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Solvent Polarity Effects on the *E/Z* Conformational Equilibrium of *N*-1-naphthylamides

Jaan Leis[a], Karel D. Klika[b] and Mati Karelson[a*]

[a] Department of Chemistry, University of Tartu, 2 Jakobi St., Tartu, EE2400, Estonia

[b] Department of Chemistry, University of Turku, FIN-20014, Turku, Finland

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Abstract: The ratio of the *E* and *Z* conformers of *N*-alkyl-*N*-1-naphthylformamides has been measured in a series of solvents using NMR spectroscopy. A linear relationship was found between the free energy of the conformational equilibrium, ΔG^0, and the relative dielectric permittivity of the solvent. The comparison of NMR data with quantum-chemically calculated SCRF heats of equilibria reveals that the solvent effect is a combination of both the electrostatic and specific solute-solvent interactions, the latter being directly connected to the solvent-induced sterical deformations of the solute molecule.
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INTRODUCTION

The importance of the amide bond isomerisation caused by the hindered rotation around this bond, is recognised in many processes that require alternation of peptide structure. Also, the isomeric composition of synthetic polyamides, products of the retro synthesis[1-3] and the rate of polymerisation processes may be affected by the conformational distribution of the monoamides. Since most of these processes occur in solution, the solvent effects may, in principle, affect the conformational dynamics and equilibria at amide bond. The NMR spectroscopy is perhaps the most widely used method in determining the ratio of *cis/trans* (or *E/Z*) conformers in amides[4]. Applicable in different solvents, it also allows direct measurement of the solvent effects on the conformational equilibria. Although the influence of the solvent through its polarity on the conformational equilibrium has been discussed in the case of several amides[4-8], the detailed mechanism of these effects is still not well understood. For instance, it has been found that in the case of secondary amides the specific solvation plays an important role through the inter- and intramolecular hydrogen bonding[4,5,9,10]. However, the specific solvent effects should be less significant in the case of tertiary amides and the conformational equilibria should be predetermined by the nonspecific interactions arising from the polarity of the environment.

In this work, the solvent effect on the conformational equilibrium of the series of *N*-alkyl substituted *N*-1-naphthylformamides was investigated using the nuclear magnetic resonance spectroscopy (NMR). This

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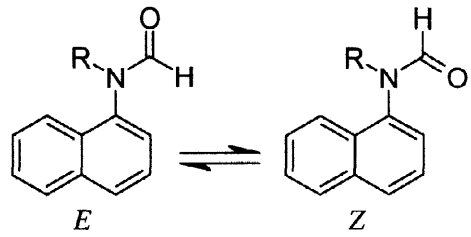
equilibrium is defined between the *E* (oxygen atom *cis* to the alkyl group) and *Z* (oxygen atom *trans* to the alkyl group) conformers (Scheme 1) of amides[11,12]. In addition, the influence of the solvent polarity on the equilibrium was modelled quantum chemically using AM1 semiempirical parameterisation[13] within the MOPAC 6.0 SCF[14] and SCRF[15] program packages. Both the single-cavity (SCa SCRF)[15] and multi-cavity (MCa SCRF)[16,17] reaction field models were applied.



1 R = Et
2 R = ^{t}BuCH$_2$
3 R = ^{i}Pr
4 R = ^{t}Bu

Scheme 1

RESULTS AND DISCUSSION

The Nuclear Magnetic Resonance (NMR) spectroscopy.

The ratio of *E* and *Z* conformers of *N*-1-naphthylamides was determined from the integrated NMR signals of formyl proton recorded in solvents of varying polarity. The respective experimental results are presented in Table 1. All measurements were carried out at 298 K.

Table 1. The Ratio (X_Z = [*Z*]/[*E*]) of the *Z* and *E* Conformations of *N*-alkyl-*N*-1-naphthylformamides (**1-4**) in the Solvents of Different Relative Permittivity (ε).

Solvent	ε (25°C)[18]	**1**	**2**	**3**	**4**
$CDCl_3$	4,7	0,11	0,15	0,18	0,57
$C_2D_2Cl_4$	8,2	0,14	0,18	0,26	0,95
$(CD_3)_2CO$	20,5	0,19	0,27	0,28	0,58
CD_3OD	32,6	0,29	0,33	0,48	1,23
DMSO-d_6	46,8	0,38	0,53	0,62	1,72

It has been shown that in formanilide the chemical shift of the formyl proton is independent of the solute concentration[5]. The data presented in Table 2 demonstrate that the chemical shifts of formyl proton in both conformers are also almost independent of solvent and only very small upfield shift can be observed with the increase of solvent polarity. Also, as the molecules examined differed only by the alkyl substituents at the

carbonyl group, the electronic effects within these compounds should be similar and the variance in chemical shifts would be caused mainly by the steric effects. Accordingly, the difference in the chemical shifts of the *E* conformers of the studied compounds can be attributed to the differences in the torsion angle between the amide and the naphthyl groups. Thus, the formyl proton of the sterically bulky *N*-isopropyl- (**3**) and *N-tert*-butyl-*N*-1-naphthylformamide (**4**) is more shielded due to the diamagnetic field of the naphthyl ring as compared to the sterically less restricted compounds **1** and **2**. This observance is well supported by the AM1 MCa SCRF calculated torsion angles between the formyl proton and the N-C1-C9 plane. In the case of the polarisable medium with the relative dielectric permittivity $\varepsilon = 4.7$, the calculated angle was 97.6, 101.3, 75.5 and 77.4° in *E* conformers of **1-4**, respectively. The shielding of the formyl proton by the naphthyl ring is negligible in the *Z* conformation, however, other factors may affect the respective proton NMR shift. For instance, the shift of the formyl proton signal to the low field in compound **4** (Table 2) can be attributed to the weak intramolecular interaction between formyl proton and *tert*-butyl group.

Table 2. Chemical Shifts (δ, ppm) of Formyl Proton Relative to Tetramethylsilane (TMS).

Compound	$CDCl_3$	$C_2D_2Cl_4$	$CD_3C(O)CD_3$	CD_3OD	DMSO-d6
1 *E*	8.23	8.19	8.18	8.17	8.17
1 *Z*	8.58	8.50	8.56	8.53	8.52
2 *E*	8.36	8.32	8.31	8.31	8.30
2 *Z*	8.52	8.47	8.53	8.51	8.48
3 *E*	8.16	8.10	8.10	8.10	8.06
3 *Z*	8.67	8.58	8.64	8.62	8.58
4 *E*	8.18	8.13	8.10	8.10	8.05
4 *Z*	8.96	8.88	8.94	8.92	8.88

From the data presented in Table 1, the Gibbs energies of equilibria were calculated as follows:

$$\Delta G^0 = -RT\, lnX_Z \qquad (1)$$

The graphical representation of the results (Figure 1) witnesses the existence of an approximately linear relationship between ΔG^0 and ε. This is somewhat unusual as a linear relationship between ΔG^0 and the Kirkwood function $(\varepsilon\text{-}1)/(2\varepsilon+1)$ would be expected from the theoretical considerations[19]. The slopes (a) of the linear relationship $\Delta G^0 = a\varepsilon + b$ appear to be constant for different compounds, indicating the presence of an uniform solvent effect on the equilibria. The intercept (b) is characteristic to the solute molecule. The decrease in the population of the *E* isomer with the increase of the polarity of the solvent may be attributed to the increase in the steric interaction between oxygen atom and the alkyl substituent. Notably, the dimensions of

oxygen atom depend on the state of ionization, e.g., the van der Waals radii are 1.40 Å for O^0 and 1.76 Å for O^-, respectively[18]. The SCRF calculations indicate that in the polar media the amide group is more polarized with increased partial negative charge on the oxygen atom[20]. For instance, the MCa SCRF calculated Mulliken charge in carbonyl oxygen of formamide is -0.418 in $CHCl_3$ (ε = 4.7) and -0.437 in DMSO (ε = 46.8). Hence, this atom is expected to have larger van der Waals radius in high dielectric constant media and, correspondingly, stronger sterical interaction with the rest of the molecule.

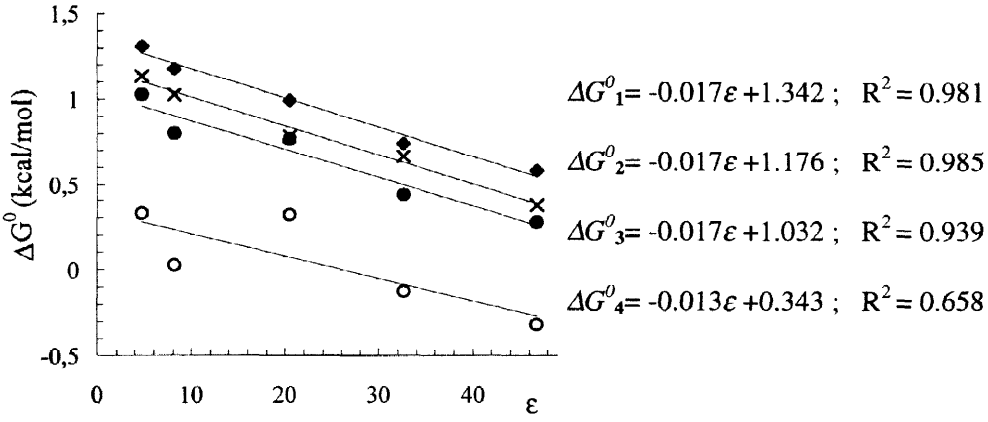


Fig. 1. The relationship between the free energy of conformational equilibrium (1), ΔG^0, and the relative permittivity of the solvent, ε.

The poorer correlation for the compound **4** shows that additional factors besides of the solvent dielectric properties may become important for sterically more restricted compounds. Gerothanassis *et al.*[21] have recently demonstrated using the heteronuclear Overhauser effect spectroscopy (HOESY) that *E*/*Z* isomers of *tert*-butylformamide are a differently hydrated in aqueous solution. They concluded that significant decrease in the population of the *Z* isomer as compared to the *E* isomer should be attributed to the combined effect of reduced hydration of the *Z* amide CO group and out-of-plane deformation of the amide group due to the bulky *tert*-butyl group.

These conclusions are also applicable in the case of *N*-1-naphthylformamides. The AM1 MCa SCRF calculations predict a more substantial out-of-plane torsion of the carbonyl group from amide plane in the *E* conformation as compared to the *Z* conformation. For instance, the respective torsion angle is 26.9, 22.3, 26.8 and 27.5° in *E* forms, and 0.03, 4.60, 1.23 and 0.87° in *Z* forms of **1**-**4**, respectively.

The HOESY studies by Gerothanassis[21] were carried out in aqueous solutions and, therefore, it is difficult to predict how the differential solvation would be affected by the size or shape of the solvent molecules. The difference in the size and shape of solvent molecules could be the additional factor leading to the poor correlation between ΔG^0 and ε for the compound **4**.

We have also examined the dependence of the X_Z on the temperature. The observed trend is consistent with the dependence of ε on temperature. In dimethylsulfoxide (DMSO), the *Z/E* ratio of compound **4** was found to be 1.49, 1.43 and 1.32 at 35, 50 and 75°C, respectively. Thus, the decrease of ε with increase of temperature is accompanied with the shift of the conformational equilibrium in favour of the *E* form.

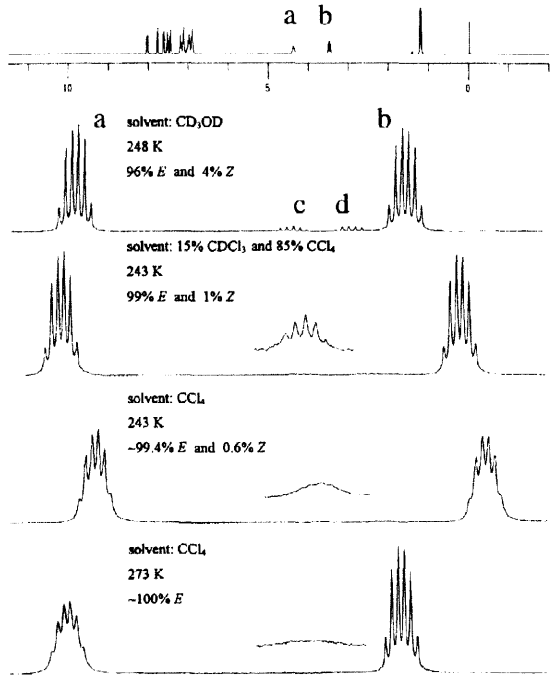


Fig. 2. The NMR signals (a,b,c and d) of the methylene protons of the ethyl group of compound **5** in different solvents. The increased image of the down-field band of minor conformer (c) is shown additionally. The full spectrum of compound **5** (recorded in tetrachloromethane at 273K) is presented on the top.

Therefore, our results suggest that the variation of temperature and solvent could enable to observe experimentally the minor conformers at amide bonds (cf. Figure 2). For instance, in the case of *N*-ethyl-*N*-1-naphthylbenzamide (**5**), only one conformer (*E*) is experimentally observable in low polarity solvents. However, significant population (4%) of the minor conformer (*Z*) was recorded in methanol at low temperatures.

Semiempirical calculations.

The quantum-chemical calculations were carried out at the semiempirical level using Austin Model 1 (AM1)[13] parameterisation. The non-specific solvation effects were described using the self-consistent reaction field (SCRF) approach[14-16,22-23]. The single-cavity self-consistent reaction field (SCa SCRF) model performed poorly due to the relatively large size and flexibility of the title compounds. The calculated solvation energies were too small and as a result the calculated ratio of amide conformers was very little dependent on the solvent polarity. The more realistic estimate of the solvation energy of *N*-1-naphthylamides was obtained using the

multi-cavity self-consistent reaction field (MCa SCRF) model. Indeed, this method described the observed conformational equilibria changes better, but still only qualitatively (cf. Fig. 3).

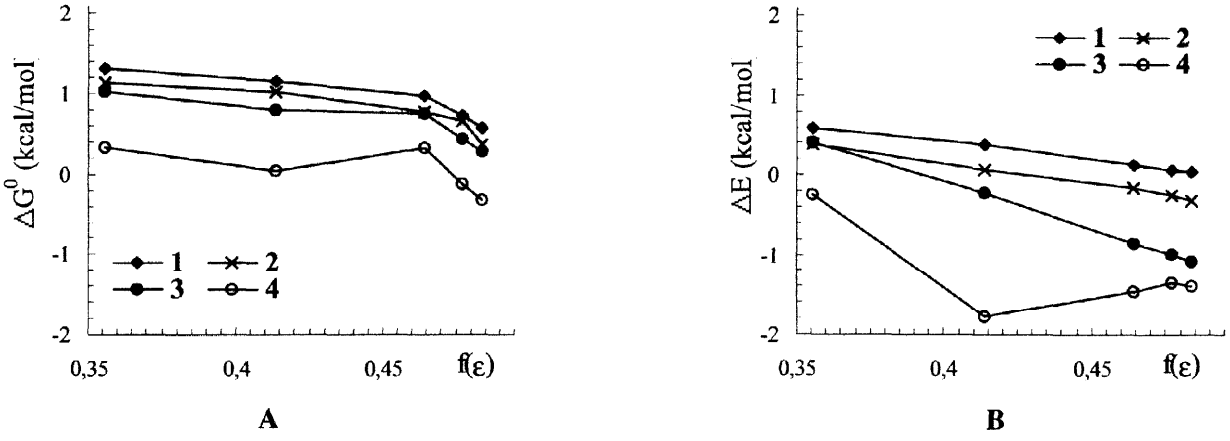


Fig. 3. The relationship of experimental ΔG^0 (Eq. (1)), **A**, and AM1 MCa SCRF calculated ΔE (kcal/mol), **B**, on the Kirkwood-Onsager function, $f(\varepsilon)=(\varepsilon-1)/(2\varepsilon+1)$.

Consequently, our results indicate that the electrostatic reaction field model alone is not sufficient to describe the solvent effect on the conformational equilibria at the amide bond. The methods that reflect the molecular dynamics and the specific solvent-solute interactions should be applied and will be considered by us in further studies.

CONCLUSIONS

The present study reveals that the solvent effect on the conformational equilibria of amides involves a simultaneous influence of the non-specific and specific solute-solvent interactions. In the sterically hindered *N*-1-naphthylamides, the relative stability of the *Z* isomer increases with the increase of polarity of the solvent. The free energy of the respective *E*/*Z* conformational equilibrium is linearly related to the relative dielectric permittivity of the solvent. The discrepancy between the experimental data and the results of self-consistent reaction field calculations indicates that this dielectric effect cannot be explained within the simple Kirkwood-Onsager electrostatic model. However, the quantum-chemical calculations revealed a substantial out-of-plane deformation of the carbonyl group in the *E* isomers. Such deformation leads to the different solvation in *E* and *Z* isomers, similar to that observed in the case of *tert*-butylformamide. Thus, the solvent effect upon the conformational equilibrium in *N*-alkyl-*N*-1-naphthylformamides is determined by the combination of the nonspecific interaction of the solute molecules with the dielectric medium and the differential solvation of the *E* and *Z* isomers by adjacent solvent molecules.

EXPERIMENTAL

Compounds **1-4** were synthesised by formylation of respective *N*-alkyl-*N*-1-naphthylamines with the formic acid. The detailed description of the syntheses and the spectral characteristics of compounds obtained have been reported elsewhere[11]. *N*-ethyl-*N*-1-naphthylbenzamide (**5**) was prepared by reacting of benzoyl chloride with *N*-ethyl-1-naphthylamine for 48 h at room temperature. Compound **5** was identified as follows: ^{1}H NMR (CD_3OD, TMS, 248 K, 400 MHz, δ (ppm)) 1.086 (t, 3H, CH_3(min), J 7.1), 1.235 (t, 3H, CH_3(maj), J 7.1), 3.559 (m, 1H, CH_2(maj)), 3.702 (m, 1H, CH_2(min)), 3.870 (m, 1H, CH_2(min)), 4.452 (m, 1H, CH_2(maj)), 6.99-8.05 (m, 12H, ArH) (cf. Fig. 2).

^{1}H NMR spectra were recorded on JEOL LAMBDA 400 and ALPHA 500 instruments in the deuterated solvents at 25°C. The variable temperature measurements were performed on the ALPHA 500 spectrometer.

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