been noted for chloroform[11]). The DMSO-d_6 interaction is of the same nature as a previously reported amide–amide self-association.[12] Thus for *N*-methyl-*N*-(2-phenyl)propylacetamide, $C_2D_2Cl_4$ might cause a hydrogen (deuterium) bonded stabilization of the

ground state which is slightly larger in magnitude than the dipole–dipole stabilization in DMSO-d_6.

Finally, it must be emphasized that the observed differences in thermodynamic and kinetic parameters represent small energy differences. Hence, care should be exercised not to overinterpret the experimental data.

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