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THE INFLUENCE OF SIDE-CHAINS ON THE COMPLEXATION OF CATIONS BY CROWNS. SYNTHESIS AND Cu(II) COMPLEXATION OF N,N'-DIARYL-DIAZA-18-CROWN-6

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Abstract—Various N,N'-diaryl derivatives of 1,4,10,13-tetraoxa-7,16-diazacyclooctadecane were synthesized. 7,16-diphenyl-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane had only a low affinity for cations. On the contrary, diamide derivatives of 7,16-di[(2-amino)phenyl]-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane were deprotonated by Cu(II) and formed stable chelates. Spectral data suggest that monodeprotonation gives dissymmetric 1 : 1-complexes and dideprotonation gives symmetric 1 : 1-complexes.

Diaza-crown ethers are versatile complexing agents because their properties (e.g. affinity for cations, hydrophobicity etc.) can be optimised by introducing suitable substituents on the nitrogen atoms. The cation complexing ability of diaza-crown ethers are dramatically modified by the substituents attached to the nitrogens if they bear chelating functions oriented toward the centre of the macrocycle (e.g. in the case of cryptates).[1]

We undertook the study of a family of diaza-crown ethers of type 7 (Chart 1) where the R groups situated in the ortho position of phenyl substituents are well placed to interact with cations sitting at the centre of the macrocycle. An X-ray structural investigation performed on the free ligand **7b** showed indeed that the tosylamide functions where folded back above and below the macrocycle, creating, as in cryptates, a tridimensional cavity.[2a]

We wish to report here the synthesis of the crowns **7a-d** and the screening of their cation complexing properties. The synthetic approach has been the object of a preliminary communication.[2b]

RESULTS AND DISCUSSION

Synthesis of **7a-d**. The synthetic route is outlined in Chart 1. Diamine **5a** was synthesized by solvolysis of **1** in neat aniline. Diamine **5b** was prepared by reduction of the corresponding diamide **4** by lithium–aluminium hydride. Good yields of the macrocycles **6a-b** were obtained by reaction of diamines **5a-b** with diacid dichloride **3** in high dilution conditions. Diborane was the reagent of choice to reduce **6a** to the macrocyclic diamine **7a**. On the contrary, an attempted reduction of **6b** by diborane gave only tarry materials; in this case the use of lithium-aluminium hydride was more satisfactory. A number of methods[3] were tried to detosylate **7b** to **7c**, but the only successful one was the reductive cleavage by sodium-naphtalene in cold THF.[4] Acylating **7c** with succinic anhydride gave a diamide **7d** similar to **7b** but water-soluble in neutral conditions (the tosylamide **7b** was insoluble in water and only sparingly soluble in methanol).

Cu(II) *complexation by* **7b**. Compound **7b** may be considered as a bis-[o-(tosylamino)aniline]. o-(Tosylamino)aniline itself was described as a good complexing agent for transition metals,[5,6] the tosylamide function easily loosing a proton to link the metal cation.

In the solvent system used (CH_2Cl_2–CH_3OH 4 : 1), Cu(II) chloride solutions (4×10^{-3} M) were green. When the colourless ditosylamide **7b** was mixed with such a solution in a 1 : 1 molar ratio, the initially green colour turned to light yellow. The yellow colour was intensified by addition of one equivalent of base (NaOH or CH_3COOK). A second equivalent or a large excess of base changed the colour to blue. A control experiment showed that Cu(II) chloride alone or **7b** alone, in this solvent system, did not give any soluble coloured compound on addition of base.

It appeared thus that ditosylamide **7b** formed two distinct soluble complexes with Cu(II); a yellow monodeprotonated one and a blue dideprotonated one.

The 1 : 1 stoichiometry of the complexes was established by a UV spectrophotometric titration of the ligand by Cu(II) chloride. It was also verified that the pH effect on the UV spectra was reversible, i.e. the protonated ligand and the yellow and blue complexes were reversibly interchanged by appropriate addition of acid or base. The UV-VIS absorption maxima of **7b**, of its disodium salt (i.e. both tosylamides ionized by NaOH) and of its yellow and blue Cu(II) complexes are reported in Table 1. The UV absorptions due to the chromophore of the ligand are relatively similar for the disodium salt and the blue Cu(II) complex, confirming the dideprotonated nature of the latter.

Generally speaking, diaza-crown ethers bearing chelating functions on the two nitrogen atoms are able to form two types of 1 : 1 complexes with Cu(II). For large rings, the functionalized macrocycle (e.g. the cryptate bis-tren) may successively complex a first

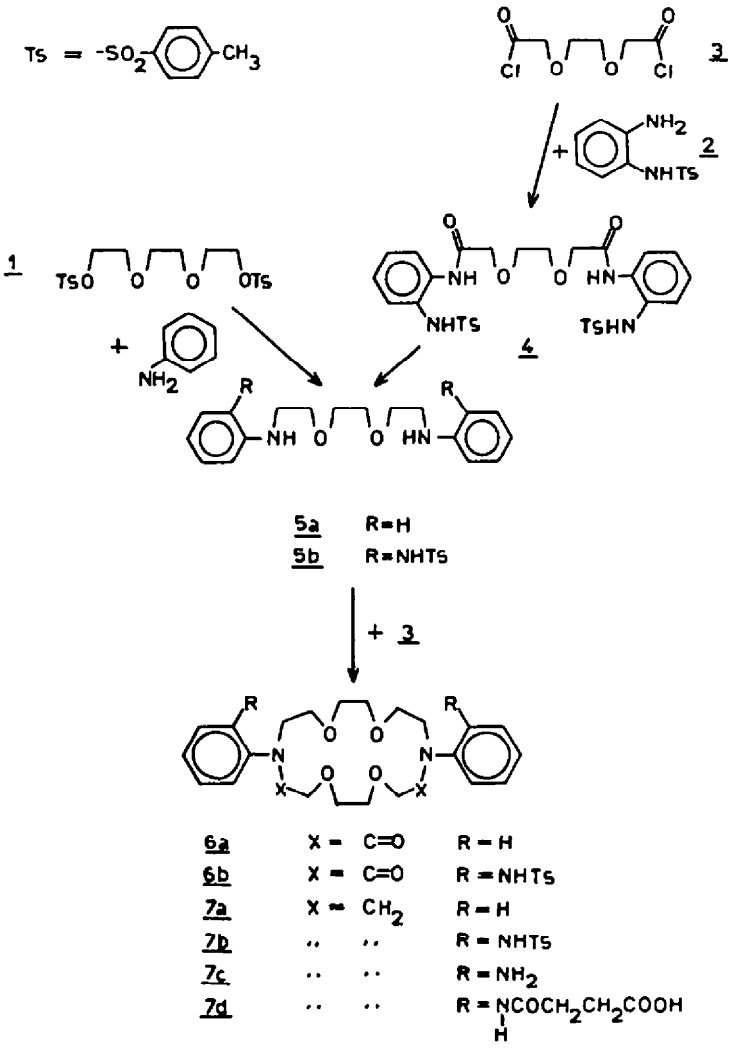

Chart 1. Synthetic route to **7a–d**.

Table 1. Visible and UV spectra of the ligands and their Cu(II) complexes (λ_{nm}^{max}, log ϵ given between parenthesis)

Compound	UV(CH_3OH)[a]	Visible(CH_3OH–CH_2Cl_2, 1 : 4)[a]
7a	257(4.53), 301(3.64)	—
7b	223(4.55)	—
7b disodium salt	223(4.55), 248(4.36), 285[b](3.96)	—
7b. $CuCl_2$ yellow complex	223(4.54), 245[b] (4.36), 345(3.55)	444[b](2.00), > 740[c]
7b. $CuCl_2$ blue complex	223(4.49), 243(4.43)	624[c](1.74)
7c	221(4.33), 293(3.68)	—
7c·$CuCl_2$ green complex	232(3.92)[d]	(CH_3OH) 615[c](2.15)
7c·$4H^+$	236(3.71)	—
7d	(H_2O) 232(4.43), 252[b](4.31), 232[b] (3.66)	—
7d·$CuCl_2$ green complex	(H_2O)235[b](4.34), 250(4.38), 280[b](3.86)	(H_2O) 395 (2.03), 680[c](1.85)

[a]Except when otherwise stated; [b]shoulder; [c]maximum of the envelope of the d-d transitions; [d]broad featureless absorption culminating at this wavelength.

and then a second copper atom. The 1 : 1 complex is disymmetric, one moiety of the molecule behaving as a tetradentate ligand (complex of type A, Chart 2).[7] For smaller rings on the contrary, centrosymmetric complexes may be observed (complex of type B).[8]

The yellow Cu(II) complex of **7b** being monodeprotonated, it is rational to conclude that in this case the Cu(II) cation is preferentially linked to one o-(tosylamino)aniline moiety of the ligand. The yellow complex is thus probably of type A. On the contrary, the blue complex should be of type B; this interpretation was confirmed by an IR study (Table 2). The yellow complex featured both the symmetric stretching band of the free sulfonamide group at 1165 cm^{-1} and the band at 1090 cm^{-1} characteristic of the ionized tosylamide function. It was thus clear that one tosylamide was ionized, the other remaining unaffected by the presence of Cu(II). In the blue complex, the band at 1165 cm^{-1} was completely lacking, both tosylamide functions being ionized.

The examinations of space-filling models showed that the nitrogens of the tosylamide functions may link a cation sitting at the center of the ring if one nitrogen approached the cation from above the macrocycle and the other from below. In fact, the tosylamide side-chains are already so oriented in the free ligand.[2a] Moreover, this conformation has indeed been observed for the Cu(II) complex of N,N′-di(carboxymethylene)-diaza-18-crown-6,[8] a ligand of the same overall topology as **7b**.

The complexation of Cu(II) by **7b** was selective: two other transition metal cations, Co(II) and Ni(II), that were known to be well complexed by o-(tosylamino)aniline, were tested: they did not give any complex with **7b**.

Cu(II) *complexation by* **7c** *and* **7d**. The diamine **7c** also gave a 1 : 1 complex with Cu(II). Its UV spectrum (Table 1) resembled that of the tetraprotonated from of **7c**, suggesting a complex of type B with the four nitrogens linked to the Cu(II) cation.

Ligand **7d** (a diamide derivative, like **7b**) was water-soluble at a pH > 5 because ionization of its two carboxylic acid functions. The free ligand obviously had no other protons titrable in aqueous solution above this pH. When, however, an equimolar quantity of Cu(II) chloride was added to an aqueous solution of **7d**, a green Cu(II) complex was formed that contained one more titrable proton above pH 5. One amide function of **7d** was thus deprotonated to form a green copper chelate of 1 : 1 stoichiometry (an excess of Cu(II) precipitated in the form of its hydroxide in the slightly alkaline conditions used). It was the major species present in solution in the pH range 6–9. At lower pH, the chelate was decomposed by protonation of the ligand and at higher pH, copper hydroxide was formed.

The ability of Cu(II) to deprotonate amides is well known. Once deprotonated, the amide nitrogen coordinates to the metal.[9–11] The structure of the green Cu(II) complex of **7d** is probably similar to that of the yellow Cu(II) complex of **7b**, i.e. of type A: both complexes are monodeprotonated species and their

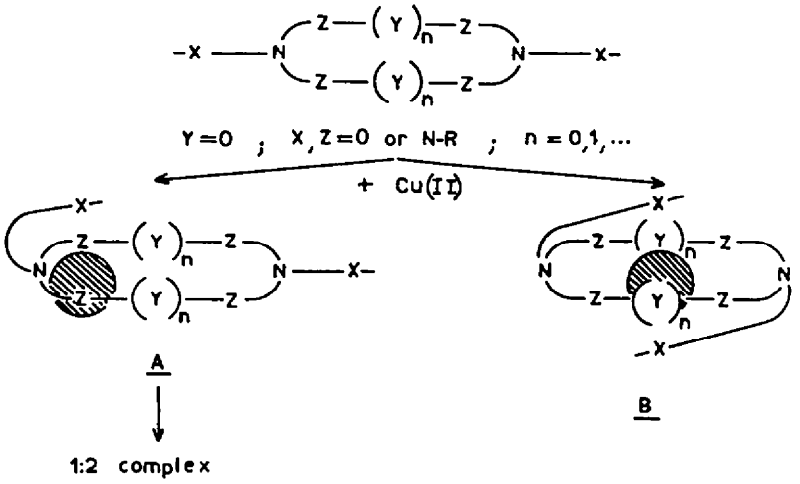

Chart 2. Two possible types of 1 : 1 Cu(II) complexes of crown compounds.

Table 2. Infrared absorptions of the ligand **7b** and its Cu(II) complexes in the range 1050–1200 cm^{-1} (Nujol mull)

7b	1165(s)	1140(w), 1115(w)
7b disodium salt	—	1125(s), 1090(s)
7b yellow complex	1165(s)	1140(w), 1125–1115(w) 1090(s)
7b blue complex	—	1125(m), 1090(s)

visible spectra (Table I) present two absorptions on each side of the visible domain. Only one maximum was observed for the complexes of type B (i.e. the blue complex of **7b** and the complex of **7c**).

Complexation of alkaline, alkaline-earth and ammonium cations by **7a,b,d**. There was no evidence of complexation of these cations by **7b** in methanol or **7d** in water. The selectivity of **7b** for Cu(II) was thus rather pronounced. Compound **7a** had only a weak affinity for K^+; an association constant of 13 $lmol^{-1}$ (in methanol) was determined by using the hypsochromic shift and decrease in intensity of the UV band of the ligand situated at 301 nm, upon complexation. The affinity of **7a** for Na^+, NH_4^+ and Ba^{2+} was even lower. The weak affinity of **7a** for cations, as compared with other diaza-18-crown-6,[1] is probably due to two factors, firstly, the lone pairs of the ring nitrogens of **7a** are less available for complexation because they are conjugated with phenyl substituents and secondly, a considerable conformational change of the free ligand[2a] would be necessary to orient the nitrogen lone pairs toward the interior of the ring.

CONCLUSION

The side-chains *R* of compounds of type 7 are essential for complexation of Cu(II). Compound **7a** did not form any stable complex with Cu(II). The results described also suggest that although the 18-crown-6 ring is too small to accomodate two Cu(II) cations, it is still too large to provide the maximum possible stability to centrosymmetric complexes of type B. Dissymmetric complexes of type A may be preferred.

EXPERIMENTAL

The following instruments were used: Varian XL-200 or T-60 ^1H NMR spectrometers, Varian CFT-20 ^{13}C NMR spectrometer, Perkin-Elmer 681 IR spectrometer, Cary 210 UV spectrometer. Starting materials were synthesized according to published procedures (triglicolic acid and acid chloride,[12] triethyleneglycol ditosylate **1**,[13] 2-(p-tosylamino) aniline **2**[5a]).

1,2-*Di*(2-*phenylaminoethoxy*)*ethane* **5a** (*hydrochloride*)

The ditosylate **1** (38.8 g) was kept under argon at 100° in freshly distilled aniline (200 ml) for 6 h. After cooling, the p-toluenesulfonic salt of aniline was precipitated by addition of ether. The excess of aniline was removed under vacuum (100°, 0.5 mm Hg). The resulting oil was dissolved in ethyl acetate and filtered on alumina. The bis-hydrochloride (26.6 g, 84%) was cristallized from methanol: ether (m.p. 140° with decomposition. Calc C, 57.90; H, 7.03; N, 7.50; Found: C, 57.91; H, 7.00; N, 7.52%.

Triglycolic acid Di-(2-*p-tosylamino*)*anilide* **4**

Triglicolic acid dichloride **3** (9 g) in 200 ml of dry CH_2Cl_2 was added dropwise (2 hr) to a stirred and cooled (0°) solution of **2** (21.2 g) in 300 ml of CH_2Cl_2 containing 10 ml of pyridine. The resulting diamide precipitated quantitatively from the reaction mixture after standing overnight at room temperature. Recrystallisation in chloroform: methanol (19.7 g 73%)(m.p. 230° with decomposition. Calc C, 57.66; H, 5.10; N, 8.41; Found, C, 57.50; H, 5.15; N, 8.22%.

1,2-*Di*{2-[2-(*p-tosylamino*)*anilino*]*ethoxy*}*ethane* **5b**

The diamide **4** (11.6 g) was added portionwise to a slurry of $LiAlH_4$ (6.7 g) in 500 ml of THF. The mixture was refluxed under argon for 4 h. After cooling to 0°, the excess of hydride was destroyed by addition of water under argon. The pH was adjusted to about 7 by addition of concentrated HCl. The upper phase was decanted and the inorganic residue washed three times with a mixture of CH_2Cl_2 and ether (2 : 1). The solid obtained by evaporation of the organic extracts was dissolved in boiling methanol (600 ml) and the title compound (9.3 g, 84%) was precipitated by addition of water (500 ml). The compound was a pale brown colored powder; its solutions darkened when exposed to air. Mass spectrum: M^+, Calc *m/e* 638.2239; Found 638.1982.

9,18-*Diphenyl*-1,8-*dioxo*-3,6,12,15-*tetraoxa*-9,18-*diazacyclooctadecane* **6a**

Regular glassware and an ordinary mechanical stirrer were used. Benzene was dried over sodium and pyridine distilled from KOH. Two solutions (*A*, *B*) of equal concentration in reagents were prepared: A = free diamine **5a** (8.8 g), pyridine (10 ml), benzene (240 ml); B = acid chloride **3** (8.0 g), benzene (320 ml). Both solutions were added simultaneously and portionwise (2 ml each 3 minutes) to 500 ml of stirred benzene (alternatively, a peristaltic pump was used). When the diamine solution was consumed, the remaining acid chloride solution (70 ml) was slowly added to ensure total consumption of unreacted diamine (control by TLC). The solution was filtered after standing overnight. The product (9.4 g, 73%) was isolated from the filtrate by column chromatography on silica using ethyl acetate as eluent. Crystallization was from ethyl acetate, m.p. 135°. Calc C, 65.13; H, 6.85; N, 6.33; Found, C, 65.18; H, 6.91; N, 6.40%.

9,18-*Di*[2-(*p-tosylamino*)*phenyl*]-1,8-*dioxo*-3,6,12,15-*tetraoxa*-9,18-*diazacyclooctadecane* **6b**

The same procedure was used as for **6a**. Solution A: diamine **5b** (10.1 g), pyridine (8 ml), benzene (600 ml) (heating was necessary to ensure complete dissolution of the diamine). Solution B: acid chloride **3** (4.4 g), benzene (700 ml). The product (7.6 g, 62%) was isolated by column chromatography on silica (a gradient of methanol in ethyl acetate was used). Crystallization was from ethyl acetate, m.p. 190°. Calc C, 58.46; H, 5.64; N, 7.18; Found C, 58.45; H, 5.59; N, 7.05).

7,16 - *Diphenyl* - 1,4,10,13 - *tetraoxa* - 7,16 - *diaza* - *cycloocta-decane* **7a**

The diamide **6a** (4 g) was dissolved in dry THF (80 ml). A 1 M solution of diborane in THF (44 ml) was added using a syringe. The mixture was refluxed under argon for 3 h. After cooling, the excess of diborane was destroyed by addition of water. The mixture was evaporated, suspended in water and reevaporated to dryness. The solid residue was triturated with chloroform and filtrated. The product was isolated from the filtrate by column chromatography on silica using ethyl acetate as eluent. The fractions migrating first were allowed to evaporate slowly, leaving the cristalline title compound (2.65 g, 71%), m.p. 90°, ^{13}C NMR, see Ref. 2*b* ^1H NMR (60 MHz, $CDCl_3$) $\delta^{ppm}_{TMS} = 7.27$ (dd, 4H, $J_1 = 7$ Hz, $J_2 = 8$ Hz), 6.5–6.9 (m, 6H), 3.63 (m, 24H). Calc C, 69.52; H, 8.28; N, 6.76; Found C, 69.63; H, 8.20; N, 6.87).

7,16-*Di*[2-(*p-tosylamino*)*phenyl*]-1,4,10,13-*tetraoxa*-7,16-*diazacyclooctadecane* **7b**

The reduction of diamide **6b** (8.1 g) by $LiAlH_4$ (4.5 g) in THF (500 ml) followed the same procedure as that for **5b**. The inorganic residue was washed with THF and the solvent was decanted. The combined washings were evaporated to dryness and the title compound (4.8 g., 61%) isolated by column chromatography on silica using a mixture of ethyl acetate and chloroform 1 : 4 as eluent, followed by crystallization from the fractions eluted first, by addition of petroleum ether. Recrystallization in ethyl acetate: chloroform gave material m.p. 195°. ^{13}C NMR ($CDCl_3$, δ^{ppm}_{TMS}:

143.3, 140.1, 137.0, 135.6, 129.3, 127.4, 126.0, 123.6, 123.5, 117.7 (10 symmetry-non equivalent carbons of the aromatic rings), 70.6, 68.7, 54.6 (N–$\underline{C}H_2$–$\underline{C}H_2$–O–$\underline{C}H_2$), 21.5 (CH_3). 60 MHz ^{1}H NMR ($CDCl_3$) δ^{ppm}_{TMS}, ca. 9.17 (broad signal, 2H), 8.1–6.8 (m, 16H), 3.83 (s, 8H), 3.50 (t, 8H, J = 5Hz), 3.00 (t, 8H, J = 5 Hz), 2.38 (s, 6H). Mass spectrum: (M + 1) *m/e* 753. Calc C, 60.64; H, 6.38; N, 7.45; Found, C, 60.53; H, 6.36; N, 7.39%.

7,16-Di[(2-amino)phenyl]-1,4,10,13-tetraoxa-7,16-dizacyclooctadecane **7c**

A freshly prepared solution of sodium–naphthalene in THF (0.6 g Na, 3.4 g naphthalene, 40 ml THF) was added using a syringe to a cooled (− 10°) suspension of **7b** (1.0 g) in THF (10 ml). After stirring for 1.5 h at − 10°, 2ml of water was added. The reaction mixture was partitioned between water and CH_2Cl_2. The residue of evaporation of the CH_2Cl_2 phase was dissolved in a mixture of ether and aqueous HCl (10%). The naphthalene was removed by repeated ether extractions. The water phase was made alkaline (KOH) and extracted with CH_2Cl_2. The title compound (0.4 g, 70%) was obtained spectroscopically pure by filtration on alumina using ethyl acetate, benzene (1 : 1) as eluent. Its solution were very oxygen-sensitive. ^{13}C NMR, see Ref. 2b, 60 MHz ^{1}H NMR ($CDCl_3$ + D_2O), δ^{ppm}_{TMS}, 7.4–6.2 (m, 8H), 3.47 (s, 8H), 3.37 (t, 8H, J = 5 Hz) 3.10 (t, 8H, J = 5Hz). Mass spectrum: M + 1: 445. The product was further characterized as a derivative (i.e. **7d**).

7,16-Dis[2-(3-carboxypropionylamino)]phenyl-1,4,10,13-tetraoxa-7,16-diazacyclooctadecane **7d**

The diamine **7c** (0.31 g) was dissolved in dry pyridine (10 ml). An excess of succinic anhydride (0.22 g) was added and the mixture stirred for 24 h. The residue after evaporation was dissolved in CH_2Cl_2 and extracted with aqueous HCl (10%). The resulting extracts were alkalized (solid Na_2CO_3) and washed with CH_2Cl_2. The pH of the water phase was then adjusted to about 3 by addition of acetic acid and the product extracted using CH_2Cl_2.

Crystallization of the compound in isopropanol gave a 1 : 1 isopropanol solvate (0.24 g, 50%), two types of crystals: needles and/or polyhedrons, mp 192–195° with decomposition. IR (KBr, cm^{-1}, 3500–2500 (OH and NH stretching), 1732 (COOH stretching), 1670–1642 (amide I, two bands), 1525 (amide II). 200 MHz ^{1}H NMR ($CDCl_3$), δ^{ppm}_{TMS}, 9.58 (broad s, 2H), 8.38 (dd, 2H, J_1 = 1.5 Hz, J_2 = 8.0 Hz), 7.4–6.9 (m, 8H), 3.67 (s, 8H), 3.55 (t, 8H, J = 6.1 Hz), 3.14 (t, 8H, J = 6.1 Hz), 2.83 (m, 4H), 2.62 (m, 4H): the isopropanol present in the solvate featured peaks at *ca* 5.0 (very broad: O-H), 4.01 (sept., J = 6.1 Hz), 1.20 ppm (d, J = 6.1 Hz). ^{13}C NMR ($CDCl_3$), δ^{ppm}_{TMS}, 179.3, 170.1 (two types of C = 0), 139.6, 136.3, 126.3 123.6, 123.0 119.9 (–C_6H_4–), 71.4, 69.4, 53.8 (N–$\underline{C}H_2$–$\underline{C}_2$–O–$\underline{C}H_2$), 31.7 29.9 (–CO–$\underline{C}H_2$–$\underline{C}H_2$–CO–); the isopropanol present in the solvate featured peaks at 64.5 and 25.4 ppm. Mass spectrum (M + 1) *m/e* 645. Calc C, 59.63; H, 7.45; N, 7.95; Found C, 59.65; H, 7.67; N, 7.78%.

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