Revealing CSA Tensors and Hydrogen Bonding in Methoxycarbonyl Urea: A combined ^{13}C , ^{15}N and $^{13}\text{C}^{14}\text{N}_2$ Dipolar Chemical Shift NMR and DFT Study

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Dedicated to Prof. Dr. Hans-Heinrich Limbach on the occasion of his 60th birthday

(Received March 28, 2003; accepted June 18, 2003)

Solid State NMR / ^{13}C -CSA / ^{15}N -CSA / Dipolar Chemical Shift NMR / Ab Initio / Hydrogen Bond / Methoxycarbonyl Urea / Chemical Shift Referencing

Methoxycarbonyl urea (MCU), a potential long-term nitrogen fertilizer, is studied by ^{13}C and ^{15}N dipolar chemical shift NMR spectroscopy and *ab initio* calculations. Employing a combination of dipolar chemical shift NMR, selective isotope labeling and *ab initio* gas phase calculations, possible molecular structures and chemical shielding tensors of all ^{15}N nuclei and of two out of the three ^{13}C nuclei were revealed.

Four possible stable configurations of the molecule with different energies were found in the calculations. The CSA tensors were calculated for these configurations. While the calculated ^{13}C (urea) CSA tensor orientation of the configuration with the lowest energy is in good agreement with the experimental tensor orientation, there are pronounced differences between calculated and experimental tensor eigenvalues. These differences are a clear indication of the presence of intermolecular hydrogen bonds in the experimental sample, which are neglected in the gas phase calculations.

Four different possible orientations of the experimental ^{13}C (urea) CSA tensor exist, due to symmetry. This ambiguity is solved by comparison with results from GIAO calculations of the ^{13}C CSA tensor, employing the minimum energy configuration (EEZ). It is found that the orientation, where δ_{11} points approximately in direction of N(imide), δ_{22} approximately in direction of the C=O bond, and δ_{33} is oriented perpendicular to the molecular frame, is adopted in the molecule.

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1. Introduction

In recent years, ^{13}C and ^{15}N solid state NMR spectroscopy has become an important tool for the structure elucidation of organic and bioorganic compounds like peptides and proteins (see *e.g.* Refs. [1–4]. Especially the potential of dipolar solid state NMR for structural investigations under static [5–8], and Magic Angle Spinning conditions [9, 10] has been shown where magnetic dipolar interactions are determined which give direct geometrical information about internuclear distances.

Owing to the axial symmetry of the dipolar interaction, most information about the relative orientation of the coupled nuclei is not accessible directly. This information can be recovered *via* a second interaction like the chemical shift (chemical shielding), a local interaction which depends mostly on the electronic structure close to the nuclei of interest, which is strongly correlated to the molecular structure [11, 12]. Both the isotropic chemical shift (CS) and the chemical shift anisotropy (CSA) are sensitive probes for structural properties of the molecule and they contain information *e.g.* about hydrogen bonding [13] and primary/secondary structures [3].

In contrast to the dipolar interaction, there is no straightforward interpretation of the chemical shift [14]. Instead, one has to resort to quantum chemical *ab initio* calculations of the molecular groups under investigation (see *e.g.* Refs. [12, 15] or to comparison with molecules of closely related structures. For organic molecules of intermediate size, such quantum chemical calculations have only recently achieved a sufficient level of accuracy for allowing a quantitative correlation with experimental data.

It is advantageous to apply a combined analysis of the chemical shift anisotropy and dipolar interaction. This approach allows for an orientation of the dipolar vector in the frame of the chemical shift interaction (see *e.g.* Refs. [3–8, 16]).

In the present study, this technique is employed for the structural characterization of N-methoxycarbonyl urea (MCU). MCU, also known *e.g.* as allophanic acid methylester or methyl N-carbamoyl carbamate, was synthesized in the beginning of the 20th century by Dains and Wertheim [17] and by Biltz and Jeltsch [18]. Some decades later, Johnston and Opliger [19] found MCU in their search for potential anticancer agents. Later MCU was extracted as a natural product from the outer seed coat of *Butea monosperma* (Lam.) Kuntze (Fam. Leguminosae) [20], which is known to possess antifertility activity, and from the roots of *Echinops echinatus* (common name: globe thistle, Fam. Compositae, Asteraceae) [21–23], which are of general medical use (see Ref. [23] and Refs. therein). Additionally, the closely related substance N-ethoxycarbonyl urea is patented by Hoechst as a textile additive and plastics stabilizer [24].

In a recent search for potential new long-term nitrogen fertilizers supported by the BASF AG, MCU and several related urea compounds were

Fig. 1. Primary structure of methoxycarbonyl urea with different ^{13}C and/or ^{15}N labeling schemes. Double arrows mark strong heteronuclear dipolar couplings. The configuration (EEZ) is the global minimum structure from DFT calculations. Lower left box: naming of C and N atoms and of torsional angles.

studied [25]. The simplest urea compounds with the highest nitrogen content are urea ($\text{NH}_2(\text{C}=\text{O})\text{NH}_2$) with 47 mass-% and biuret ($\text{H}[\text{NH}(\text{C}=\text{O})]_2\text{NH}_2$) with 41 mass-%. Both compounds are unsuitable as long time fertilizers. MCU ($\text{NH}_2(\text{C}=\text{O})\text{NH}(\text{C}=\text{O})\text{OCH}_3$, Fig. 1), which is not phytotoxic and which has a 470 times lower molar solubility in water at room temperature than urea has been found to be a good choice as a new long-term nitrogen-fertilizer [25].

Understanding the solubility properties of MCU could help in a more efficient screening of further urea derivatives. For this understanding, knowledge of the molecular configuration and of hydrogen bonding properties of urea derivatives is necessary. Since attempts to obtain this information from diffraction techniques were futile due to the poor crystallization properties of MCU [25], we decided to study non-oriented powder samples by dipolar solid state NMR.

For this dipolar chemical shift NMR study, selective chemical ^{13}C and ^{15}N labeling (chemical editing) is necessary, since the relatively broad CSA signals of different homonuclei in a molecule are usually not resolved. Therefore, unlabeled and specifically ^{13}C and/or ^{15}N -labeled MCU samples were chosen and synthesized. Liquid state NMR experiments are performed on these samples for characterization. *E.g.* several J couplings like $^1J(^{13}\text{C}, ^{15}\text{N})$ are determined.

To simplify the later discussions of J couplings and CSA tensor orientations we precede the study with some considerations concerning the planarity

(in the sense that all heavy atoms of the molecule are in a common plane) of MCU.

Fig. 1 shows the primary structure of MCU. From the amide, urea and ester functions of MCU, all C, N and O atoms apart from the methyl-C atom are expected to be mainly sp^2 hybridized as in urea and biuret [26, 27]. Thus, a planar arrangement is formed (apart from the methoxy-H atoms) and the CN bonds show a partly double bond character.

This assumption is supported by known structures (X-ray, neutron diffraction) of similar molecules as *e.g.* urea [26], biuret ($\cdot 0.6 \text{ H}_2\text{O}$) [27], methoxycarbonyl biuret [25] (MCB- H_2O) and N,N'-diacetyl biuret [28]. Furthermore, molecular modeling and DFT calculations also resulted in a planar molecule for most configurations (see below).

Only in special cases, this planarity is not achieved in similar molecular systems. *E.g.* sterically demanding substituents as phenyl rings can lead to a bending of the molecule determined by X-ray diffraction [29, 30] or a complete substitution of the H atoms with ethyl groups in biuret and triuret leads to a helicity of the whole molecule as found by low temperature NMR spectroscopy [31]. In MCU, no such substituents exist and therefore a planar molecule is most likely. In smaller molecules like N,N-dimethyl formamide, slightly pyramidal configurations around the N atom were determined by gas electron diffraction (GED) [32], but these effects are very small and are thus negligible in the present study.

In the main part of this study, ^{13}C as well as ^{15}N dipolar chemical shift NMR spectra are presented and CSA tensors are extracted. A $^{13}\text{C}^{14}\text{N}_2$ spin system with two heteronuclear $^{13}\text{C}^{14}\text{N}$ dipolar couplings is used for the orientation of the ^{13}C CSA tensor in the molecular frame. Since the detailed theory of an IS_2 spin system ($I = \text{spin } 1/2$, $S = \text{spin } 1$) in the solid state has not been published to our knowledge, it is worked out in the theory section. Due to the symmetry of the dipolar interaction the dipolar CSA calculations do not uniquely specify the orientation of the CSA tensor in the molecular frame. This ambiguity can be solved by DFT calculations, which allow to choose between symmetry equivalent orientations of the CSA tensor.

The remainder of this article is organized as follows. First the theory of a IS_2 spin system in the solid state is developed, then a brief survey of the chemical syntheses is given, followed by the description of our experimental and calculation setup. Next the experimental results and the results of DFT calculations of the molecular structure and of CSA tensors are presented, discussed and finally summarized.

2. Theory

As is well known for a long time, the anisotropic interactions in solid state NMR can be described by second rank tensors, *i.e.* real symmetric 3×3 matrices

(see *e.g.* Refs. [33–37]). For $I = 1/2$ nuclei and non-conducting organic solids, there are the chemical shielding tensor $\vec{\sigma}$, the dipolar interaction tensor $\vec{D}$ and the J -coupling (which, however, can be neglected in our systems). For $S = 1$ nuclei additionally the quadrupolar tensor interaction is present which is neglected in this study because, in first order, it does not contribute to the I -spin spectrum.

Because of the strong ^{13}C -CSA interaction, only strong (*i.e.* single bond) dipolar couplings contribute significantly to dipolar chemical shift NMR spectra, all dipolar couplings between two spins separated by more than one bond can be neglected in this study.

Thus for a three spin system IS_2 , the relevant solid state spin Hamiltonian $\hat{H}$ can be written as:

$$\begin{aligned} \hat{H} = & \gamma_I \vec{B}(1 - \vec{\sigma}_I) \hat{I} + \gamma_S \vec{B}(1 - \vec{\sigma}_{S1}) \hat{S}_1 + \hat{I} \vec{D}_1 \hat{S}_1 + \gamma_S \vec{B}(1 - \vec{\sigma}_{S2}) \hat{S}_2 + \hat{I} \vec{D}_2 \hat{S}_2 \\ & + \hat{S}_1 \vec{D}_{\text{hom}} \hat{S}_2. \end{aligned} \quad (1)$$

Since the homonuclear dipolar interaction between the two nitrogens in MCU is much smaller than the heteronuclear dipolar and chemical shift interactions, the Hamiltonian can be further simplified by omitting the homonuclear dipolar coupling (last term in Eq. (1)).

The matrix elements of the two heteronuclear dipolar interaction tensors are given as [36]:

$$\vec{D}_{p,mn} = -\frac{\mu_0}{4\pi} \hbar \gamma_I \gamma_S \frac{3 (\vec{e}_m \cdot \vec{r}/r) (\vec{e}_{n,p} \cdot \vec{r}_p/r_p) - \vec{e}_m \cdot \vec{e}_{n,p}}{(r_p)^3} \quad (2)$$

with $m, n = x, y, z$; $p = 1, 2$.

In high magnetic field only the secular part of the interaction is effective. If B_0 is pointing in the z -direction one obtains :

$$\begin{aligned} \hat{H} = & \gamma_I B_0 (1 - \sigma_{Izz}) \hat{I}_z + \gamma_S B_0 (1 - \sigma_{S1zz}) \hat{S}_{1z} + \hat{I}_z D_{1zz} \hat{S}_{1z} \\ & + \gamma_S B_0 (1 - \sigma_{S2zz}) \hat{S}_{2z} + \hat{I}_z D_{2zz} \hat{S}_{2z}. \end{aligned} \quad (3)$$

All terms in this Hamiltonian commute and it is diagonal with the energy eigenvalues calculated as:

$$\begin{aligned} E_q = & f_a \frac{1}{2} \gamma_I B_0 (1 - \sigma_{Izz}) + f_b \frac{1}{2} \gamma_S B_0 (1 - \sigma_{S1zz}) + f_c \frac{1}{4} D_{1zz} \\ & + f_d \frac{1}{2} \gamma_S B_0 (1 - \sigma_{S2zz}) + f_e \frac{1}{4} D_{2zz}. \end{aligned} \quad (4)$$

The factor f_a corresponds to $+1$, or -1 , and the factors f_n ($n = b, c, d, e$) correspond to $+1$, 0 , or -1 (denoted in Table 1 as $+$, 0 and $-$, respectively) and there exist eighteen energy eigenvalues (s. Table 1).

Table 1. Calculation of the eighteen energy eigenvalues of the IS_2 spin system according to Eq. (4). The corresponding wave functions are given in the second column. The factor f_a corresponds to +1, or -1, and the factors f_n ($n = b, c, d, e$) correspond to +1, 0, or -1 (denoted here as +, 0 and -, respectively). For each of the factors f_n , the affiliation to spin I , S_1 or S_2 and to the CS or the dipolar interaction term is given.

q	$ m_I m_{S1} m_{S2}\rangle$	f_a [I , CS]	f_b [S_1 , CS]	f_c [S_1 , D]	f_d [S_2 , CS]	f_e [S_2 , D]
1	$ \alpha++\rangle$	+	+	+	+	+
2	$ \alpha+0\rangle$	+	+	+	0	0
3	$ \alpha+-\rangle$	+	+	+	-	-
4	$ \alpha 0+\rangle$	+	0	0	+	+
5	$ \alpha 00\rangle$	+	0	0	0	0
6	$ \alpha 0-\rangle$	+	0	0	-	-
7	$ \alpha-+\rangle$	+	-	-	+	+
8	$ \alpha-0\rangle$	+	-	-	0	0
9	$ \alpha--\rangle$	+	-	-	-	-
10	$ \beta++\rangle$	-	+	-	+	-
11	$ \beta+0\rangle$	-	+	-	0	0
12	$ \beta+-\rangle$	-	+	-	-	+
13	$ \beta 0+\rangle$	-	0	0	+	-
14	$ \beta 00\rangle$	-	0	0	0	0
15	$ \beta 0-\rangle$	-	0	0	-	+
16	$ \beta-+\rangle$	-	-	+	+	-
17	$ \beta-0\rangle$	-	-	+	0	0
18	$ \beta--\rangle$	-	-	+	-	+

The allowed transitions between energy levels ($a-b$) for spin I are (1–10), (2–11), (3–12), (4–13), (5–14), (6–15), (7–16), (8–17), (9–18) with the corresponding transition frequencies:

$$\nu_{ab}^I = \gamma_I B_0 (1 - \sigma_{Izz}) + \frac{i}{2} D_{1zz} + \frac{j}{2} D_{2zz} \quad (5)$$

with $i, j = -1, 0, 1$ and a, b according to Table 2.

For ν_{ab}^I , the values for i and j correspond to the transitions between the eigenvalues given in Table 2.

The tensors $\vec{D}$ and $\vec{\sigma}$ can be expressed from their diagonal representation in their principal axis system via a rotation $R(\alpha\beta\gamma)$, which can be parametrized using the Euler angles $(\alpha\beta\gamma)$. In general the CSA and the dipolar interaction tensor will have different principal axis systems. Thus for each tensor, a separate set of Euler angles is necessary for the transformation.

$$\begin{aligned} \vec{D} &= R(\alpha^D \beta^D \gamma^D) \vec{D}_{\text{PAS}} R(\alpha^D \beta^D \gamma^D)^{-1} = R_D \vec{D}_{\text{PAS}} R_D^{-1} \\ \vec{\sigma} &= R(\alpha^C \beta^C \gamma^C) \vec{\sigma}_{\text{PAS}} R(\alpha^C \beta^C \gamma^C)^{-1} = R_C \vec{\sigma}_{\text{PAS}} R_C^{-1}. \end{aligned} \quad (6)$$

However, it is always possible to first transform the dipolar interaction tensor from its principal frame into the frame of the CSA tensor (D_{CSA}) by

Table 2. Values in Eq. (5) for i and j (+, 0, − represent +1, 0, −1) corresponding to the transitions between energy levels a and b .

a	b	i	j
1	10	+	+
2	11	+	0
3	12	+	−
4	13	0	+
5	14	0	0
6	15	0	−
7	16	−	+
8	17	−	0
9	18	−	−

a rotation R_{CD} and then do a common transformation into the lab frame:

$$\vec{D} = R_C R_{\text{CD}} \vec{D}_{\text{PAS}} R_{\text{CD}}^{-1} R_C^{-1} = R_C \vec{D}_{\text{CSA}} R_C^{-1}. \quad (7)$$

The dipolar tensors in the CSA frame, $\vec{D}_{1,\text{CSA}}$ and $\vec{D}_{2,\text{CSA}}$, and the CSA tensor $\vec{\sigma}$ can then be combined to effective shielding tensors

$\vec{\Sigma}_{\text{PAS}}^{ij}$ in the PAS frame of $\vec{\sigma}$. These effective tensors are in general no longer diagonal:

$$\begin{aligned} \vec{\Sigma}_{\text{PAS}}^{ij} &= \vec{\sigma}_{\text{PAS}} + i \vec{D}_{1,\text{CSA}} + j \vec{D}_{2,\text{CSA}} = \vec{\sigma}_{\text{PAS}} + i R_{1,\text{CD}} \vec{D}_{1,\text{PAS}} R_{1,\text{CD}}^{-1} \\ &\quad + j R_{2,\text{CD}} \vec{D}_{2,\text{PAS}} R_{2,\text{CD}}^{-1} \end{aligned} \quad (8)$$

with $i, j = -1, 0, 1$.

Transforming the effective interaction tensors into the lab frame, the equation for the transition frequencies for spin I can be rewritten as:

$$\nu_{a,b}^I = \gamma_I B_0 \left(1 - \vec{\Sigma}_{zz}^{I;i,j} \right) \quad (9)$$

with $i, j = -1, 0, 1$, and a, b according to Table 2.

While in single crystals only two lines for each spin are observable, in a powder the average over all possible orientations has to be taken into account. Due to the axial symmetry of the magnetic field, it is sufficient to integrate over two angles (ϑ, ϕ) only. Thus, assuming that T_2 is the transversal relaxation time, which for simplicity is assumed to be orientational independent, the spectrum can be calculated as

$$I(\nu) = \int_0^\pi d\vartheta \sin(\vartheta) \int_0^{2\pi} d\phi \left(\sum_{i,j} \frac{T_2^I}{1 + 4\pi^2 T_2^I (\nu - \nu_{a,b}(\vartheta, \phi))^2} \right) \quad (10)$$

with $i, j = -1, 0, 1$ and a, b according to Table 2.

Fig. 2. ^1H chemical shift of H(imide) (squares), H(amide,b) (circles) and H(amide,a) (triangles) in MCU depending on the composition of the solvent THF/DMSO ('NMR titration'). For the signal, which shows the weakest dependency on the solvent composition (circles), a linear fit is performed (straight line) as guide of the eye. For the other two signals, exponential associates are fitted to the data as guides of the eye in order to clarify the trend of the chemical shifts.

The result is for each I spin a superposition of nine powder patterns, where the singular values of the two patterns are determined by the principal values of the tensor $\vec{\Sigma}^{I:i,j}$. As the effective interaction tensor $\vec{\Sigma}^{I:i,j}$ depends, *via* the rotations $R_{1,\text{CD}}$ and $R_{2,\text{CD}}$, on the mutual orientations of the chemical shift and dipolar interaction tensors, it is possible to orient the dipolar vectors in the coordinate frame of the shielding interaction by simulating the I spin spectrum (using Eq. (10)).

3. Experimental

3.1 Sample preparation and characterization

3.1.1 Labeling schemes

For the determination of $J(^{13}\text{C}, ^{15}\text{N})$, the CSA tensors of selected ^{13}C and ^{15}N spins and the orientation of these tensors in the molecular frame, several differently isotope labeled MCU samples were used (see Fig. 2): (a) ^{15}N (amide)-MCU for the determination of the ^{15}N (amide) CSA tensor, (b) $^{13}\text{C}^{15}\text{N}_2$ -MCU with ^{15}N in the amide and imide positions and a ^{13}C spin in the methoxy position for the ^{15}N (imide) and ^{13}C (methoxy) CSA tensors, and (c) $^{13}\text{C}_2$ -MCU with ^{13}C in the urea and methoxy positions for the determination of the ^{13}C (urea) CSA tensor and its orientation in the molecular frame by two $^{13}\text{C}^{14}\text{N}$ dipolar couplings (indicated as double arrows in Fig. 2c).

All unlabeled and spin labeled (^{13}C , ^{15}N)-MCU samples were synthesized in house. Enrichment in ^{13}C and ^{15}N is between 97% and 99%. Triuret ($\text{H}[\text{NH}(\text{C}=\text{O})]_3\text{NH}_2$) has been obtained as a side product which was removed by recrystallization from water. The absence of solvent molecules in the micro-crystalline material was controlled by elementary analysis (water) and ^{13}C solid state NMR spectroscopy (organic solvents).

3.1.2 Sample synthesis

(1) Methoxycarbonyl isocyanate

1.2 mole oxalylchloride are dissolved in 1,2,4-trichlorobenzene. 1 mole urethane is added in portions within 30 min holding the temperature below 10°C . The mixture is stirred for 30 min at room temperature, heated up to 70°C within 2 h and then stirred for 1 h at 70°C . The product is distilled.

b.p. 98°C , colorless liquid, intense smell

^1H NMR (CDCl_3): δ (ppm) = 3.70 (s, 3 H, CH_3).

^{13}C NMR (CDCl_3): δ (ppm) = 149.7 (s, 1 C, $\text{N}-\text{C}=\text{O}$); 129.9 (s, 1 C, $\text{N}=\text{C}=\text{O}$), 55.1 (s, 1 C, CH_3).

(2) Methoxycarbonyl urea

Gaseous ammonia produced in a vacuum line from 1 g (18 mmol) ammonium chloride and a concentrated aqueous solution of potassium hydroxide is solved in a solution of 0.9 g (9 mmol) methoxycarbonyl isocyanate (1) in 100 ml dry tetrahydrofuran. The mixture is stirred for 2 h at room temperature, then the solvent is removed by distillation. The product is recrystallized from water.

m.p. 214°C (decomp., Ref. [20] $207\text{--}209^\circ\text{C}$, Ref. [38] $215\text{--}216^\circ\text{C}$, Ref. [39] 221°C after sublimation), colorless needles

^1H NMR ($\text{DMSO}-d_6$): δ (ppm) = 9.86 (s, 1 H, $\text{NH}(\text{imide})$); 7.20/7.16 (2 s, 2 H, $\text{NH}_2(\text{amide})$); 3.64 (s, 3 H, $\text{CH}_3(\text{methoxy})$).

^{13}C NMR ($\text{DMSO}-d_6$): δ (ppm) = 154.9 (s, C(carbamate)); 153.5 (s, C(urea)); 52.2 (s, C(methoxy)).

Elementary analysis: C 30.49 (calc. 30.51), H 4.83 (calc. 5.12), N 23.74 (calc. 23.72).

(3) $^{15}\text{N}(\text{amide})$ Methoxycarbonyl urea

Same procedure as for (2), but using ^{15}N ammonia instead of unlabeled ammonia. ^{15}N Ammonia was produced from ^{15}N ammonium chloride (99% ^{15}N , purchased from Chemotrade, Leipzig).

^1H NMR ($\text{DMSO}-d_6$): as for (2), but $\text{NH}_2(\text{amide})$: $^1J(^1\text{H}, ^{15}\text{N}) = 91$ Hz each.

^{13}C NMR ($\text{DMSO}-d_6$): as for (2), but C(urea): $^1J(^{13}\text{C}, ^{15}\text{N}) = 21$ Hz).

(4) $^{13}\text{C}(\text{methoxy})^{15}\text{N}_2$ Methoxycarbonyl urea

This procedure is similar to the one described in Ref. [38] but performed here with labeled reactants in smaller portions:

32 mmol $^{15}\text{N}_2$ urea (99.2% ^{15}N , purchased from Witega, Berlin) are dried *in vacuo*. 11 mmol ^{13}C (methoxy) chloroformic acid methyl ester are added (^{13}C (methoxy) chloroformic acid methyl ester is synthesized similarly to the procedure given for other chloroformic acid alkyl esters in Ref. [40] using ^{13}C methanol [99.2% ^{13}C purchased from Isotec, USA]). The mixture is heated for 1 h at 100 °C. The product is filtered and recrystallized from water.

^1H NMR (DMSO- d_6): as for (2), but NH(imide): $^1J(^1\text{H}, ^{15}\text{N}) = 91$ Hz; NH_2 (amide): $^1J(^1\text{H}, ^{15}\text{N}) = 91$ Hz each; CH_3 (methoxy): $^1J(^1\text{H}, ^{13}\text{C}) = 150$ Hz.

^{13}C NMR (DMSO- d_6): as for (2), but C(carbamate): $^1J(^{13}\text{C}, ^{15}\text{N}(\text{imide})) = 23.7$ Hz, $^2J(^{13}\text{C}, ^{13}\text{C}(\text{methoxy})) = 1.9$ Hz; C(urea): $^1J(^{13}\text{C}, ^{15}\text{N}(\text{amide})) = 21.5$ Hz, $^1J(^{13}\text{C}, ^{15}\text{N}(\text{imide})) = 17.4$ Hz; CH_3 (methoxy): $^1J(^1\text{H}, ^{13}\text{C}) = 147.6$ Hz.

(5) $^{13}\text{C}_2(\text{urea}, \text{methoxy})$ Methoxycarbonyl urea

Same procedure as for (4), but using ^{13}C urea (99.2% ^{13}C , purchased from Chemotrade, Leipzig) instead of $^{15}\text{N}_2$ urea.

^1H NMR (DMSO- d_6): as for (2), but CH_3 (methoxy): $^1J(^1\text{H}, ^{13}\text{C}) = 150$ Hz.

^{13}C NMR (DMSO- d_6): as for (2).

3.2 Liquid state NMR spectroscopy

The liquid state NMR 1D spectra were recorded on a Bruker AMX 500 NMR spectrometer at room temperature at a magnetic field of 11.7 T, *i.e.* at resonance frequencies of 500.0 MHz for ^1H , 125.7 MHz for ^{13}C , and 50.7 MHz for ^{15}N . The deuterated solvent was used for deuterium-locking. For the chemical shift calibration of the NMR spectra, TMS (^1H , ^{13}C) or a sample of neat liquid nitromethane (^{15}N) were employed as external standards.

3.3 Solid state NMR spectroscopy

All solid state NMR measurements were performed at room temperature on a Varian InfinityPlus NMR spectrometer operating at a field of 14 T. Resonance frequencies are 599.97 MHz for ^1H , 150.87 MHz for ^{13}C , and 60.79 MHz for ^{15}N . For all experiments, a triply tuned MAS-probe was employed (Chemagnetics 5 mm probe of T3 type). The powdered samples were packed into zirconium oxide rotors. For MAS experiments, the sample spinning frequency was adjusted in the range of 1 to 10 kHz, respectively, and was stabilized to *ca.* ± 2 Hz. Typical π pulse lengths were 9.7 μsec for the ^{13}C channel and 12.0 μsec for the ^{15}N channel. For 1D MAS-spectra, the CPMAS technique [41–45] was combined with a rotor synchronized Hahn echo [46], which eliminates the dead time of the probe. Residual $^1\text{H}\text{X}$ dipolar couplings were suppressed using TPPM decoupling [47, 48] with a B_1 field of 50 kHz. Ramped amplitude cross-polarization (RAMP-CP) [49] was used to enhance the CP efficacy at higher spinning rates. Owing to the relatively long spin-lattice relaxation times typical relaxation delays between 1 and 5 min were employed. For

each FID between 200 and 1500 scans were accumulated. The typical time for recording of the static spectrum of a sample was about one day.

Processing of spectra and simulations are performed employing laboratory written programs in MATLAB [50] code.

3.4 DFT calculations

3.4.1 Calculation methods

All quantum chemical calculations of geometry, energy and vibrations were carried out with the GAUSSIAN98 program [51] on a Origin 2000 (SGI) computer with 16 processors MIPS R10000 and three Gigabyte memory. Evaluation of the output was accomplished using laboratory written programs in MATLAB [50] code.

The *ab initio* methods used are Hartree–Fock (HF) and density functional theory (DFT) with the B3LYP functional [52, 53], combined with standard basis sets 3-21G or 6-31G for initial geometry optimizations and then 6-31++G(d,p) for modeling of the hydrogen bonding. Only results from B3LYP calculations are reported since the results from HF calculations are comparable. After each geometry optimization, a calculation of the vibrational frequencies was performed in order to ensure that the calculated geometry corresponds to a (local) minimum and not a saddle point on the energy hypersurface.

For chemical shielding calculations, the Gauge Included Atomic Orbital (GIAO) [54, 55] approach was used in conjunction with the 6-31++G(d,p) and 6-31++G(2d,2p) basis sets with the DFT method [56].

The calculated chemical shielding values σ were converted to chemical shifts δ using the absolute chemical shielding of TMS at 188.1 ppm and the absolute chemical shielding of ammonium chloride at 206.7 ppm (see next chapter).

3.4.2 Referencing

The principal components of the calculated chemical shielding tensors are absolute shielding values, *i.e.* $\sigma = 0$ corresponds to the shielding of the “bare” nucleus. The chemical shielding σ can be converted to chemical shift δ by $\delta = A - \sigma$ (Eq. (11)). There are four solutions for determining the parameter A in this conversion:

- a chemical shielding is used which is obtained experimentally [57]
- a chemical shielding is used which is calculated for a standard like tetramethylsilane (TMS) [57]
- a chemical shielding is used which is calculated for a rather isolated nucleus in the molecule of interest. This nucleus can be *e.g.* a methylene-C in a long alkyl chain, where shifts due to charge distribution, intermolecular interactions etc. can be neglected (‘internal standard’) [58]

Table 3. Experimental ^{13}C and ^{15}N chemical shifts δ of ‘standards’ relative to TMS and nitromethane. *: see section about chemical shift referencing for literature references.

substance	δ/ppm	reference substance and lit.	σ/ppm (calc.)	σ/ppm (exp.)
TMS	0		182.3	188.1, Ref. [66]
adamantane (solid)	29.5 (CH)	TMS [88]	157.5	
	38.6 (CH_2)	TMS [88]	150.7	
methane (gas)	-1.8	TMS [89] with $\sigma(\text{benzene})$ = 129 ppm	197.9	
ammonia (gas)	-398.9	CH_3NO_2 (neat liquid)*	267.3	264.5, Ref. [61]
	-60.8	NH_4Cl (solid)*		

- a series of shielding tensors is calculated for a ‘family’ of molecules fitting the data to a linear correlation $\delta = a - b\sigma$ (Eq. (12)) [59].

No conversion is necessary, if (a) only the shape of a CSA tensor, *i.e.* anisotropy and asymmetry, and the orientation of the CSA tensor in the molecular frame are studied, or (b) if the relative chemical shieldings/shifts of two nuclei in the molecule are compared with respect to a change of the molecular structure (*e.g.* different configurations of the molecule, with/without an adjacent molecule etc.).

In this study, the value of the parameter A is obtained by the first and second solution from the list above. For the second solution, chemical shifts are calculated for the ‘standard compounds’ TMS, adamantane and methane for ^{13}C and ammonia for ^{15}N . The experimental chemical shifts of these standards to TMS and nitromethane, our calculated chemical shieldings σ for these standards and some experimental values from literature are given in Table 3.

For ammonia, some conversions had to be applied. The following values are used which are calculated by taking the mean values of all literature data available (no margins of error are given in most of these publications):

- $\delta(\text{NH}_3, \text{liq.}) - \delta(\text{NH}_3, \text{gas.}) = 17.7 \text{ ppm}$ from 15.9 ppm [60] and 19.47 ppm [61]
- $\delta(\text{CH}_3\text{NO}_2, \text{liq.}) - \delta(\text{NH}_3, \text{liq.}) = 381.2 \text{ ppm}$ from 380.2 ppm [62], 380.4 ppm (note the misprint of 380.9 ppm in this ref.) [61], 381.9 ppm [63], 382.1 [64]
- $\delta(\text{CH}_3\text{NO}_2, \text{liq.}) - \delta(\text{NH}_4\text{Cl}, \text{solid}) = 338.1 \text{ ppm}$ [65].

Thus from calculations of ^{13}C chemical shieldings, $A(^{13}\text{C}, \text{TMS}) = 182.3 \text{ ppm}$ (using TMS), $A(^{13}\text{C}, \text{TMS}) = 188.2 \text{ ppm}$ (using the mean of both adamantane signals), or $A(^{13}\text{C}, \text{TMS}) = 196.1 \text{ ppm}$ (using methane). Because

of the non-uniform results, the experimental chemical shielding of TMS [66] is used for the parameter A , *i.e.* $A(^{13}\text{C}, \text{TMS}) = 188.1$ ppm in this study. This value is close to the mean of the three calculated values for A , namely 188.9 ppm.

From calculations of ^{15}N chemical shieldings, $A(^{15}\text{N}, \text{nitromethane}) = -131.4$ ppm and $A(^{15}\text{N}, \text{NH}_4\text{Cl}, \text{solid}) = 206.7$ ppm. The calculated and experimental values (see Table 3) for the chemical shielding of ammonia are in good agreement (difference of 2.8 ppm). Again the experimental chemical shielding is used for the parameter A , namely $A(^{15}\text{N}, \text{NH}_3) = 264.5$ ppm [61].

4. Results and discussion

Before presenting NMR and DFT calculation results, the nomenclature of the calculated configurations of MCU is explained.

With the assumption of a planar molecule, the secondary structure of the MCU backbone is characterized by three torsional angles. These torsional angles are indicated as Ψ_1 , Ψ_2 and Ψ_3 in Fig. 1 (lower left box). Owing to the sp^2 hybridization, they are expected to adopt values of 0° or 180° .

Calculations employing the molecular modeling program SPARTAN [67] reveal that there are six sterically allowed configurations of MCU. Half of them contain an intramolecular hydrogen bond. For the denotation of these six configurations, the IUPAC recommended *E*, *Z* nomenclature is used here. *I.e.* *E* corresponds to $\Psi = 180^\circ$ and *Z* corresponds to $\Psi = 0^\circ$. For this nomenclature, the substituent with higher priority is determined on either side of the (partial) double bond. The substituents are ordered in a list of priority as $\text{O}(\text{CH}_3) > \text{O}(\text{=C}) > \text{N} > \text{H}$ [68]. Further details on the structures are given in the section about the DFT calculations.

4.1 Liquid state NMR spectra

4.1.1 Results

^1H , ^{13}C and ^{15}N spectra of MCU were recorded in the solvents DMSO- d_6 and THF- d_8 which both contain at least one H-accepting group. DMSO is chosen because MCU is very good soluble in this solvent. Solutions of MCU in THF were used for low temperature experiments but the solubility of MCU in THF is only poor.

Spectra of differently spin labeled MCU samples in DMSO at room temperature revealed chemical shifts and several heteronuclear J couplings which are summarized in Table 4. The chemical shifts are in very good agreement with previously reported data of MCU although partly different solvents were used for ^1H NMR spectra, namely benzene- d_6 , chloroform- d_1 [20] and acetonitrile- d_3 [39]. For ^{13}C NMR spectra DMSO- d_6 was used in Ref. [39]. The J couplings are reported here for the first time and contain $J(^1\text{H}, ^{13}\text{C})$, $J(^1\text{H}, ^{15}\text{N})$, $J(^{13}\text{C}, ^{13}\text{C})$, and $J(^{13}\text{C}, ^{15}\text{N})$ couplings.

Table 4. ^1H and ^{13}C chemical shifts δ of MCU (differently ^{13}C , ^{15}N labeled) in DMSO- d_6 from liquid state NMR spectra (observed nuclei in the left column). J couplings are 1J couplings unless indicated otherwise (see text). The sign of the J couplings is not considered.

	δ/ppm	J coupling [Hz] to:		
		C(methoxy)	N(amide)	N(imide)
H(methoxy)	3.64	147.7		
H(amide),a	7.16		90.5	
H(amide),b	7.20		90.8	
H(imide)	9.86			91.3
C(methoxy)	52.2			
C(urea)	153.5		21; 21.5	17.4
C(carbamate)	154.9	1.9 $^2J_{\text{CC}}$ (or $^3J_{\text{CN}}$)		23.7

In Table 5, chemical shifts and 1J couplings are summarized which are extracted from ^1H and ^{15}N NMR spectra of $^{15}\text{N}_2$ -MCU in THF at room temperature and at low temperature (175 K). The assignment of ^1H and corresponding ^{15}N signals is based on the $^1J(^1\text{H}, ^{15}\text{N})$ couplings.

Additionally, a NMR titration experiment was performed on MCU in DMSO by adding THF. Thus, the H(amide) and H(imide) chemical shifts are monitored as shown in Fig. 2. This allows for the discrimination of the two H(amide) atoms due to their different dependency on the DMSO/THF ratio.

4.1.2 Discussion

$^1J(^{13}\text{C}, ^{15}\text{N})$ couplings for MCU in DMSO

From literature [69–71] 1J couplings of amides, imides and ureas are known. Amides and N-substituted phthalimides show 1J couplings of 9 to 15 Hz, for ureas 1J couplings of 20 to 22 Hz are reported. In general, $|J(^{13}\text{C}, ^{15}\text{N})|$ depends on the molecular charge distribution. A larger $|J(^{13}\text{C}, ^{15}\text{N})|$ may also be caused by an increase in the product of the s characters of the overlapping hybrid orbitals in the C–N bond. The larger $|J(^{13}\text{C}, ^{15}\text{N})|$ of ureas relative to amides and imides is essentially attributed a charge effect, namely to the (–)I effect of the second NH_2 group [70, 71].

In MCU dissolved in DMSO, the 1J coupling for N(amide), C(urea) is in full agreement with that of urea (0.1 M in H_2O , 20.2 Hz) [69], but the asymmetric 1J couplings for N(imide) and the two neighboring C atoms are striking. In particular, $^1J(^{13}\text{C}(\text{urea}), ^{15}\text{N}(\text{imide})) = 17.4$ Hz is in between the two areas of known 1J couplings for amides/imides on one hand and ureas on the other hand. Since the same N atom shows two different $^1J(^{13}\text{C}, ^{15}\text{N})$ couplings to

Table 5. ^1H chemical shifts δ of $^{15}\text{N}_2$ -MCU in THF-d8 from liquid state NMR spectra (observed nuclei in the left column), referenced to TMS and neat nitromethane, respectively. The sign of the $^1J(^1\text{H}^{15}\text{N})$ couplings is not considered.

	multi- plicity	δ/ppm			$^1J(^1\text{H}^{15}\text{N})$ coupling/Hz	
		175 K	298 K	difference	175 K	298 K
H(methoxy)	1	3.66	3.68	0	—	—
H(amide,a)	2	7.22	6.28	−0.84	91.3	91.0
H(amide,b)	2	7.56	7.35	−0.21	90.1	90.2
H(imide)	2	9.79	9.11	−0.68	91.6	91.7

its neighboring C atoms, the origin is either different partial charges on these C atoms or a different s character of the two C atoms. In case of the second argument this implies, that C(carbamate) has a higher s character than C(urea) by a factor of $23.7/17.4 = 1.36$ [70, 71].

$^1J(^1\text{H}, ^{15}\text{N})$ couplings for MCU in DMSO and THF

$^1J(^1\text{H}, ^{15}\text{N})$ couplings are measured for all three NH bonds for MCU in DMSO and in THF. Individual values of 90.1 Hz to 91.7 Hz show that the NH bonds are strong. In THF, a temperature independence of all $^1J(^1\text{H}, ^{15}\text{N})$ couplings is observed.

^1H chemical shifts of MCU in DMSO and THF at room and low temperature

Comparing the room temperature chemical shifts from the spectra of MCU in DMSO and in THF shows, that mainly one of the two H(amide) signals and the H(imide) signal are shifted low-field from THF to DMSO. This is an indication of a general solvent effect or alternatively of different configurations of MCU concerning at least Ψ_1 (see Fig. 1 for numbering of torsional angles). An assignment of the two H(amide) signals is not possible with the ^1H NMR data alone.

Low temperature ^1H NMR spectra of MCU in THF

^1H NMR spectra of MCU in THF were recorded at room temperature and at 175 K (see Table 5). The mutual assignment of the ^1H to the corresponding ^{15}N signals (^{15}N data not shown) is performed employing the $^1J(^1\text{H}, ^{15}\text{N})$ couplings. The chemical shift of H(methoxy) is unaffected by the change of the temperature from 175 K to 298 K. The amide and imide hydrogens exhibit different behavior. For the amide hydrogens high-field shifts of −0.68 ppm {H(amide,a)} and −0.21 ppm {H(amide,b)} are found. For H(imide) a high-field shift of −0.84 ppm is observed (see Table 5). Additionally, only N(amide)

exhibits a large shift of -3 ppm, while N(imide) shows only a small shift of -0.3 ppm.

These results have an important consequence: Since the two amide protons are both distinguishable at 175 K and 300 K, it is evident that there is a fairly high rotational barrier for the rotation of the amide group around the CN-bond. Such a high barrier must be attributed to hydrogen bonding of the amide protons. In principle there are two possibilities, namely an intramolecular hydrogen bonding or intermolecular hydrogen bonding to neighboring solvents (THF) molecules.

MCU in THF/DMSO solvent mixtures

To distinguish between these two possibilities we varied the solvent from pure THF over THF/DMSO mixtures of varying concentrations to pure DMSO. The corresponding ^1H NMR spectra were recorded ('NMR titration', see Fig. 2) and thus the solvent effect on the H(amide) and H(imide) chemical shifts were monitored. By this method, the two H(amide) signals of MCU in these two pure solvents can be linked. For the H(amide,b) signal, which shows the weakest dependency on the solvent composition (circles), a linear fit gives a good simulation of the experimental data (straight line). For the other two signals, the addition of small amounts of DMSO to pure THF causes large low-field shifts. This solvent effect is primarily due to hydrogen bonds between MCU and solvent molecules and not an effect of changing the dielectric constant since high-field as well as low-field shifts are observed. Since the H(amide,b) signal is practically not affected on the solvent composition one can conclude that the H(amide,b) is attached in an intramolecular hydrogen bond and not in an intermolecular one. Accordingly the hydrogen bond of H(amide,a) is an intermolecular hydrogen bond to the solvent molecules.

4.2 ^{13}C and ^{15}N CPMAS spectra

4.2.1 Results

The first step in the solid state NMR study of the MCU is the determination of the isotropic chemical shifts in the solid state and their comparison to the liquid state shifts. For this purpose the ^{13}C (natural abundance) and ^{15}N CPMAS spectra (spectra not shown) of unlabeled MCU and $^{13}\text{C}^{15}\text{N}_2$ -MCU (see Fig. 3) were recorded. The lines are well resolved and the isotropic chemical shift (CS) values are given in Table 6. The assignment for the CS values of C(urea) and C(carbamate) is not straightforward since they are close to each other. However, this unequivocal assignment was possible employing a REDOR experiment (spectra not shown) *via* $^{13}\text{C}^{15}\text{N}$ dipolar couplings (see *e.g.* [2, 58, 72]). In the ^{15}N MAS spectrum (Fig. 3 trace a) additional small signals are observed at 50 ppm, 54 ppm and 85.6 ppm (marked with 'x' in Fig. 3).

Fig. 3. ^{15}N CP-MAS spectrum of $^{13}\text{C}(\text{methoxy})^{15}\text{N}_2\text{-MCU}$. a: before recrystallization from water showing additional signals of $^{15}\text{N}_4\text{-triuret}$ (marked with 'x'). b: after nearly complete separation from $^{15}\text{N}_4\text{-triuret}$ by several recrystallization procedures. Lower spectra: simulation of spectrum a and separation of signals of MCU and triuret. Spectrum a is interpreted as the spectrum of separated MCU and triuret microcrystals rather than that of MCU/triuret cocrystals (see text).

4.2.2 Discussion

The ^{13}C chemical shifts of MCU from ^{13}C -CPMAS experiments are similar to the ^{13}C chemical shifts of MCU dissolved in DMSO. Compared to those the largest difference of $\Delta\delta = 4$ ppm is found for the ^{13}C chemical shift of C(urea). This might be an effect due to intermolecular interactions in the crystal (hydrogen bonds), due to solvent effects or due to different configurations in solution and solid state.

As expected, there are two dominant signals in the ^{15}N NMR spectra of $^{13}\text{C}^{15}\text{N}_2\text{-MCU}$. In addition there are small signals at 50 ppm, 54 ppm and 85.6 ppm. In principal these signals could be caused either by a chemical impurity as side product of the reaction or by a different, thermodynamically less favorable, conformer of MCU.

To decide between these two possibilities we recrystallized the sample several times from water and measured the ^{13}C -spectrum. After each recrystallization process the signal intensities of the small lines became weaker (see trace b in Fig. 3). This observation indicates a reaction side product as impurity. From the reaction mechanism the most probable side reactions are biuret or triuret. Therefore we synthesized reference samples (syntheses given in Ref. [25]) of $^{15}\text{N}_3\text{-biuret}$ and $^{15}\text{N}_4\text{-triuret}$ and recorded their ^{15}N CPMAS spectra (spectra not shown). The ^{15}N chemical shifts extracted from these spectra are 45.0 ppm (NH_2), 48.2 ppm (NH_2) and 80.2 ppm (NH) for $^{15}\text{N}_3\text{-biuret}$; and 49.8 ppm (NH_2), 54.0 ppm (NH_2), and

Table 6. First part: CSA data of all ^{13}C and ^{15}N atoms in MCU. Second part: CSA data of urea (this study) and other selected molecules (from literature) for comparison with the MCU data. Third part: CSA data from DFT calculations of MCU in four different configurations. δ_{iso} : isotropic chemical shifts from MAS experiments. δ_{aniso} and η : if $(\delta_{11} - \delta_{\text{iso}}) > (\delta_{\text{iso}} - \delta_{33})$, then $\delta_{\text{aniso}} = \delta_{11} - \delta_{\text{iso}}$ and $\eta = (\delta_{22} - \delta_{33})/\delta$, else $\delta_{\text{aniso}} = \delta_{33} - \delta_{\text{iso}}$ and $\eta = (\delta_{11} - \delta_{22})/\delta$ (Haeberlen convention [90]). † : data in first row from $^{15}\text{N}(\text{amide})\text{-MCU}$, data in second row from $^{15}\text{N}_2\text{-MCU}$ (see text). All ^{13}C chemical shifts referenced to TMS, ^{15}N chemical shifts to solid $^{15}\text{NH}_4\text{Cl}$. *: Referenced to solid solid $^{15}\text{NH}_4\text{NO}_3$. For conversion of phthalimide ^{15}N chemical shift data from Ref. [82] to $\delta(\text{NH}_4\text{Cl})$, we measured and used $\delta(\text{glycine}) - \delta(\text{NH}_4\text{Cl}, \text{solid}) = -6.4$ ppm. Accuracies are 1 ppm for CSA data and 0.1 ppm for data from MAS experiments.

no.	molecule	nucleus	δ_{33}/ppm	δ_{22}/ppm	δ_{11}/ppm	$\delta_{\text{iso}}/\text{ppm}$	$\delta_{\text{aniso}}/\text{ppm}$	Asymmetry η
1	MCU	$^{13}\text{C}(\text{urea})$	95	152	231	159	72	0.79
			simulation with two $^{13}\text{C}^{14}\text{N}$ dipolar couplings:					
			$D_1 = D_2 = 870 \text{ Hz}$ ($r = 1.36 \text{ \AA}$), $\beta_1 = \beta_2 = 90^\circ$, $\alpha_1 = 20^\circ$, $\alpha_2 = \alpha_1 + 116^\circ$					
2		$^{13}\text{C}(\text{carbamate})$	6.7	70.5	85.0	54.0	-47.3	-0.31
3		$^{13}\text{C}(\text{methoxy})$	3	8	121	43.5	77	0.06
4 †		$^{15}\text{N}(\text{amide})$	1	14	117	73	0.18	
5		$^{15}\text{N}(\text{imide})$	42	56	148	81.5	66	0.21
1	urea	$^{13}\text{C}(\text{urea})$	85	182	225	163.3	79	0.54
			simulation with two $^{13}\text{C}^{14}\text{N}$ dipolar couplings:					
			$D_1 = D_2 = 910 \text{ Hz}$ ($r = 1.34 \text{ \AA}$), $\beta_1 = \beta_2 = 90^\circ$, $\alpha_1 = 10 \pm 10^\circ$, $\alpha_2 = \alpha_1 + 117^\circ$, with r and $\angle(\text{N}_1\text{-C-N}_2)$ fixed to values from Ref. [26]					
			94	173	247	171	-77	-0.96
			100	183	243	175	-75	-0.80
3	acetanilide [8] gluconamide (fiber) [8] dimethyl carbonate [78] methyl formate [78] methyl acetate [78] dimethyl oxalate [79]	$^{13}\text{C}(\text{amide})$ $^{13}\text{C}(\text{methoxy})$	7 7 7 14	72 63 75 70	78 75 91 85	52 48 58 56	-45 -41 -51 -42	-0.13 -0.29 -0.31 -0.36
4	urea acetanilide [8] gluconamide (fiber) [8]	$^{15}\text{N}(\text{amide})$ $^{15}\text{N}(\text{N-subst. amide})$	-1 77	29 89	83 245	39.4 137	46 108	0.65 0.11
5	uracil [81] phthalimide [82]	$^{15}\text{N}(\text{imide})$	57 79* 56	76 131* 130	239 200* 159	124 135.9* 115.1	115 64 -59	0.17 0.81 -0.49

Table 6. continued.

no.	molecule	nucleus	δ_{33} /ppm	δ_{22} /ppm	δ_{11} /ppm	δ_{iso} /ppm	$\delta_{\text{anisotropy}}$ /ppm	Asymmetry η
1	MCU, DFT calculation, EEZ	$^{13}\text{C}(\text{urea})$	91.8	104.4	228.8	141.7	87.1	0.15
2		$^{13}\text{C}(\text{carbamate})$	105.9	106.9	228.7	147.2	81.5	0.01
3		$^{13}\text{C}(\text{methoxy})$	2.5	68.5	79.0	50.0	-47.5	-0.22
4		$^{15}\text{N}(\text{amide})$	-31.7	16.0	90.2	24.8	65.4	0.73
5		$^{15}\text{N}(\text{imide})$	18.0	67.0	138.6	74.5	64.1	0.76
1	MCU, DFT calculation, EZZ	$^{13}\text{C}(\text{urea})$	90.2	106.8	224.7	140.6	84.1	0.20
2		$^{13}\text{C}(\text{carbamate})$	103.2	107.4	218.9	143.2	75.8	0.05
3		$^{13}\text{C}(\text{methoxy})$	2.6	68.0	80.6	50.4	-47.8	-0.26
4		$^{15}\text{N}(\text{amide})$	-32.0	19.7	85.1	24.2	60.8	0.85
5		$^{15}\text{N}(\text{imide})$	33.2	81.0	121.1	78.5	-45.2	-0.89
1	MCU, DFT calculation, EEE	$^{13}\text{C}(\text{urea})$	92.9	104.9	229.0	142.3	86.8	0.14
2		$^{13}\text{C}(\text{carbamate})$	101.3	106.6	222.8	143.6	79.3	0.07
3		$^{13}\text{C}(\text{methoxy})$	0.2	74.3	74.7	49.7	-49.5	0.00
4		$^{15}\text{N}(\text{amide})$	-28.8	15.5	93.2	26.6	66.6	0.66
5		$^{15}\text{N}(\text{imide})$	23.1	48.4	141.4	70.9	70.4	0.36
1	MCU, DFT calculation, ZEZ	$^{13}\text{C}(\text{urea})$	95.1	97.4	234.3	142.2	92.1	0.03
2		$^{13}\text{C}(\text{carbamate})$	89.7	113.7	238.5	147.3	91.2	0.26
3		$^{13}\text{C}(\text{methoxy})$	2.4	71.3	82.8	52.2	-49.8	-0.23
4		$^{15}\text{N}(\text{amide})$	-53.3	35.5	76.8	19.7	-72.9	-0.57
5		$^{15}\text{N}(\text{imide})$	-8.1	52.3	154.4	66.2	88.2	0.68

85.5 ppm (2NH) for $^{15}\text{N}_4$ -triuret [ref. $\text{NH}_4\text{Cl}(\text{solid})$] reveal triuret as the reaction side product. The fact that no shift of the ^{15}N CPMAS signals is observed after any recrystallization procedure indicates that the samples consist of a mixture of MCU and triuret microcrystals and not of MCU/triuret cocrystals respectively solid solutions of triuret in MCU (see Fig. 3 lowest trace).

4.3 ^{13}C and ^{15}N spectra of static and slow spinning powder samples

At magnetic fields above 2.1 Tesla, ^{13}C - and ^{15}N -Solid State-NMR spectra of static or slow spinning powder samples of organic compounds are usually dominated by the CSA interaction with some contributions of dipolar couplings. If these dipolar couplings show a significant effect in the spectrum, they can be used for the orientation of the CSA tensor in the molecular frame by simulation of the dipolar CSA spectrum (see theory section).

For MCU and urea, all homonuclear ^{13}C or ^{15}N dipolar couplings can be neglected in the simulations of the static spectra since they occur between atoms separated by at least two bonds (internuclear distance *ca.* 2.3 Å) intramolecularly and more than 3 Å intermolecularly. Thus, these dipolar couplings only lead to small line broadening effects. A similar argument holds for the weak heteronuclear dipolar couplings in $^{13}\text{C}(\text{methoxy})^{15}\text{N}_2$ -MCU, which are of the order of 100 Hz and below (obtained by REDOR experiments, not shown here).

In addition to the ^{15}N -couplings in the doubly labeled compounds there are also strong one bond ^{14}N - ^{13}C couplings in the ^{13}C -labeled compounds. For $^{13}\text{C}(\text{urea})$ and $^{14}\text{N}(\text{amide})/^{14}\text{N}(\text{imide})$ they are expected to be in the range of 800 to 950 Hz ($r(\text{C},\text{N}) = 1.40$ to 1.32 Å). These couplings are used for the orientation of the $^{13}\text{C}(\text{urea})$ CSA tensor in the molecular frame (see below).

4.3.1 Results

Currently there exist only very few CSA data of $^{13}\text{C}(\text{amide, urea})$ and $^{15}\text{N}(\text{amide, imide})$ nuclei. Therefore we determined these data for MCU.

The spectra of slowly spinning or static powder samples were recorded of $^{15}\text{N}(\text{amide})$ -MCU (not shown), $^{13}\text{C}(\text{methoxy})^{15}\text{N}_2$ -MCU and $^{13}\text{C}_2(\text{urea, methoxy})$ -MCU. Experimental spectra and simulations are depicted in Fig. 4. ^{13}C and ^{15}N CSA tensor values extracted from the simulations are summarized in Table 6. For comparison, the ^{13}C CSA tensor of ^{13}C -urea (^{13}C 99.2%, purchased from Chemotrade, Leipzig) and the ^{15}N CSA tensor of $^{15}\text{N}_2$ -urea (^{15}N 99%, purchased from Chemotrade, Leipzig) were determined (see Table 6).

The simulations of the resolved $^{13}\text{C}(\text{methoxy})$ and $^{15}\text{N}(\text{amide})$ CSA tensors follow our previous work [8] and are not discussed in detail. The situation for the $^{15}\text{N}_2(\text{amide, imide})$ -MCU spectrum is more complex due to the overlap of

Fig. 4. CP spectra of labeled MCU (static powder samples). Left panel: ^{13}C spectra of $^{13}\text{C}_2(\text{urea, methoxy})\text{-MCU}$, right panel: ^{15}N spectra of $^{13}\text{C}(\text{methoxy})^{15}\text{N}_2\text{-MCU}$. a + d: experimental static sample spectra, b: ^{13}C slow spinning spectrum ($\nu_{\text{rot}} = 1 \text{ kHz}$) with indication of isotropic peaks by arrows, c + e simulations, f + g: decomposition of simulated spectrum e into $^{15}\text{N}(\text{imide})$ (f) and $^{15}\text{N}(\text{amide})$ spectrum (g) together with MAS spectra.

the lines. For the simulation of the $^{13}\text{C}(\text{urea})^{14}\text{N}_2\text{-MCU}$ spectrum, a more complex IS_2 spin system of a spin $1/2$ coupled to two $I = 1$ spins must be treated. Since this system has not yet been discussed in literature it is treated here more in detail.

$^{13}\text{C}(\text{urea})$ CSA tensor

On the left side of Fig. 4, ^{13}C -CP spectra of $^{13}\text{C}(\text{urea})^{14}\text{N}_2\text{-MCU}$ (static and slow spinning sample) are presented along with a simulation of the line shape respectively spinning sideband envelope. While the overall reproduction of the experimental line shape is very good there are some deviations in the line shape at 40 ppm for the high-field signal and at 120 ppm and 180 ppm for the low-field signal. These deviations can be attributed to an inefficient cross polarization for ^{13}C spins with orientations close to the magic angle. Since the positions of the singularities are not affected by these CP effects, the CSA data can be extracted from the spectra without losses in accuracy. These results are corroborated by the slow spinning spectra, which are, however, less sensitive on the tensor elements.

While in principle a full least squares fit of the static spectrum under the influence of the CSA and the dipolar interactions is possible, in practice such a fitting in general leads to numerical stability problems owing to the different cross polarization efficiencies of the various molecular orientations with respect to the laboratory frame. Therefore it is advantageous to employ a simulation where the compliance with the characteristic features of the experimental spectra, aka the positions of the singularities, are employed as measure of the quality of the simulation.

Fig. 5. Simulation of the ^{13}C CP spectra of labeled MCU (static powder samples, see Fig. 4a,c). The simulation of the $^{13}\text{C}(\text{urea})^{14}\text{N}_2$ spectrum was performed with the Euler angle α_1 and the relaxation time T_2 as parameters. Panel a: simulation (upper trace) and experimental spectrum (lower trace). Panel b: simulation with different values for the Euler angle α_1 . The simulation process focused on the low-field flank of the signal, because it is the part which shows the most sensitive structure (see vertical arrows). In parallel, the width of the central part of the Pake spectra is used for adjusting the relaxation time T_2 .

For the simulation of the spectrum of the $^{13}\text{C}(\text{urea})^{14}\text{N}_2$ spin system, the magnitudes of the two $^{13}\text{C}^{14}\text{N}$ dipolar couplings are fixed to the values taken from the CN distances obtained from the DFT calculation of the global minimum conformation EEZ (1.35 and 1.42 Å, corresponding to 890 and 760 Hz, respectively). Concerning the Euler angles (definition here as in Ref. [73]) describing the orientation of the dipolar coupling in the ^{13}C CSA frame, the side-condition is used that D_1 and D_2 incline the angle $\angle(\text{N}_1\text{--C--N}_2) = 116^\circ$ (value also from DFT calculation). Thus α_1 and α_2 (azimuthal angles) are related by $\alpha_2 = \alpha_1 + 116^\circ$. Furthermore, β_1 and β_2 (polar angles) are set to $\beta_1 = \beta_2 = 90^\circ$ like in other amides studied before [8]. The simulation of the $^{13}\text{C}(\text{urea})^{14}\text{N}_2$ spectrum was performed with the Euler angle α_1 and the relaxation time T_2 as free parameters. The simulation focused on the low-field flank of the signal, because this is the part which shows the most sensitive structure in the shoulders (see Fig. 5a,b), owing to the fact that the corresponding CSA element δ_{11} exhibits the largest difference $|\delta_{nn} - \delta_{iso}|$ ($n = 1, 2, 3$;

$\delta_{11} > \delta_{22} > \delta_{33}$). In parallel, the relaxation time T_2 was adjusted to reconcile both the structure of the low-field flank and the width of the central peak of the experimental signal with the calculated spectrum (see Fig. 5b). The simulation reveals $\alpha_1 = 20(15)^\circ$ and $D(^{13}\text{C}, ^{14}\text{N}) = 870(30) \text{ Hz}$ ($r = 1.36(2) \text{ \AA}$) with a T_2 of 1.3 ms (corresponding to a line width of 1.8 ppm) used for line broadening in the simulation. The margins of error, especially for the Euler angle, is estimated from the simulations shown in Fig. 5b.

The $^{13}\text{C}(\text{urea})^{14}\text{N}_2$ static spectrum of the ^{13}C -urea sample was treated in the same way (spectra not shown). Due to a less significant structure of the signal, the $^{13}\text{C}^{14}\text{N}$ dipolar couplings were fixed to $D_1 = D_2 = 910 \text{ Hz}$ corresponding to the CN distance $r = 1.34 \text{ \AA}$ from neutron diffraction studies [26, 74]. Furthermore, the relation $\alpha_2 = \alpha_1 + 117^\circ$ were obtained from the neutron diffraction structures. The polar angles are set $\beta_1 = \beta_2 = 90^\circ$. Best agreement between experimental and simulated spectra is obtained for the azimuthal angle $\alpha_1 = 10 \pm 10^\circ$.

$^{15}\text{N}(\text{amide})$ and $^{15}\text{N}(\text{imide})$ CSA tensors

On the right side of Fig. 4, the static ^{15}N static sample spectrum of $^{13}\text{C}(\text{methoxy})^{15}\text{N}_2\text{-MCU}$ is presented. The spectrum is simulated as superposition of two independent subspectra with different CSA tensors. For the low-field signal, *i.e.* the N(imide) signal, all three singularities are clearly visible in the spectrum and a good agreement between experimental spectrum and simulation is achieved. The position of δ_{11} of the high-field signal, *i.e.* the N(amide) signal, is obscured. Therefore, the isotropic chemical shift from the corresponding MAS experiment is used in conjunction with δ_{22} and δ_{33} for the calculation of δ_{11} of the $^{15}\text{N}(\text{amide})$ CSA (see Table 6, second line in corresponding row). In addition a second static experiment on singly labeled $^{15}\text{N}(\text{amide})\text{-MCU}$ sample was performed (not shown, see Table 3, first line in corresponding row for CSA data). The corresponding spectrum shows the well-known Pake-pattern due to a single CSA tensor [75, 76]. While the span of the ^{15}N -CSA tensor, $\delta_{11} - \delta_{33}$, is essentially the same in both data sets, a difference of 0.12 emerges for η (see Table 6).

4.3.2 Discussion

$^{13}\text{C}(\text{urea})$ CSA tensor

The $^{13}\text{C}^{14}\text{N}$ dipolar coupling and the azimuthal angle obtained from the simulation are comparable to our previous results obtained for acetanilide and the fiber modification of N-octyl-gluconamide [8], where $\alpha = 33^\circ$ and 43° , respectively, and $D(^{13}\text{C}, ^{14}\text{N}) = 870 \text{ Hz}$ were observed.

From comparison with single crystal studies of molecules containing sp^2 hybridized C atoms, where the CSA tensor orientation is determined unequivocally, it is well-known that the high-field component δ_{33} usually is oriented perpendicular to the molecular frame [77].

Fig. 6. $^{13}\text{C}(\text{urea})$ CSA tensor orientations in MCU obtained from the simulations. Due to symmetry there exist four possible orientations characterized by Euler angles and numbered No. 1 to 4 (see text). In the chemical structures, N_1 and N_2 replace N(amide) or N(imide) as indicated below the figure. Each pair of arrows corresponds to a unique orientation of δ_{11} , δ_{22} of the $^{13}\text{C}(\text{urea})$ CSA tensor. δ_{33} is perpendicular to the molecular plane. Left panel: Euler angle $-\alpha_1$ rotating the δ_{11} axis from the $\text{C}(\text{urea})\text{N}_1$ bond towards the $\text{C}=\text{O}$ bond. Right panel: Euler angle $+\alpha_1$ rotating the δ_{11} axis from the $\text{C}(\text{urea})\text{N}_1$ bond towards the $\text{C}(\text{urea})\text{N}_2$ bond. The hatched areas indicate the margin of error for the Euler angle α_1 ($\pm 15^\circ$).

Thus only the directions of the tensor principle axes δ_{11} and δ_{22} have to be determined. From the azimuthal angles, there are four possible orientations of the $^{13}\text{C}(\text{urea})$ CSA tensor in the molecular frame (see Fig. 6) due to the axial symmetry of the dipolar interaction tensors. These four orientations are characterized by the following pairs of Euler angles (α_1 between δ_{11} principle axis and $\text{C}-\text{N}(\text{amide})$ bond with the $\text{C}-\text{N}(\text{imide})$ bond at 116°): No. 1 ($\alpha_1 = -20^\circ$, $\alpha_2 = -136^\circ$), No. 2 ($\alpha_1 = 20^\circ$, $\alpha_2 = -96^\circ$), No. 3 ($\alpha_1 = 44^\circ$, $\alpha_2 = 160^\circ$), No. 4 ($\alpha_1 = 84^\circ$, $\alpha_2 = -160^\circ$). For two of the four orientations (No. 1 and No. 3), the δ_{22} principle axis is close to the CO bond direction, for the other two orientations it is close to the CN bond direction. Since the O atom exhibits the highest electronegativity, the intermediate component δ_{22} is expected to point in the direction of the CO bond. These facts lead to the orientations denoted as No. 1 and No. 3 in Fig. 5. A similar result was found for the orientations of the $^{13}\text{C}(\text{amide})$ CSA tensor of acetanilide and gluconamide [8].

A comparison of these principal elements with the CSA tensors of urea and amides shows that the shape of the $^{13}\text{C}(\text{urea})$ tensor of MCU resembles more those of acetanilide and gluconamide [8] than those of urea, the parent molecule.

$^{13}\text{C}(\text{methoxy})$ CSA tensor

The $^{13}\text{C}(\text{methoxy})$ CSA tensor obtained is similar to those of C(methoxy) in the esters dimethyl carbonate, methyl formate, methyl acetate [78], and dimethyl oxalate [79] (see Table 6). As the methyl group in an ester function usually interacts only weakly with other atoms, the CSA is expected to differ only slightly in these esters. For the five examples given in Table 6, the CSA tensor values exhibit maximum absolute differences from the mean of 8 ppm, 7 ppm and 6 ppm for δ_{11} , δ_{22} and δ_{33} , respectively. The $^{13}\text{C}(\text{methoxy})$ CSA tensor values of MCU are very close to the mean values with differences of -2 ppm, 0 ppm and -2 ppm, respectively.

$^{15}\text{N}(\text{amide})$ and $^{15}\text{N}(\text{imide})$ CSA tensors

The resulting CSA tensors of $^{15}\text{N}(\text{amide})$ and $^{15}\text{N}(\text{imide})$ are similar in shape (see asymmetry parameter δ and anisotropy η given in Table 6), only the isotropic chemical shifts differ largely by 40 ppm. The low-field component δ_{11} is expected to point approximately to an H atom like *e.g.* in acetanilide and gluconamide [8]. For both CSA tensors, the high-field and intermediate components δ_{33} and δ_{22} exhibit only a weak asymmetry owing to their small differences of 13 ppm and 14 ppm for N(amide) and N(imide), respectively. Therefore, it is not possible to decide which of these components is oriented perpendicular to the molecular frame. This question could, at least in principle be solved, by studying a deuterated sample where the dipolar $^{15}\text{N}^2\text{H}$ interaction is employed as a second constraint for the orientation of the tensor.

Comparing the $^{15}\text{N}(\text{amide})$ CSA tensor of MCU with that of urea (s. Table 6), a good agreement between the isotropic chemical shifts is observed. However, anisotropy and asymmetry disagree. Furthermore, while the asymmetry is comparable for the ^{15}N CSA tensors of MCU and gluconamide (and acetanilide), the isotropic chemical shifts and anisotropies are very different. These observations can be attributed (a) to the different primary structures ($\text{R}^1\text{C}=\text{O})\text{NHR}^2$ with $\text{R}^2=\text{H}$ and $(\text{C}=\text{O})\text{R}$ for N(amide) and N(imide) of MCU, and $\text{R}^2=\text{Ph}$ and $\text{CH}(\text{OH})\text{R}$ for acetanilide and gluconamide, (b) to a different degree of sp^2/sp^3 hybridization of the N atom, and (c) to different N–H distances due to intra- or intermolecular hydrogen bonds [13, 80]. Additionally, the larger system of conjugated double bonds in MCU, *i.e.* the more delocalized bonding nature in MCU compared to the amides, may have some effect on the ^{15}N CSA tensor.

Only few CSA data are reported in literature on $^{15}\text{N}(\text{amide})$ nuclei. Concerning $^{15}\text{N}(\text{imide})$ nuclei only uracil [81] and phthalimide [82] were studied. For further discussion, CSA data of more molecular systems need to be gathered systematically. Surprisingly, the value for δ_{22} is different for all $^{15}\text{N}(\text{imide})$ CSA tensors compared here. In MCU, δ_{22} is found to be high-field shifted near δ_{33} like in amides, whereas in phthalimide (and some

Fig. 7. DFT calculated configurations, ordered with increasing energy. Amide and imide H atoms are omitted for clarity. Arrows indicate those torsional angles which have to be changed by 180° in order to obtain the global minimum structure EEZ.

N-substituted phthalimides) δ_{22} is found to be low-field shifted near δ_{11} [82]. In uracil [81], η is close to one, *i.e.* δ_{22} is found in the middle between δ_{11} and δ_{33} .

Further interpretation of the ^{13}C and ^{15}N CSA tensors of MCU follows in the DFT calculations chapter.

4.4 DFT calculations of the molecular geometry

4.4.1 Results

The six sterically possible configurations obtained by molecular modeling calculations using SPARTAN [67], were studied by gas phase *ab initio* methods. For the ZZZ and ZEE configuration no stable geometries were found. In case of the ZEE configuration, the geometry optimization results in a change to the ZEZ configuration. In case of the ZZZ configuration, large negative vibrational frequencies occur when fixing the corresponding torsional angle (here Ψ_3). This indicates a geometry corresponding to a saddle point instead of a (local) minimum of the energy hypersurface. Therefore, these two configurations are excluded and only the remaining four configurations are considered (see Fig. 7) in the following. For these four configurations, relative energies are calculated as $\text{EEZ} \equiv 0$, $\text{EZZ} = 4.3$, $\text{EEE} = 10.1$, $\text{ZEZ} = 10.2$ kcal/mol (torsional angles, which are different with respect to the global minimum structure EEZ, are in bold type).

4.4.2 Discussion

The global minimum gas phase structure of MCU obtained from the calculations (EEZ, see Fig. 7) coincides with the configuration of the MCU part of $\text{MCB} \cdot \text{H}_2\text{O}$. This structure is characterized by an intramolecular, nonlinear

Fig. 8. ^{13}C (left) and ^{15}N (right) isotropic chemical shifts from solid state NMR (lowest line) and GIAO calculations (upper lines). The calculated stick spectra are ordered with respect to the energy calculated for each structure (*i.e.* EEZ is the global minimum structure). The signal of C(urea) is marked by an 'u' in each ^{13}C stick spectrum.

hydrogen bond between N(amide) and O(carbamate/carbonyl) with a calculated NO distance of 2.75 Å. The structure with the second lowest energy (EZZ) shows a hydrogen bond between N(amide) and O(methoxy) instead of O(carbamate/carbonyl) with a calculated NO distance of 2.72 Å. Rotating the methoxy group by 180° with respect to the global minimum structure EEZ yields a structure in which the similarly charged H(imide) and two of the H(methoxy) atoms come closer together (configuration EEE). But the H,H distances are still rather large (2.2 Å) compared with van der Waals radii. For the rotation about Ψ_3 the same amount of energy is needed as for the rotation around Ψ_1 . The ZEZ configuration is the only configuration without an intramolecular hydrogen bond which could be realized with gas phase DFT calculations.

4.5 DFT calculations of the CSA tensors

The chemical shieldings are calculated and converted to chemical shifts as described above for the four configurations with stable geometry (EEZ, EZZ, EEE and ZEZ). The resulting CSA data are given in Table 6 and depicted in Fig. 8

The calculated ^{13}C isotropic chemical shieldings are relatively similar for all four configurations. For ^{15}N (amide) and ^{15}N (imide), the isotropic chemical shieldings depend more strongly on the configurations.

The calculated ^{13}C (methoxy) isotropic chemical shieldings are in good agreement with the experimental value with differences of *ca.* 7 ppm. All other ^{13}C and ^{15}N isotropic chemical shifts exhibit stronger differences (7 to 24 ppm) between the experimental and calculated values.

These differences are a strong indication that the chemical shift parameters of these positions are strongly influenced by intermolecular hydrogen bonding, which is not taken into account in the gas phase calculations. *E.g.* formation of an intramolecular hydrogen bond between $^{15}\text{N}(\text{amide})$ and $^{13}\text{C}(\text{carbamate}/\text{carbonyl})$ shifts the $^{15}\text{N}(\text{amide})$ signal *ca.* 8 ppm low-field (see double arrow in Fig. 8). It should be noted that all calculations predict a high-field shift from $^{13}\text{C}(\text{carbamate})$ to $^{13}\text{C}(\text{urea})$ whereas from the REDOR experiment an unequivocal assignment of the ^{13}C solid state NMR signals is found with $^{13}\text{C}(\text{urea})$ low-field shifted with respect to $^{13}\text{C}(\text{carbamate})$. Again, this effect can be attributed to the neglect of the intermolecular hydrogen bonds in the calculations.

Next, the shape of the calculated chemical shielding tensors, *i.e.* anisotropy and asymmetry, is compared with experimental CSA values. As above in the comparison of isotropic chemical shifts, C(methoxy) shows the best agreement concerning the anisotropy (± 2 ppm for $^{13}\text{C}(\text{methoxy})$, ± 7 ppm for $^{15}\text{N}(\text{imide})$, ± 14 ppm for $^{15}\text{N}(\text{amide})$, ± 20 ppm and opposite sign for $^{13}\text{C}(\text{urea})$). The values for the asymmetry η of C(methoxy) are comparable (-0.22 to -0.26 compared to -0.31 from experiment) except for the EEE configuration ($\eta = 0.00$). The asymmetry is not well reproduced for other nuclei than $^{13}\text{C}(\text{methoxy})$.

The question now arises, how strong these CSA tensors are affected by hydrogen bonding. In the case of weak hydrogen bonds, like in MCU and similar amides, the binding orbitals are only weakly affected by the hydrogen bond. Accordingly mainly the strength of the CSA interaction is influenced, as was found in various studies on the influence of hydrogen bonding on isotropic chemical shifts [83–86]. In these works it was shown that the isotropic chemical shift can be employed as a locator of the hydrogen position in the hydrogen bond [13, 87]. In a computational study (to be published elsewhere), we evaluated the dependence of the calculated CSA tensor values on the number of hydrogen bonds: ^{13}C and ^{15}N CSA tensors of urea are calculated for an isolated urea molecule and for urea with systematically added neighbored (hydrogen bonded) urea molecules using geometries of a neutron diffraction study. In this case, the principal elements of the CSA tensors show changes of up to 50 ppm (formation of four hydrogen bonds with a $^{13}\text{C}=\text{O}$ group). This reveals the strong influence of intermolecular hydrogen bonds on calculated CSA tensors and the limited information if these hydrogen bonds are neglected in calculations. However, the orientation of CSA tensors in the molecular frame is expected to be practically independent on the hydrogen bonding in the present case.

Concerning the calculated CSA tensor orientations in MCU, the high-field component of the calculated chemical shielding tensors is oriented perpendicular to the molecular plane for all sp^2 hybridized C and N atoms as expected.

For the $^{13}\text{C}(\text{urea})$ CSA tensor in the EEZ configuration (global minimum configuration) and EEE configuration (methoxy group rotated by 180°), the

intermediate component is oriented nearly in the direction of the C=O bond (10° off) and the low-field component is *ca.* 19° off the $^{13}\text{C}(\text{urea})\text{--}^{15}\text{N}(\text{imide})$ bond. This is in excellent agreement with the orientation No. 3 depicted in Fig. 6. In the EZZ configuration, on the other hand, the intermediate component shows a larger tilt from the C=O bond (32° off) and the low-field component is practically parallel to the $^{13}\text{C}(\text{urea})\text{--}^{15}\text{N}(\text{imide})$ bond. This means that the intermediate component is -24.6° off from the $^{13}\text{C}(\text{urea})\text{--}^{15}\text{N}(\text{amide})$ bond which is in good agreement with the orientation No. 2 depicted in Fig. 6.

Comparing the configurations EEZ and EEE, all tensor orientations are similar apart from $^{13}\text{C}(\text{methoxy})$. In both configurations, the intermediate component of the $^{13}\text{C}(\text{methoxy})$ calculated chemical shielding tensor is oriented perpendicular to the molecular plane. In the EEZ configuration, the high-field component is oriented to O(methoxy) whereas in the EEE configuration, this C=O bond bisects the angle spanned by the high-field and the low-field components. The latter orientation is rather unusual compared to literature data and it could be used to distinguish between these two possible configurations if the orientation of the $^{13}\text{C}(\text{methoxy})$ chemical shift tensor was obtained experimentally.

It can be concluded (1) that the calculated CSA tensor of $^{13}\text{C}(\text{methoxy})$ is well reproduced while for other ^{13}C and ^{15}N nuclei only the anisotropy is comparable with the experimental results and independent on the configurations. The differences between experimental and calculated CSA tensors are caused by the intermolecular hydrogen bonds present in the crystal. (2) With the global minimum configuration EEZ, a $^{13}\text{C}(\text{urea})$ CSA tensor is calculated whose orientation fits very well to one of the possible orientations found from the experiment (see No. 3 in Fig. 6).

Further dipolar solid state NMR experiments may be performed in order to obtain the orientation of the $^{15}\text{N}(\text{amide})$ and $^{15}\text{N}(\text{imide})$ CSA tensors in the molecular frame using $^{15}\text{N}(\text{amide})^2\text{H}_3\text{-MCU}$ and/or $^{15}\text{N}_2^2\text{H}_3\text{-MCU}$.

5. Conclusions

For this structural study, selectively $^{13}\text{C}/^{15}\text{N}$ isotope labeled samples of MCU were synthesized. Characterization by liquid state ^1H , ^{13}C and ^{15}N -NMR revealed isotropic chemical shift values and several previously unknown J -couplings were extracted. The resolved $^1\text{H}(\text{amide})$ chemical shifts, low temperature NMR and NMR titration experiments gave an indication of the presence of an intramolecular hydrogen bond.

In the second step the molecular structure of MCU was studied by gas phase DFT calculations. All stable configurations found in these calculations predicted planarity of the molecule. The EEZ configuration is the DFT calculated configuration with lowest energy. This result indicates that the molecular structure of MCU is similar to known structures (X-ray, neutron diffraction)

of related molecules like urea [26], biuret(0.6 H₂O) [27], methoxy carbonyl biuret [25] (MCB·H₂O) and N,N''-diacetyl biuret [28].

In the third step chemical shielding tensors of several ¹³C and ¹⁵N nuclei in MCU were obtained experimentally from dipolar chemical shift measurements and compared to calculated tensors from DFT calculations. The tensor eigenvalues show pronounced differences between calculations (EEZ configuration) and experiment. These differences are interpreted as the effect of intermolecular hydrogen bonds, which are present in the experimental sample but not in the calculation.

While the tensor eigenvalues can be uniquely determined from the simulation of the experimental spectra, this is not the case for the orientation of the principal axes system of the tensors, which show some orientational ambiguity due to the axial symmetry of the dipolar interaction. The orientations of the tensor principal axes systems (PAS) in the molecular frame are less affected by hydrogen bonds or other weak intermolecular contact interactions. Accordingly they can be employed to select between the possible PAS orientations.

Comparing the orientation of the calculated C(urea) CSA tensor with the four possible orientations of the C(urea) CSA tensor obtained by dipolar chemical shift spectra, a very good agreement between calculation and experiment was found for the orientation with δ_{11} approximately in direction of N(imide), δ_{22} approximately in direction of the C=O bond, and δ_{33} perpendicular to the molecular frame (see orientation No. 3 depicted in Fig. 6).

In summary we have shown that the combination of ¹H, ¹³C, ¹⁵N-liquid state NMR, ¹³C, ¹⁵N solid state NMR, ¹³C¹⁴N₂ Dipolar Chemical Shift NMR and DFT calculation reveals important structural details of compounds which are unfavorable to conventional diffraction methods. The determined ¹³C and ¹⁵N CSA tensors can serve as input for full *ab initio* calculations on a higher level, including neighbored (maybe truncated) MCU molecules. For a full Solid State NMR structure determination ("NMR-Crystallography") of the molecule and the crystal packing, further structural constraints are necessary, which can be obtained for example from dipolar recoupling techniques like REDOR. The results of such a study will be reported in a subsequent publication.

Acknowledgement

Financial support by the German-Israeli-Foundation (GIF) under contract I – 595-43.09/98 and the Deutsche Forschungsgemeinschaft (DFG) SFB-498 is gratefully acknowledged. S.M. thanks the DFG for a postdoctoral stipend in the Research Training Programme GK-788.

We thank Dr. A. Schäfer and S. Sharif for recording liquid state NMR spectra, R. Zander for help with syntheses, and Prof. G. Koßmehl and Prof. H.-H. Limbach for fruitful discussions.

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