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On the conformation of the cellulose solvent *N*-methylmorpholine-*N*-oxide (NMMO) in solution

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Abstract

The *N*-oxide group of the cellulose solvent *N*-methylmorpholine-*N*-oxide showed a strong preference for the axial position compared with *N*-methyl as determined by NMR experiments and computational studies. In solvents with negligible solvent–solute interaction, about 95% of the NMMO molecules obtained a typical chair conformation with an axial N–O (**1**) while 5% had an equatorial N–O (**2**) at room temperature (25 °C). Other conformations (boat and twist) are energetically largely disfavored. *N*-Benzylmorpholine-*N*-oxide was prepared as reference compound possessing 100% axial N–O. Aprotic solvents of increasing polarity slightly shifted the conformation equilibrium towards the more polar conformer **2**. The effect of protic solvents, capable of forming H-bonds, was more pronounced, with water increasing the percentage of **2** to 25% of the total population. Addition of sugar model compounds reversed this effect, so that formation of **2** was suppressed and exclusively **1** was found, indicating a strong interaction between the latter conformer and the carbohydrate.

Keywords: *N*-Methylmorpholine-*N*-oxide; Conformation; Cellulose

1. Introduction

Apart from being widely applied as an oxidant in organic synthesis [1], *N*-methylmorpholine-*N*-oxide (NMMO) has found major interest due to its ability to dissolve cellulose [2,3]. Because of this remarkable property, it is nowadays used as a bulk solvent in industrial fiber-making processes (Lyocell process) [4,5]. The dissolution of cellulose in NMMO/water mixtures is a physical process that does not require chemical derivatization of the solute. This is in contrast to conventional approaches to cellulose fiber production, all of which employ chemical derivatization of cellulose to obtain soluble and spinnable dopes, for instance the viscose process that employs NaOH and CS_2 to obtain alkali-soluble xanthates. In addition to the avoidance of derivatization chemicals, the NMMO-based processes are distinguished by a nearly complete recycling of the solvent [6], which moreover is non-toxic and fully biodegradable [7]. Thus, the Lyocell process emerges as an environmentally benign alternative to the viscose process and similar conventional processes for cellulose fiber production.

The processes occurring on the molecular level during dissolution of cellulose in NMMO remain largely unknown. Swelling and dissolution of cellulose must obviously be caused by a far-reaching rearrangement of the hydrogen-bond networks in the system, meaning breakage of intramolecular and intermolecular H-bonds in cellulose and in NMMO/water, with concomitant formation of new H-bonds between solvent and cellulose. However, these processes are extremely complex, and no individual steps have been identified so far. Computational modeling of the interactions between NMMO and cellulose or cellulose model compounds is a promising way to identify possible contact sites, as for instance the type of preferentially attacked hydroxyl groups along cellulose chains. For those computational studies, the conformational equilibrium, i.e. conformer structure and conformer distribution of NMMO, must be known. In the present work, this information is obtained by a combination of experimental, NMR-spectroscopic and DFT computational studies.

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2. Materials and methods

All chemicals and solvents used were of highest purity available. Computational results reported throughout this paper used conformational search and density functional theory (DFT) methods, as implemented through the Spartan Pro 02 package (Wavefunction Inc., Irvine, CA, USA). The stable minimum conformers were obtained by conformational search, followed by pre-optimization of their geometry by the semi-empirical PM3 method. For full geometry optimization of each conformer structure (**1**–**5**), the widely employed hybrid method denoted by B3LYP [8], which includes a mixture of HF and DFT exchange terms and the gradient-corrected correlation functional of Lee, Yang and Parr [9], as proposed and parametrized by Becke [10], was used, along with the double-zeta split valence basis sets 6-31 + G* [11], which includes diffuse functions. Vibrational analysis was performed on the same level of theory.

^{1}H NMR spectra were recorded at 30013 MHz, ^{13}C NMR spectra at 75.47 MHz at room temperature, with the solvents given in the text and TMS as the internal standard. Chemical shifts are listed in ppm throughout, peaks from two magnetically equivalent carbons are denoted 'd.i.'.

N-Methylmorpholine-*N*-oxide (NMMO). NMMO was recrystallized once from chloroform and twice from acetone to a pure product in long white needles, mp 184 °C (dec.). ^{1}H NMR ($CDCl_3$, 0.1 M): δ 3.11 (dd, 2H, N–CH_{eq}), 3.26 (s, 3H, N–CH_3), 3.38 (dt, 2H, N–CH_{ax}), 3.78 (dd, 2H, O–CH_{eq}), 4.44 (dt, 2H, O–CH_{ax}). For the coupling constants see the running text. ^{13}C NMR ($CDCl_3$, 0.1 M): δ 60.86 (N–CH_3), 61.52 (N–CH_2), 65.72 (O–CH_2).

N-Benzylmorpholine-*N*-oxide (NBnMO, **6**). Benzyl chloride (10 mmol) was added dropwise to a solution of morpholine (20 mmol) in chloroform (100 ml). The mixture was stirred for 30 min at room temperature and refluxed for 2 h. After cooling to 0 °C in ice water and addition of *n*-hexane (50 ml), the white, crystalline precipitate formed (morpholinium chloride) was removed by filtration, and the solvents were evaporated under reduced pressure. The residue, crude *N*-benzylmorpholine, was dissolved in ethanol (50 ml) and hydrogen peroxide (30% in H_2O, 5 ml) was added. The mixture was stirred overnight, excess H_2O_2 was destroyed by slowly adding the reaction mixture to a suspension of MnO_2 (10 mg) in ethanol (5 ml). Removal of MnO_2 by filtration and evaporation of the solvent under reduced pressure provided **7**, which was recrystallized from acetone (24% overall yield, mp 136 °C). ^{1}H NMR ($CDCl_3$, 0.1 M): δ 2.94 (dd, 2H, N–CH_{eq}), 3.53 (dt, 2H, N–CH_{ax}), 3.78 (dd, 2H, O–CH_{eq}), 4.16 (dt, 2H, O–CH_{ax}), 4.43 (s, 2H, N–CH_2–Ph), 7.44 (m, 3H, Ph), 7.58 (m, 2H, Ph). For the coupling constants see the running text. ^{13}C NMR ($CDCl_3$, 0.1 M): δ 62.40 (O–CH_2), 64.40 (N–CH_2), 75.96 (N–CH_2–Ph), 129.46 (Ph, d.i., C-3, C-5), 130.26 (Ph, C-1), 130.80 (Ph, C-4), 134.20 (Ph, d.i., C-2, C-6).

3. Results and discussion

3.1. Conformers of NMMO

NMMO, a tertiary, aliphatic amine *N*-oxide, forms a flexible, fully saturated, six-membered heterocycle [12], the conformation of which can in principle be extracted from NMR experiments. However, for analysis of the NMR spectra—and other analytical data as well—it must be known beforehand how many stable conformers of the molecule exist and which of them are stable enough to contribute to the observed overall property at a specific temperature.

A complete search of the conformational space of NMMO revealed five local minima, corresponding to two chair conformations (**1** and **2**), two boat conformations (**3** and **4**), and one twist conformation (**5**) of the ring system, which is in complete agreement with the expected behavior of an unrestrained, flexible six-membered ring. The two boat conformers and the two chair conformers, respectively, differ in the spatial arrangement of the two substituents at the quaternary nitrogen (O and CH_3), with the oxygen being placed either axially (O_{ax}, **1** and **3**) or equatorially (O_{eq}, **2** and **4**).

The energy differences between the five different conformers were obtained from density functional theory (DFT) computations with full geometry optimization of each structure on the B3LYP/6-31+G* level. It was evident that the energy gap between the two most stable chair conformations **1** and **2** on one side and the two boat and one twist conformation on the other side is so large that at relevant temperatures (i.e. below the decomposition temperature of NMMO at 184 °C) only the two chair conformations **1** and **2** would be occurring in solutions of NMMO,[1] see Fig. 1, the number of molecules of the latter three conformers (**3**–**5**) in an equilibrium mixture thus being negligibly small. The zero point energies difference between the two main conformers **1** and **2** is quite low (0.24 kJ/mol) and so is the difference in entropy ($T\Delta S = 0.145$ kJ/mol at 298 K), so that the contribution of these factors to the total energy difference of 7.6 kJ/mol is negligibly small.

[1] The absolute energy values naturally changed through application of different solvation models. The solvation energy differences between different solvents were in the range of 1.0–3.8 kJ/mol, which is of similar magnitude compared to the energy difference between the two chair conformations, but much smaller than the energy gap between the chair and boat/twist conformers. The ratio of the two chair conformations can thus be well influenced by solvent effects, whereas the energy gap to the two boat forms and the twist form is too large for the solvent to have any noticeable influence. Thus, the qualitative description of the conformer distribution—with the two strongly favored chair conformers being the only conformers present in solution—remains valid independent of the solvent considered.

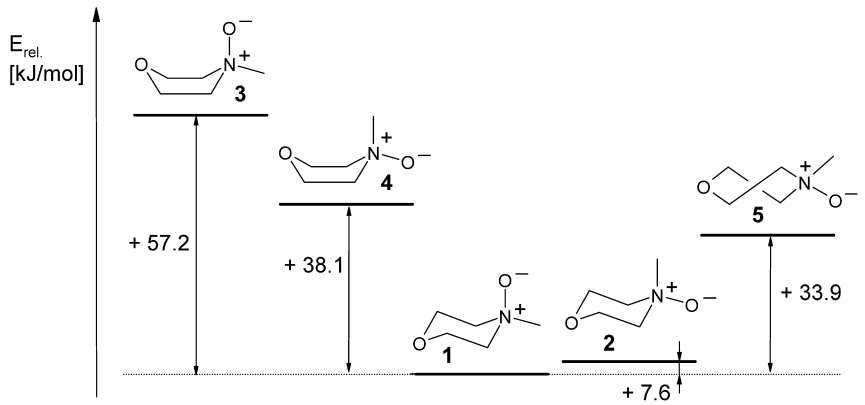

Fig. 1. Conformers of NMMO with calculated energy differences.

3.2. Chair conformations of NMMO in solution

Little is known about the conformational preference of an *N*-oxide function in a system of the type **1** ⇄ **2**, while corresponding *S*-oxide [13,14] or *N*-alkylammonium groups [15] are quite well studied. A conformational analysis of simple flexible six-membered ring systems can be performed by ^{1}H NMR spectroscopy, based on analysis of the proton coupling constants. Assuming the presence of two equilibrium conformers, the observed *trans*-coupling constant $^{3}J_{trans,\mathrm{obs}}$ is a time-averaged value arising from the two conformers which are in fast equilibrium. $^{3}J_{trans,\mathrm{obs}}$ thus represents a superposition of the axial–axial coupling ($^{3}J_{\mathrm{aa}}$) and the equatorial–equatorial coupling ($^{3}J_{\mathrm{ee}}$), see Eq. (1), since the chair-to-chair conversion changes 1,2-bisaxial into 1,2-bisequatorial protons and vice versa. The contribution of the two conformers n_1 and $n_2 = (1 - n_1)$ can thus easily be obtained according to Eq. (2).

$$J_{trans,\mathrm{obs}} = n_1 \times J_{\mathrm{aa}} + (1 - n_1)J_{\mathrm{ee}} \quad (1)$$

$$n_1 = \frac{J_{trans,\mathrm{obs}} - J_{\mathrm{ee}}}{J_{\mathrm{aa}} - J_{\mathrm{ee}}} \quad (2)$$

$^{3}J_{\mathrm{aa}}$ and $^{3}J_{\mathrm{ee}}$, the coupling constants of the 'pure' most stable conformer must be obtained either from computations, from low-temperature NMR on the 'frozen' conformation, or—most conveniently—from ^{1}H NMR spectra of a structurally similar compound which occurs only in one stable conformation. For this purpose, *N*-benzylmorpholine-*N*-oxide (NBnMO, **6**) was synthesized. It can be safely assumed that **6** occurs only in one conformation with the benzyl substituent in the sterically preferred equatorial position, so that the oxygen is always placed axially, and that the changes in the chemical structure—replacement of a proton in the *N*-methyl group by a phenyl ring—do not alter the values of the proton–proton coupling constants within the morpholine spin system. Computations analogous to those performed on NMMO, revealed a large energy gap of 14.9 kJ/mol between the two chair conformers of **6**, yielding a conformer ratio of 99.75%/0.25% in favor of the chair with equatorial benzyl group and axial oxygen. The differences in zero point vibrational energy (0.226 kJ/mol) and entropy ($T\Delta S = 0.207$ kJ/mol at 298 K) are very small, analogous to the chair conformers of NMMO.[2]

In the case of NMMO and NBnMO, the facile NMR approach is hampered by yet another fact. The protons in the morpholine ring are present as methylene groups so that $^{3}J_{trans,\mathrm{obs}}$ is always superimposed by the geminal ^{2}J couplings, which are of similar magnitude. The axial protons of the O–CH_2 and N–CH_2-groups appear consequently as triplets, since the minor differences between $^{3}J_{trans}$ and ^{2}J are not resolved. Due to this influence of the geminal couplings it is thus impossible to obtain accurate values of $^{3}J_{\mathrm{aa}}$ and $^{3}J_{\mathrm{ee}}$ from the simple ^{1}H spectrum of **6**, or $^{3}J_{trans,\mathrm{obs}}$ from the simple ^{1}H spectrum of NMMO. Therefore, double resonance experiments were carried out: saturation of the equatorial proton of O–CH_2 suppressed the geminal coupling, so that the axial proton of this group appeared as duplet of duplets, showing only the large $^{3}J_{\mathrm{aa}}$ and the smaller $^{3}J_{\mathrm{ae}}$ coupling. The same applies to the *N*-methylene group analogously. Repetition of the double resonance experiments with saturation of the axial proton removes the $^{3}J_{trans}$ coupling so that the accurate values of the vicinal couplings can now be retrieved. Finally, the complete system of coupling constants in the morpholine ring system was obtained for NBnMO and NMMO,[3] as summarized in Fig. 2. It shall be emphasized again that *N*-benzylmorpholine-*N*-oxide (**6**), which exists only in one conformer with equatorial benzyl group, is the quasi gauge system, which shows 'pure' coupling constants, while NMMO—and other flexible *N*-alkylmorpholine-*N*-oxides alike—produces coupling constant values that result from

[2] In addition, temperature-dependent NMR (room temperature to 60 °C, in $CDCl_3$) revealed no change in the coupling constants, which proved that at these comparatively low temperatures only one conformer was detectable. At higher temperatures (up to 130 °C, in DMSO-d_6) the J_{trans} coupling constants began to decrease indicating the beginning presence of the second, higher-energy chair conformer. The experimental energy gap of 16.1 kJ/mol, corresponding to a conformer ratio of 99.85%/0.15%, was in good agreement with the computations.

[3] The error of the *J*-values is estimated to range below ± 0.1 Hz, giving a percentage error of maximal ± 1.5% for the conformer composition.

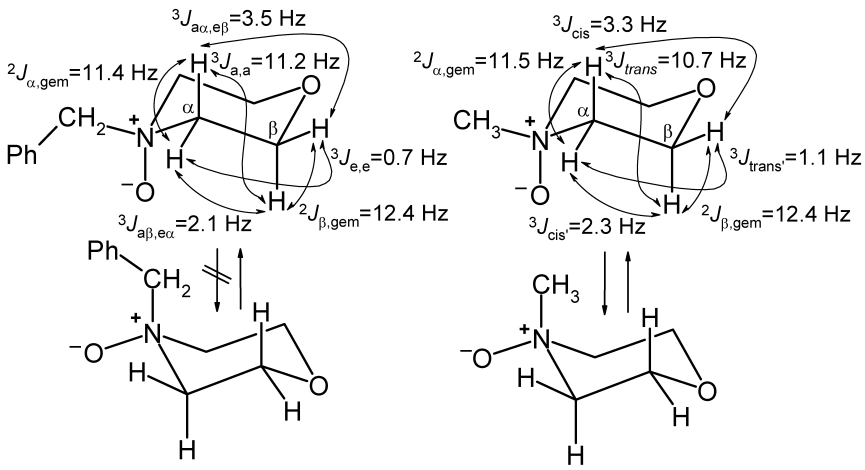

Fig. 2. Coupling constants (Hz) of NMMO (**1** ↔ **2**) and NBnMO (**6**) obtained from proton double resonance experiments (protons shown only in front side of the ring). 0.1 M solution in $CDCl_3$ at 293 k.

an equilibrium of the two conformers **1** and **2**, according to Eq. (1).

Inserting the values ${}^3J_{aa} = 11.2$ Hz, ${}^3J_{ee} = 0.7$ Hz (from NBnMO) and ${}^3J_{trans,obs} = 10.7$ Hz (from NMMO) into Eq. (2), a conformer distribution of $n_1 = 0.952/n_2 = 0.048$ was obtained.[4] Thus, a solution of NMMO in chloroform contains approx. 95% of the chair conformer with axial N–O and 5% of the conformer with equatorial N–O at room temperature. From the conformer ratio R, the energy difference between the two conformers (ΔE_{conf}) can be calculated according to Eq. (3).[5] The value of 7.4 kJ/mol obtained therefrom agrees very favorably with the computational predictions (7.6 kJ/mol), cf. Fig. 1.

$$R = \frac{n_1}{n_2} = \exp\left(\frac{-\Delta E}{RT}\right) \tag{3}$$

It should be noted that the determination of the solvent-dependent conformational equilibrium is in principle also possible by evaluation of chemical shift changes, but is rather ambiguous. Protons β-bisaxially orientated with respect to an *axial* amine-*N*-oxide (or sulphoxide) group are preferentially deshielded compared with the corresponding equatorial protons, while there is no difference between β-bisaxial and β-bisequatorial protons in the case of *equatorial* orientation of the amine oxide function [16]. This low-field shift of the β-protons is caused by the anisotropic effect of the negatively charged axial oxygen. For example, the $O-CH_2$ groups in NMMO resonate at 3.78 (H_{eq}) and 4.44 ppm (H_{ax}) in $CDCl_3$. The signal of β-H_{eq} is largely conformation-independent, whereas β-H_{ax} varies pronouncedly, as it is a time-averaged signal arising from two conformation with axial N–O (with down-field shifted β-H_{ax}) and equatorial N–O (with 'regular' β-H_{ax}). The shift difference $\Delta(\delta_{\beta\text{-H}}) = \delta(\beta\text{-H}_{ax}) - \delta(\beta\text{-H}_{eq})$ is thus sensitive to the conformational equilibrium between **1** and **2**. However, the chemical shifts are influenced by many different parameters which can superimpose the conformational influence,[6] while the coupling constants are determined only by the conformation, i.e. the vectorial nuclear moments of the coupled nuclei in a spin system. Thus, a reliable conformational analysis of NMMO and similar six-membered heterocyclic *N*-oxides, which in addition intends to encompass different solvents and additives, must rely on evaluation of *J*-couplings, instead of chemical shift differences.

3.3. The solvent effect on the chair conformer ratio

The good agreement of the theoretical computations with the experimentally obtained conformer distribution in the solvent chloroform indicates that the interactions of this solvent with the highly polar NMMO are rather weak. However, this situation changes when going to more polar solvents, for which a solvent effect on the conformer distribution between **1** and **2** was expected, with solvation energies in the range of 1–3.8 kJ/mol.[1] This value is large enough to alter the ratio of **1** and **2** (which has an energy barrier of 7.4 kJ/mol), but far too small to effect the participation of a boat (**3**, **4**) or twist (**5**) conformation to any noticeable extent (which have energy barriers of more than 30 kJ/mol, see Fig. 1). For the solvents DMSO, pyridine, *N*,*N*-dimethylacetamide (DMAc), methanol and water, the conformer distribution was determined analogously to the approach described above. The results, as summarized in Table 1, indicate the preference of an axial oxygen (as in **1**) versus an axial Me (as in **2**) in all solvents, which, however, was decreasing with increasing solvent polarity.

[4] The equation $n_1 = \frac{J^{obs}_{trans'} - J_{aa}}{J_{ee} - J_{aa}}$, which is complementary to Eq. (2), yields values of $n_1 = 0.962/n_2 = 0.038$, confirming the accuracy of the approach.

[5] This approach is based on the assumptions that the equilibrium is established, and that there are only two contributing species, which are evidently both fulfilled.

[6] The chemical shift depends on the diamagnetic and paramagnetic shielding terms, which are influenced for instance by substituents, magnetic anisotropy of neighboring groups, ring current effects, H-bonds, solvents, co-solutes and concentrations.

Table 1
Observed NMR coupling constants (Hz) in NMMO and conformer distribution (**1** ⇄ **2**) in different solvents at room temperature (25 °C) calculated according to Eq. (2)

	Chloroform[a]	DMSO	Pyridine	DMAc	Methanol	Water
$^3J_{trans}$	10.7	10.1	10.05	10.25	9.0	8.5
$^3J_{trans'}$	1.1	1.75	1.85	1.65	2.9	3.4
$^3J_{cis}$	3.3	3.3	3.3	3.3	3.1	3.0
$^3J_{cis'}$	2.3	2.4	2.4	2.4	2.5	2.5
$^2J_{\alpha,gem}$	11.5	11.4	11.4	11.5	11.4	11.4
$^2J_{\beta,gem}$	12.4	12.4	12.4	12.4	12.3	12.4
n_1/n_2[b]	0.95/0.05	0.90/0.10	0.89/0.11	0.89/0.11	0.79/0.21	0.76/0.24

[a] see also Fig. 1.
[b] $n_1 + n_2 = 1$, approximated to two decimals, for percentages multiply by 100%.

The solvents in Table 1 were selected as they are used in binary mixtures with NMMO as alternative solvents for cellulosics (with the exception of MeOH). A solvent–solute interaction can be detected by variations in the conformational equilibrium as a function of the nature of the solvent. The highly polar N–O group of NMMO will undergo electrostatic interactions with polar solvents, and the basic exocyclic oxygen of NMMO will act as proton or H-bond acceptor in protic solvents. For steric reasons, such solvation processes are expected to stabilize **2**, possessing the equatorial oxygen, to a larger extent than **1**, with the axial oxygen. It can also be argued that the changes in the equilibrium distributions are due to the difference in the polarity between the two conformers, **2** as the more polar conformer being preferred in more polar solvents.

Simple electrostatic interactions have expectedly only a minor influence on the conformer distribution: the percentages of the minor conformer **2** (with the equatorial oxygen) are in the same range for DMAc (11%), DMSO (10%), and pyridine (11%). The influence of protic solvents and hydrogen bonding on the conformational equilibrium, however, is much more pronounced: going from chloroform to methanol to water, the percentage of **2** increases from 5 to 21–24%. The axial sphere of solvation is thus less effective than the equatorial one, or in other words, the more polar conformer of NMMO with equatorial oxygen, i.e. chair conformer **2**, is increasingly favored in solvents of increasing polarity: in water as the most polar solvent tested it amounts to roughly 1/4 of the total conformer population.

3.4. Interaction of NMMO with simple sugar model compounds

NMMO, used in a binary system with water, is a solvent for cellulose. In preliminary experiments, which used cellobiose as a simple model compound for cellulose, it was investigated whether NMMO–solute interactions have an influence on the equilibrium between the two predominant chair conformers **1** and **2**.

Interestingly, adding an equimolar amount of cellobiose to an 0.1 M NMMO solution in water completely disfavored the more polar conformer **2**, so that 100% of the chair conformation with axial oxygen (**1**) were detected. While in pure water roughly one quarter of NMMO occurred as conformer **2**, this population disappeared upon addition of the sugar model compound.[7] Also in DMSO and methanol the already relatively small percentage of **2** contained in pure NMMO solution faded away completely after addition of the sugar.

This behavior cannot be attributed to an overall decreased solvent polarity, as other additives, such as acetone or methanol even in concentrations up to 30%, have no such effect on the NMMO conformer distribution in water. Even addition of compounds like benzoic acid, gallic acid, or succinic acid—which have stronger polar groups than the added carbohydrates and are capable of forming stronger H-bonds—had a negligible effect on the conformation equilibrium, the changes of which fell within experimental error.

From these preliminary experiments, it can be argued that there is a particularly strong interaction between NMMO and the sugar model compound, which strongly favors **1**, the NMMO chair conformer with axial oxygen (which also is the overall lowest energy conformer). The effect of water, which by virtue of its high polarity significantly increases the percentage of the more polar conformer **2** as compared to less polar solvents, is thus canceled out and even reversed by the presence of the sugar, so that only **1** is found. The experiments thus prove a decreased interaction between NMMO and water caused by the carbohydrate model. Whether this effect can be interpreted as an overall breaking of hydrogen bonds between NMMO and water and simultaneous formation of new hydrogen bonds between NMMO and sugar compound can only be speculated at this point.[8] The fact that

[7] This applies to other carbohydrates, such as glucose, gluconic acid, and methyl cellobioside, as well. In addition, the result seemed to be independent of the concentration as tested with 0.5 and 1.0 M solutions. However, only solutions equimolar in NMMO and additive have been investigated so far.

[8] The strength of this interaction can be estimated by the temperature-dependence of the conformer ratio in the presence of the model compounds. Results will be reported in due course.

glucuronic acid had only a small effect on the conformer equilibrium of NMMO, while glucose had the described large one,[7] might serve as an indication that there is an especially strong interaction of NMMO with the C-6 hydroxyls in the anhydroglucose units, which was also postulated from results of dielectric relaxation spectroscopy studies [17].

Future studies will concentrate on the temperature-dependence of the conformational equilibrium in pure NMMO and in NMMO containing model compounds. In the latter case, it should be possible to estimate the strength of the interaction between NMMO and model compounds.

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