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Structural analysis of *bis*-amidines and *bis*-nitriles in solid-state by combining NMR spectroscopy and molecular modeling

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ABSTRACT

The paper presents the analysis of the structures of four novel sulfonamide-based *bis*-amidines, and four novel interesting intermediates leading to them, named *bis*-nitriles, in solid-state based on ^{13}C CP/MAS NMR spectroscopy and theoretical calculations of shielding constants at DFT level of theory. We have observed double ^{13}C resonances in solid-state spectra as compared with solution spectra. The considerations of experimental chemical shifts followed by shielding computations allowed us to define essential geometric details regarding the most probable conformations in solid-state. All compounds have one independent molecule in the asymmetric unit, and a main reason of splittings of NMR signals in solid-state is different orientation of alkoxy fragments (methyl groups and linker) with reference to benzene rings.

1. Introduction

The therapy of infection due to *Pneumocystis carinii* has evolved over the past 30 years, because of an increased incidence of patients presenting with, in addition to *P. carinii*, multiple opportunistic infections, and the development of atypical, extrapulmonary presentation of disease [1–3]. The main anti-*Pneumocystis* agents are trimethoprim (TMP) – sulfamethoxazole (SMX) combination and pentamidine. However, nephrotoxicity and other side effects of full-dose of these antimicrobial agents are common, and less toxic analogs have been sought [4–6]. The modes of action of these drugs are different: TMP–SMX interferes with folate metabolism and pentamidine belongs to DNA minor groove binders. Thus, to design and obtain novel derivatives structurally similar to both groups (Fig. 1), which could potentially interact with many molecular targets in the organism, should be an interesting scientific goal. Moreover, *bis*-amidines have been studied as antitumor, antiviral, and anticoagulant agents [7–10]. Recently, many efforts have been directed at the elucidation of structural details in solid-state of new substances designed as potential chemotherapeutics. Compounds forming good single crystals can be characterized by X-ray diffraction techniques, whereas these forming merely microcrystallites can be studied by combining few methods like solid-state NMR spectroscopy and molecular modeling [11,12]. We now report the analysis of the structure of several novel sulfonamide-based *bis*-amidines, and also interesting intermediates leading to them named *bis*-nitriles in solid-state using ^{13}C CP/MAS NMR spectroscopy and molecular modeling.

2. Experimental

2.1. Syntheses

All starting substances were purchased from the major chemical suppliers as high or highest purity grade and used without any further purification.

The synthetic route to *bis*-nitriles **1c**–**4c** and *bis*-amidines **1**–**4** is outlined in Scheme 1 for clarity. In the first step *N*,*N*-*bis*(2-chloroethyl)-benzenesulfonamides **1a** and **1b** were prepared by a modification of the procedure given in [13]. The inclusion of 1-methyl-2-pyrrolidone as the solvent and the triethylamine for neutralizing the hydrogen chloride leads to more satisfactory yields and purer benzenesulfonamides **1a** and **1b**. The *bis*-nitriles **1c**–**4c** were synthesized by reactions of **1a** and **1b** with 4-hydroxybenzonitrile [14] or 4-hydroxy-3,5-dimethoxybenzonitrile [15], respectively. The conversion of **1c**–**4c** to diamidines **1**–**4** generally followed the established procedures [16–18]. The imidate ester hydrochlorides **1d**–**4d** generated as the intermediates were very hygroscopic, and thus were immediately converted into amidines without purification [19]. Unexpectedly, conversion of the dinitrile **4c** to the diamidine **4** was accompanied by hydrolysis of acetamide group at C4″ atom to the amine one.

Melting points of the products were determined with a Digital Melting Point Apparatus 9001. Elemental analyses were performed on GmbH – Vario EL III C,H,N,S Element Analyzer, and were averaged from two independent determinations. Chemical shifts

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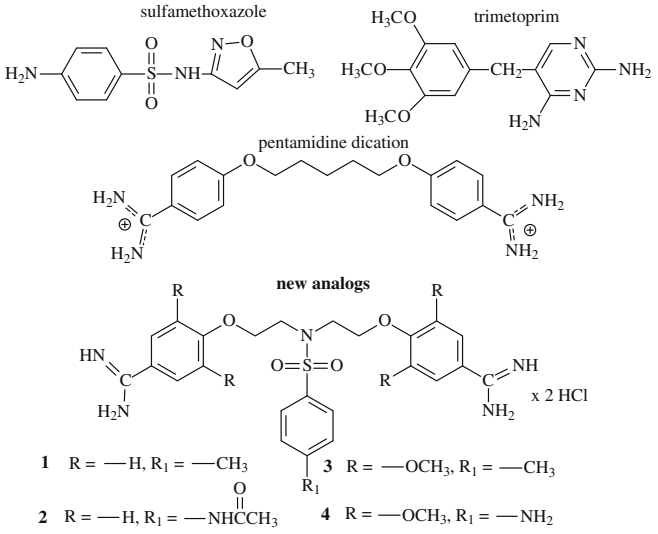


Fig. 1. Chemical formulas of main anti-*Pneumocystis* agents and new analogs.

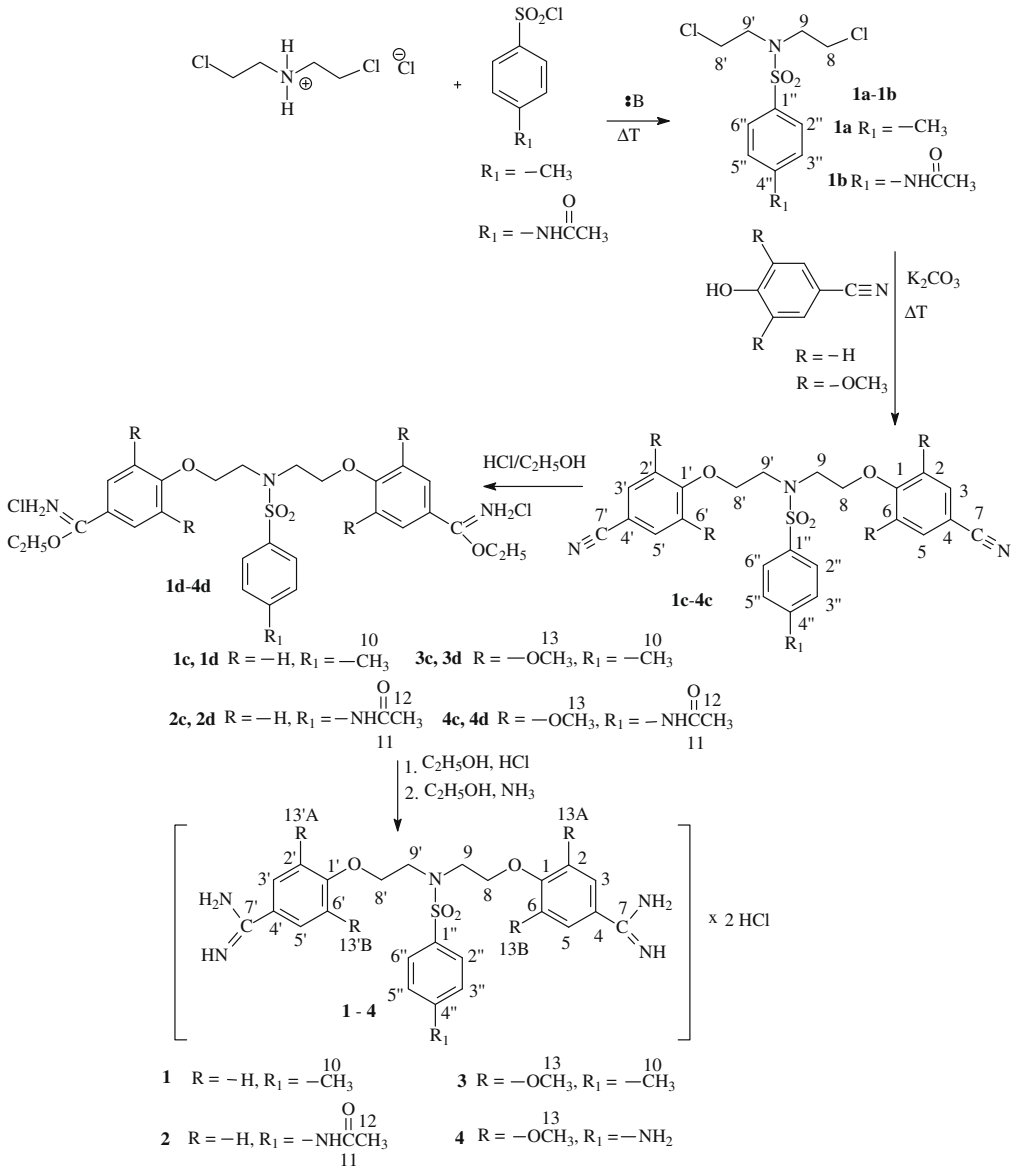
(ppm) in solutions were referenced to TMS (the kind of solvent is given next to spectral data).

2.1.1. N,N-Bis(2-chloroethyl)-4-toluenesulfonamide (**1a**) [13]

A 2.31 g (78%) of colorless crystals of **1a** was obtained from 4-toluenesulfonyl chloride (1.9 g; 10 mmol) and *bis*(2-chloroethyl)amine hydrochloride (1.78 g; 10 mmol). M.p. 46–48 °C (Ref. [13]: 46 °C); ^{1}H NMR (199.97 MHz, $CDCl_3$): δ = 2.44 (s, 3H, 10-CH_3), 3.47 (t, J = 6.9 Hz, 4H, 8-CH_2, 8′-CH_2), 3.68 (t, J = 6.9 Hz, 4H, 9-CH_2, 9′-CH_2), 7.34 (m, 2H, 3″-H, 5″-H), 7.72 (m, 2H, 2″-H, 6″-H) ppm. ^{13}C NMR (50.28 MHz, $CDCl_3$): δ = 21.44 (C-10), 42.09 (C-9, C-9′), 51.53 (C-8, C-8′), 127.09 (C-2″, C-6″), 129.90 (C-3″, C-5′), 135.48 (C-1″), 144.06 (C-4″) ppm. IR (KBr disc, cm^{-1}): 3060 (w) $\nu_{C-H\ ar}$; 2962 (m) $\nu_{CH3\ as}$; 2912 (m) $\nu_{CH2\ as}$; 2860–2850 (m) $\nu_{CH3\ sym}$ and $\nu_{CH2\ sym}$; 1597, 1493 (m) $\nu_{C=C}$; 1460–1450 (m) $\nu_{C=C}$ and $\delta_{C-H\ al}$; 1342 (s) $\nu_{SO2\ as}$; 1157 (s) $\nu_{SO2\ sym}$; 810 (s) γ_{H-C}.

2.1.2. N,N-Bis(2-chloroethyl)-4-(acetylamino)benzenesulfonamide (**1b**)

A 2.10 g (62%) of the light yellow crystals of **1b** was obtained from 4-(acetylamino)benzenesulfochloride (2.33 g; 10 mmol) and



Scheme 1. Reactions and reagents and atoms numbering used in the discussion.

bis(2-chloroethyl)amine hydrochloride (1.78 g; 10 mmol) by the procedure analogous to that for **1a**. M.p. 111–112 °C; ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 2.06 (s, 3H, 12-CH_3), 3.40 (t, J = 6.6 Hz, 4H, 9-CH_2, 9′-CH_2), 3.68 (t, J = 6.6 Hz, 4H, 8-CH_2, 8′-CH_2), 7.77 (br s, 4H, 2″-H, 3″-H, 5″-H, 6″-H), 10.35 (s, 1H, NH) ppm; ^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 24.16 (C-12), 42.26 (C-9, C-9′), 50.21 (C-8, C-8′), 118.81 (C-3″, C-5″), 128.31 (C-2″, C-6″), 131.71 (C-1″), 143.54 (C-4″), 169.10 (C-11); IR (KBr disc, cm^{-1}): 3302–3260 (m, br) $\nu_{N-H\ as}$; 3190 (m) $\nu_{N-H\ sym}$; 3059 (m) $\nu_{C-H\ ar}$; 2975–2855 (w, br) ν_{CH3} and ν_{CH2}; 1593,1497 (s) $\nu_{C=C}$; 1543 (s) δ_{N-H}; 1454 (m) $\delta_{C-H\ al}$; 1338 (s) $\nu_{SO2\ as}$; 1157 (s) $\nu_{SO2\ sym}$; 826 (m) γ_{H-C}.

2.1.3. N,N-Bis[2-(4-cyanophenoxy)ethyl]-4-toluenesulfonamide (**1c**)

N,N-Bis(2-chloroethyl)-4-toluenesulfonamide **1a** (0.89 g; 3 mmol), 4-hydroxybenzonitrile (0.71 g; 6 mmol), anhydrous K_2CO_3 (1.38 g; 10 mmol), and *N*-methyl-2-pyrrolidone (10 ml) were intensively stirred and heated at about 130 °C for 12 h. After this time the reaction mixture was poured into ice water (50 ml) to form an oil, which solidified after a few hours. The crystals were collected by filtration, washed with water and dried. Recrystallization from ethanol gave 0.55 g (40%) of colorless crystals of **1c**. M.p. 133–137 °C; $C_{25}H_{23}N_3O_4S$ (461.5): calcd. C 65.06, H 5.02, N 9.10, S 6.95%; found C 64.58, H 5.04, N 8.81, S 6.97%; ^{1}H NMR (199.97 MHz, $CDCl_3$): δ = 2.41 (s, 3H, 10-CH_3), 3.68 (t, J = 5.6 Hz, 4H, 9-CH_2, 9′-CH_2), 4.24 (t, J = 5.6 Hz, 4H, 8-CH_2, 8′-CH_2), 6.86 (m, 4H, 2-H, 2′-H, 6-H, 6′-H), 7.29 (m, 2H, 3″-H, 5″-H), 7.55 (m, 4H, 3-H, 3′-H, 5-H, 5′-H), 7.72 (m, 2H, 2″-H, 6″-H) ppm; ^{13}C NMR (50.28 MHz, $CDCl_3$): δ = 21.41 (C-10), 48.96 (C-9, C-9′), 67.35 (C-8, C-8′), 104.43 (C-4, C-4′), 114.99 (C-2, C-6, C-2′, C-6′), 118.84 (C-7, C-7′), 127.00 (C-2″, C-6″), 129.82 (C-3″, C-5″), 133.95 (C-3, C-5, C-3′, C-5′), 135.85 (C-1″), 143.91 (C-4″), 161.29 (C-1, C-1′) ppm; IR (KBr disc, cm^{-1}): 3100–3050 (w, br) $\nu_{C-H\ ar}$; 2951–2928 (m, br) ν_{CH3}; 2885–2880 (w) ν_{CH2}; 2226 (m) $\nu_{C\equiv N}$; 1605, 1574, 1512 (s) $\nu_{C=C}$; 1465–1450 (m) $\delta_{C-H\ al}$; 1308 (s) $\nu_{SO2\ as}$; 1258 (s) $\nu_{C-O\ as}$; 1153 (s) $\nu_{SO2\ sym}$; 1011 (s) $\nu_{C-O\ sym}$; 837 (s) γ_{H-C}.

2.1.4. N,N-Bis{2-[4-(ethoxyiminoyl)phenoxy]ethyl}-4-toluenesulfonamide dihydrochloride (**1d**)

Dry ethanol (40 ml) was saturated with anhydrous HCl at 0–5 °C. To this solution *N,N-bis*[2-(4-cyanophenoxy)ethyl]-4-toluenesulfonamide **1c** (1.84 g; 4 mmol) was added, and the contents were stirred in a sealed vessel for 24 h at room temperature. Then the reaction mixture was diluted with dry diethyl ether (100 ml) until colorless crystals were formed. The crystals were quickly filtered off, and dried under reduced pressure over anhydrous $CaCl_2$.

2.1.5. N,N-Bis[2-(4-amidinophenoxy)ethyl]-4-toluenesulfonamide dihydrochloride (**1**)

Dry ethanol (40 ml) was saturated with anhydrous NH_3 at 0–5 °C. To the prepared solution all amount of *N,N-bis*{2-[4-(ethoxyiminoyl)phenoxy]ethyl}-4-toluenesulfonamide dihydrochloride **1d** obtained from **1c** was added, and the whole was stirred in a sealed vessel for 24 h at room temperature. Ethanol was evaporated under reduced pressure almost to dryness. The residue was placed in a solution of NaOH (1.0 g) in water (40 ml) and stirred for 15 min. The free base, which was formed as a fine white precipitate was filtered, washed thoroughly with water, and dried under vacuum over anhydrous $CaCl_2$. The dry colorless powder was then mixed with anhydrous ethanol (10 ml), acidified with an excess of ethanolic HCl, and refluxed to obtain a homogeneous solution. After cooling, dry diethyl ether (30 ml) was slowly added with stirring. After a few minutes the colorless crystals were filtered, washed with dry diethyl ether, and dried to give 1.83 g (84%) of the pure product **1.** M.p. 228–232 °C; $C_{25}H_{29}N_5O_4S \cdot 2HCl \cdot H_2O$ (586.5): calcd. C 51.19, H 5.67, N 11.94, S 5.47%; found C 51.04, H 5.72, N 11.45, S 5.57%; ^{1}H NMR (199.97 MHz, DMSO-d_6): δ = 2.38 (s, 3H, 10-CH_3), 3.69 (br s, 4H, 9-CH_2, 9′-CH_2), 4.28 (br s, 4H, 8-CH_2, 8′-CH_2), 7.05 (m, 4H, 2-H, 2′-H, 6-H, 6′-H), 7.40 (m, 2H, 3″-H, 5″-H), 7.77 (m, 2H, 2″-H, 6″-H), 7.94 (m, 4H, 3-H, 3′-H, 5-H, 5′-H), 9.22 (br s, 4H, NH_2), 9.45 (br s, 4H, NH_2) ppm; ^{13}C NMR (50.28 MHz, DMSO-d_6): δ = 20.88 (C-10), 47.75 (C-9, C-9′), 66.75 (C-8, C-8′), 114.57 (C-2, C-6, C-2′, C-6′), 119.48 (C-4, C-4′), 126.91 (C-2″, C-6″), 129.78 (C-3″, C-5″), 130.16 (C-3, C-5, C-3′, C-5′), 135.78 (C-1″), 143.33 (C-4″), 162.27 (C-7, C-7′), 164.56 (C-1, C-1′) ppm; IR (KBr disc, cm^{-1}): 3526 (m) $\nu_{N-H\ as}$; 3400–3200 (s, br) $\nu_{N-H\ sym}$, 3055 (s) $\nu_{C-H\ ar}$; 2882 (w) ν_{CH2}; 1670 (s) $\nu_{=NH}$; 1608, 1489 (s) $\nu_{C=C}$; 1570 (w) δ_{N-H}; 1319 (s) $\nu_{SO2\ as}$; 1269 (s) $\nu_{C-O\ as}$; 1150 (s,) $\nu_{SO2\ sym}$; 1022 (s) $\nu_{C-O\ sym}$; 841 (s) γ_{H-C}.

2.1.6. N,N-Bis[2-(4-cyanophenoxy)ethyl]-4-(acetylamino)-benzenesulfonamide (**2c**)

A 0.76 g (50%) of white powder of **2c**, hardly soluble in most commonly used solvents was obtained from 1.02 g *N,N-bis*(2-chloroethyl)-4-(acetylamino)benzenesulfonamide **1b** (3 mmol) and 0.72 g 4-hydroxybenzonitrile (6 mmol) by the procedure described for **1c**. The crude product was purified by refluxing with acetone (10 ml). M.p. 215–216 °C; $C_{26}H_{24}N_4O_5S$ (504.8): calcd. C 61.89, H 4.79, N 11.10, S 6.35%; found C 61.68, H 4.70, N 10.98, S 6.27%; ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 2.09 (s, 3H, 12-CH_3), 3.60 (br s, 4H, 9-CH_2, 9′-CH_2), 4.21 (br s, 4H, 8-CH_2, 8′-CH_2), 6.99 (m, 4H, 2-H, 6-H, 2′-H, 6′-H), 7.71 (m, 4H, 3-H, 5-H, 3′-H, 5′-H), 7.72 (m, 2H, 2″-H, 6″-H), 7.77 (m, 2H, 3″-H, 5″-H), 10.31 (s, 1H, NH) ppm; ^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 24.12 (C-12), 47.74 (C-9, C-9′), 66.76 (C-8, C-8′), 103.07 (C-4, C-4′), 115.43 (C-2, C-6, C-2′, C-6′), 118.69 (C-3″, C-5″), 119.03 (C-7, C-7′), 128.15 (C-2″, C-6″), 132.22 (C-1″), 134.11 (C-3, C-5, C-3′, C-5′), 143.27 (C-4″), 161.42 (C-1, C-1′), 168.99 (C-11) ppm; IR (KBr disc, cm^{-1}): 3337 (s) $\nu_{N-H\ as}$; 3290 (m) $\nu_{N-H\ sym}$; 3101 (m) $\nu_{C-H\ ar}$; 2951–2930 (m, br) ν_{CH3} and ν_{CH2}; 2222 (s) $\nu_{C\equiv N}$; 1585, 1497 (s) $\nu_{C=C}$; 1535 (s) δ_{N-H}; 1458 (s) $\delta_{C-H\ al}$; 1323 (s) $\nu_{SO2\ as}$; 1242 (s) $\nu_{C-O\ as}$; 1153 (s) $\nu_{SO2\ sym}$; 1018 (s) $\nu_{C-O\ sym}$; 833 (s) γ_{H-C}.

2.1.7. N,N-Bis[2-(4-amidinophenoxy)ethyl]-4-(acetylamino)-benzenesulfonamide dihydrochloride (**2**)

Compound **2** was prepared by the method described for **1** from *N,N-bis*{2-[4-(ethoxyiminoyl)phenoxy]ethyl}-4-(acetylamino)benzenesulfonamide dihydrochloride **2d** (obtained from *N,N-bis*[2-(4-cyanophenoxy)ethyl]-4-(acetylamino)benzenesulfonamide **2c** (1.40 g; 2.78 mmol) by the procedure given for **1d**). The resulting colorless precipitate **2** was filtered and dried to furnish 1.14 g (64%) of fine white crystals. M.p. 274–276 °C (dec); $C_{26}H_{30}N_6O_5S \cdot 2HCl \cdot 1½H_2O$ (638.6): calcd. C 48.90, H 5.52, N 13.16, S 5.02%; found C 49.16, H 5.40, N 13.18, S 4.84%; ^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 2.10 (s, 3H, 12-CH_3), 3.63 (br s, 4H, 9-CH_2, 9′-CH_2), 4.25 (br s, 4H, 8-CH_2, 8′-CH_2), 7.04 (m, 4H, 2-H, 2′-H, 6-H, 6′-H), 7.79 (br s, 4H, 2″-H, 3″-H, 5″-H, 6″-H), 7.85 (m, 4H, 3-H, 3′-H, 5-H, 5′-H), 9.10 (br s, 4H, NH_2), 9.31 (br s, 4H, NH_2), 10.64 (s, 1H, NH) ppm; ^{13}C NMR (100.62 MHz, DMSO-d_6): δ = 24.02 (C-12), 47.82 (C-9, C- 9′), 66.84 (C-8, C-8′), 114.72 (C-2, C-6, C-2′, C-6′), 118.75 (C-3″, C-5″), 119.46 (C-4′), 119.52 (C-4), 128.08 (C-2″, C-6″), 130.20 (C-3, C-5, C-3′, C-5′), 143.20 (C-4″), 162.40 (C-7, C-7′), 164.42 (C-1′), 164.49 (C-1), 169.16 (C-11) ppm; IR (KBr disc, cm^{-1}): 3400–3200 (s, br) ν_{N-H}; 3113–3063 (s, br) $\nu_{C-H\ ar}$; 2930–2885 (m, br) $\nu_{C-H\ al}$; 1666 (s) $\nu_{=NH}$; 1612, 1585 (s) $\nu_{C=C}$; 1540–1520 (s) δ_{N-H}; 1466–1550 (s) $\delta_{C-H\ al}$; 1335 (s) $\nu_{SO2\ as}$; 1273 (s) $\nu_{C-O\ as}$; 1142 (s) $\nu_{SO2\ sym}$; 1022 (s) $\nu_{C-O\ sym}$; 845 (w) γ_{H-C}.

2.1.8. N,N-Bis[2-(4-cyano-2,6-dimethoxyphenoxy-)ethyl]-4-toluene-sulfonamide (**3c**)

Compound **3c** was obtained from *N,N-bis*(2-chloroethyl)-4-toluenesulfonamide **1a** (1.48 g; 5 mmol) and 4-hydroxy-3,5-

dimethoxybenzonitrile (1.79 g; 10 mmol) by the procedure described for **1c**. Recrystallization from large amount of ethanol with hot filtering 1.62 g (56%) of beige crystals of **3c** were obtained. M.p. 178.5–180.0 °C; $C_{29}H_{31}N_3O_8S$ (581.6): calcd. C 59.89, H 5.37, N 7.22, S 5.51%; found C 59.54, H 5.40, N 6.96, S 5.46%; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.40 (s, 3H, 10-CH_3), 3.67 (t, J = 6 Hz, 4H, 9-CH_2, 9′-CH_2), 3.79 (s, 12H, 13A-OCH_3, 13B-OCH_3 13′A-OCH_3, 13′B-OCH_3), 4.21 (t, J = 6 Hz, 4H, 8-CH_2, 8′-CH_2), 6.81 (s, 4H, 3-H, 3′-H, 5-H, 5′-H), 7.25 (m, 2H, 3″-H, 5″-H), 7.70 (m, 2H, 2″-H, 6″-H) ppm; ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 21.70 (C-10), 49.27 (C-9, C-9′), 56.42 (C-13A, C-13B, C-13′A, C-13′B), 72.48 (C-8, C-8′), 107.04 (C-4, C-4′), 109.49 (C-3, C-5, C-3′, C-5′), 119.09 (C-7, C-7′), 127.41 (C-2″, C-6″), 129.74 (C-3″, C-5″), 136.98 (C-1″), 141.34 (C-1, C-1′), 143.48 (C-4″), 153.68 (C-2, C-6, C-2′,C-6′) ppm; IR (KBr disc, cm^{-1}): 3110–3050 (w, br) $\nu_{C-H\ ar}$; 2970 (w) ν_{CH3}; 2955 (w) $\nu_{CH2\ as}$; 2839 (w) $\nu_{CH2\ sym}$; 2226 (m) $\nu_{C\equiv N}$; 1589,1504,1420 (s) $\nu_{C=C}$; 1470–1450 (m, br) $\nu_{C=C}$ and $\delta_{C-H\ al}$; 1338 (s) $\nu_{SO2\ as}$; 1238 (s) $\nu_{C-O\ as}$; 1134 (s) $\nu_{SO2\ sym}$; 1011 (m) $\nu_{C-O\ sym}$; 845 (m) γ_{H-C}.

2.1.9. N,N-Bis[2-(4-amidino-2,6-dimethoxyphenoxy)ethyl]-4-toluenesulfonamide dihydrochloride (**3**)

Compound **3** was prepared by the method described for **1** from *N,N-bis*{2-[4-(ethoxyiminoyl)2,6-dimethoxyphenoxy]ethyl}-4-toluenesulfonamide dihydrochloride **3d** (obtained from *N,N-bis*[2-(4-cyano-2,6-dimethoxyphenoxy)ethyl]-4-toluenesulfonamide **3c** (1.16 g; 2 mmol) by the procedure given for **1d**). The obtained yellow solid was filtered, washed with acetone and dried to give 0.87 g (59%) of light yellow powder of **3**. M.p. 214.5–217.5 °C (dec); $C_{29}H_{37}O_8N_5S \cdot 2HCl \cdot 2½H_2O$ (733.7): calcd: C 47.47, H 6.00, N 9.54, S 4.37%; found C 47.51, H 5.86, N 9.54, S 4.37%; ^{1}H NMR (199.97 MHz, DMSO-d_6): δ = 2.38 (s, 3H, 10-CH_3), 3.59 (t, J = 5.8, 4H, 9-CH_2, 9′-CH_2), 3.82 (s, 12H, 13A-OCH_3, 13B-OCH_3 13′A-OCH_3, 13′B-OCH_3), 4.09 (t, J = 5.8, 4H, 8-CH_2, 8′-CH_2), 7.26 (s, 4H, 3-H, 5-H, 3′-H, 5′-H), 7.39 (m, 2H, 3″-H, 5″-H), 7.69 (m, 2H, 2″-H, 6″-H), 9.20 (br s, 4H, NH_2), 9.48 (br s, 4H, NH_2) ppm; ^{13}C NMR (50.28 MHz, DMSO-d_6): δ = 20.91 (C-10), 48.38 (C-9, C-9′), 56.29 (C-13A, C-13B, C-13′A, C-13′B), 71.39 (C-8, C-8′), 105.89 (C-3, C-5, C-3′, C-5′), 122.36 (C-4, C-4′), 126.80 (C-2″, C-6″), 129.73 (C-3″, C-5″), 136.28 (C-1″), 140.51 (C-1, C-1′), 143.18 (C-4″), 152.59 (C-2, C-6, C-2′, C-6′), 164.70 (C-7, C-7′) ppm; IR (KBr disc, cm^{-1}): 3400–3010 (s, br) ν_{N-H}; 3001 (m) $\nu_{C-H\ ar}$; 2974 (m) $\nu_{CH3\ as}$; 2947 (m) $\nu_{CH2\ as}$; 2839 (w) $\nu_{CH2\ sym}$; 1670 (s) $\nu_{=NH}$; 1601, 1489, 1427 (s) $\nu_{C=C}$; 1551 (m) δ_{N-H}; 1465–1450 (s) $\delta_{C-H\ al}$; 1331 (s) $\nu_{SO2\ as}$; 1281 (s) $\nu_{C-O\ as}$; 1150–1134 (s, br) $\nu_{SO2\ sym}$; 849 (s) γ_{H-C}.

2.1.10. N,N-Bis[2-(4-cyano-2,6-dimethoxyphenoxy)ethyl]-4-(acetylamino)benzenesulfonamide (**4c**)

N,N-Bis(2-chloroethyl)-4-(acetylamino)benzenesulfonamide **1b** (1.69 g; 5 mmol), 4-hydroxy-3,5-dimethoxybenzonitrile (1.79 g; 10 mmol), anhydrous K_2CO_3 (2.76 g; 20 mmol), and *N*-methyl-2-pyrrolidone (30 ml) were mixed together and stirred at 120 °C for 5 h and then poured into water (300 ml). The precipitated solid was filtered. Recrystallization from ethanol gave 1.72 g (55%) of yellow crystals of **4c**. M.p. 184–185 °C; $C_{30}H_{32}N_4O_9S$ (624.7): calcd. C 57.68, H 5.16, N 8.97, S 5.13%; found C 57.60, H 5.11, N 8.98, S 5.16%; ^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.26 (s, 3H, 12-CH_3), 3.73 (t, J = 6.0 Hz, 4H, 9-CH_2, 9′-CH_2), 3.84 (s, 12H, 13A-OCH_3, 13B-OCH_3 13′A-OCH_3, 13′B-OCH_3), 4.25 (t, J = 6.0 Hz, 4H, 8-CH_2, 8′-CH_2), 6.84 (s, 4H, 3-H, 5-H, 3′-H, 5′-H), 7.44 (br s, 1H, NH), 7.60 (m, 2H, 3″-H, 5″-H), 7.78 (m, 2H, 2″-H, 6″-H) ppm; ^{13}C NMR (100.62 MHz, $CDCl_3$): δ = 24.94 (C-12), 49.16 (C-9, C-9′), 56.42 (C-13A, C-13B, C-13′A, C-13′B), 72.42 (C-8, C-8′), 106.92 (C-4, C-4′), 109.40 (C-3, C-5, C-3′, C-5′), 119.16 (C-3″, C-5″), 119.30 (C-7, C-7′), 128.53 (C-2″, C-6″), 134.83 (C-1″), 141.26 (C-1, C-1′), 141.94 (C-4″), 153.58 (C-2, C-6, C-2′, C-6′), 168.90 (C-11) ppm; IR (KBr disc, cm^{-1}): 3371 (s) $\nu_{N-H\ as}$; 3170 (w) $\nu_{N-H\ sym}$; 3098–3067 (m, br) $\nu_{C-H\ ar}$; 2966 (m) $\nu_{CH3;}$ 2839(m) ν_{CH2}; 2233 (s) $\nu_{C\equiv N}$; 1597, 1497, 1420 (s) $\nu_{C=C}$; 1550 (s) δ_{N-H}; 1465–1455 (m) $\delta_{C-H\ al}$; 1327 (s) $\nu_{SO2\ as}$; 1250 (s) $\nu_{C-O\ as}$; 1134 (s) $\nu_{SO2\ sym}$; 1011 (s) $\nu_{C-O\ sym}$; 841 (s) γ_{H-C}.

2.1.11. N,N-Bis[2-(4-amidino-2,6-dimethoxyphenoxy)ethyl]4-aminobenzenesulfonamide dihydrochloride (**4**)

Compound **4** was prepared by the method described for **1** from *N,N-bis*{2-[4-(ethoxyiminoyl)2,6-dimethoxyphenoxy]ethyl}-4-(acetylamino)benzenesulfonamide dihydrochloride **4d** (obtained from *N,N-bis*[2-(4-cyanophenoxy)ethyl]-4-(acetylamino)benzenesulfonamide **4c** (1.25 g; 2 mmol) by the procedure given for **1d**). The resulting colorless precipitate was filtered, washed with a small amount of acetone and dried to give 1.1 g (70%) of **4**. M.p. 178.5–181.5 °C (dec); $C_{28}H_{36}N_6O_8S \cdot 2HCl \cdot 5H_2O$ (779.7): calcd. C 43.13, H 6.16, N 10.77, S 4.11%; found C 43.12, H 5.85, N 10.56, S 4.33%; ^{1}H NMR (500.61 MHz, DMSO-d_6): δ = 3.51 (t, J = 6.5, 4H, 9-CH_2, 9′-CH_2), 3.83 (s, 12H, 13A-OCH_3, 13B-OCH_3 13′A-OCH_3, 13′B-OCH_3), 4.07 (t, J = 6.5, 4H, 8-CH_2, 8′-CH_2), 4.52 (br s, 2H, NH_2), 6.11 (m, 2H, 3″-H, 5″-H), 7.27 (s, 4H, 3-H, 5-H, 3′-H, 5′-H), 7.51 (m, 2H, 2″-H, 6″-H), 9.21 (br s, 4H, NH_2), 9.49 (br s, 4H, NH_2) ppm. ^{13}C NMR (125.88 MHz, DMSO-d_6): δ = 48.26 (C-9, C-9′), 56.22 (C-13A, C-13B, C-13′A, C-13′B), 71.36 (C-8, C-8′), 105.82 (C-3, C-5, C-3′, C-5′), 114.80 (C-3″, C-5″), 122.29 (C-4, C-4′), 126.26 (C-1″), 128.64 (C-2″, C-6″), 140.46 (C-1, C-1′), 149.84 (C-4″), 152.55 (C-2, C-6, C-2′, C-6′), 164.67 (C-7, C-7′) ppm; IR (KBr disc, cm^{-1}): 3450–3000 (s, br) ν_{N-H} and $\nu_{C-H\ ar}$; 2970 (m) $\nu_{CH3\ as}$; 2920 (m) $\nu_{CH2\ as}$; 2860 (m) $\nu_{CH3\ sym}$; 2839 (m) $\nu_{CH2\ sym}$; 1678 (s) $\nu_{=NH}$; 1597, 1489, 1420 (s) $\nu_{C=C}$; 1543 (w) δ_{N-H}; 1454 (m) δ_{CH2}; 1327 (s) $\nu_{SO2\ as}$; 1265 (m) $\nu_{C-O\ as}$; 1134 (s) $\nu_{SO2\ sym}$; 1088 (m) $\nu_{C-O\ sym}$; 837 (w) γ_{H-C}.

2.2. NMR spectra measurements and molecular modeling details

^{1}H NMR and ^{13}C NMR spectra in solution were recorded at 25 °C with a Varian Unity plus-200 or plus-500 spectrometers, and standard Varian software was employed. Several (as indicated) ^{1}H NMR and ^{13}C NMR spectra in solution were recorded with a Bruker Avance DMX 400 spectrometer. The ^{13}C CP/MAS NMR spectra in solid-state were recorded with a Bruker Avance DMX 400 spectrometer. Samples were contained in 4 mm ZrO_2 rotors and mounted in standard 4 mm MAS probe. The powdered samples were spun at 8 kHz. Contact time of 2.0–4.0 ms, repetition time of 10–12 s, and spectral width of 24 kHz were used for accumulation of 4000 scans. Nonprotonated carbons and methyl groups were selectively observed by dipolar-dephasing experiment with delay time 50 μs. Chemical shifts δ (ppm) were referenced to TMS. IR spectra in KBr tablets were recorded on a FTIR-8300 Shimadzu instrument.

Theoretical shielding constants were computed at DFT level of theory with B3LYP/6-31G(2d,p) hybrid functional and GIAO CPHF (gauge invariant atomic orbitals coupled-perturbed Hartree–Fock) approach [20] for geometries optimized at PM3 level of theory [21] for all analyzed compounds. To check the applicability of the computational methods we have compared the results for *N,N-bis*[2-(4-cyanophenoxy)ethyl]-4-toluenesulfonamide (**1c**) obtained at DFT level with hybrid functionals B3LYP/6-31G(2d,p) for geometry optimization and B3LYP/6-311(2d,p) for NMR properties calculation with the data obtained at PM3 level for geometry optimization and B3LYP/G-31G(2d,p) level for NMR shielding constants calculation. The results obtained using DFT method correlate well with those obtained at PM3/DFT level, and the approximation used is appropriate.

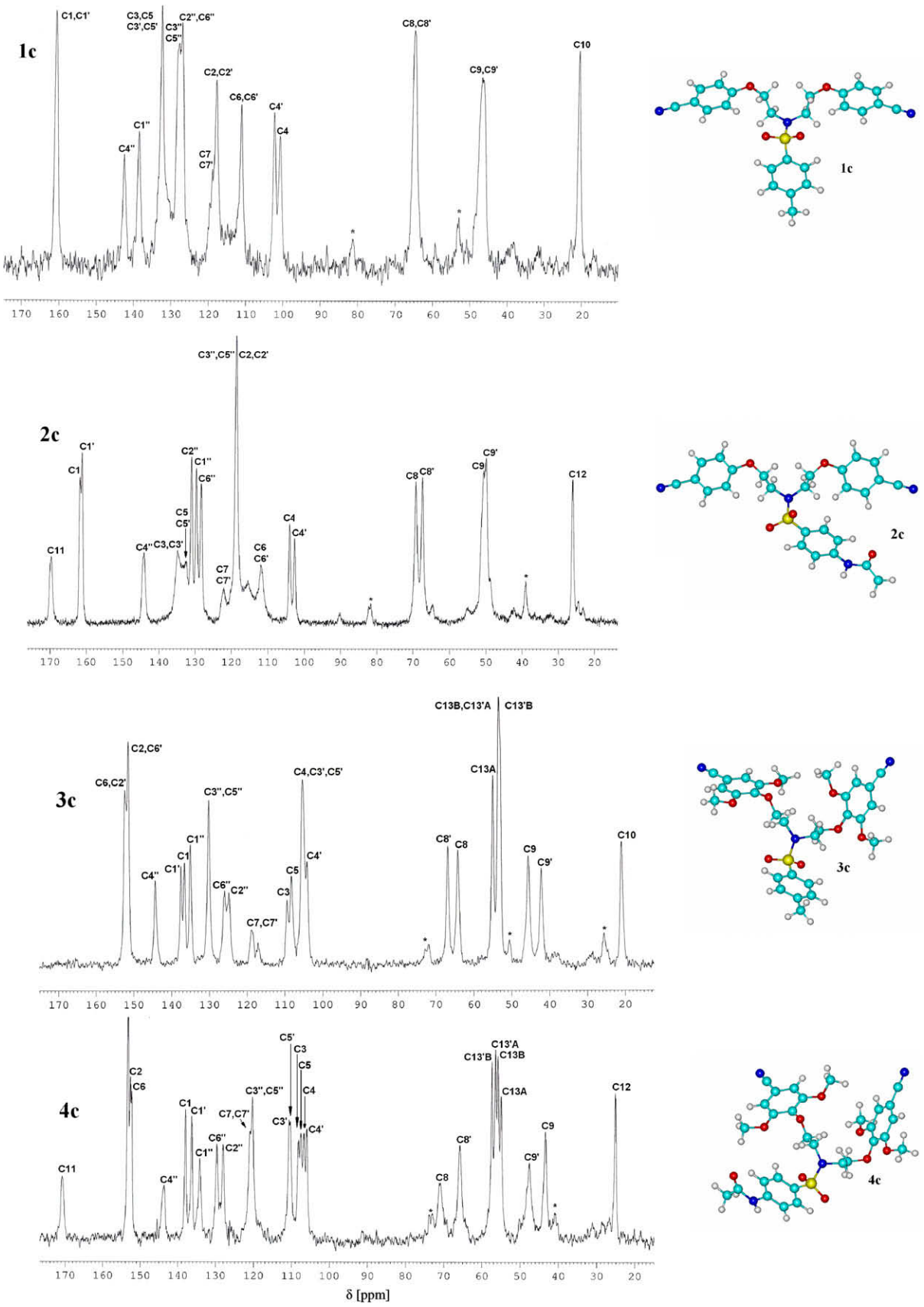


Fig. 2. The ^{13}C CP/MAS NMR spectra of *bis*-nitriles **1c**–**4c** in the solid-state together with hypothetical conformations in the solid shown on the right-hand side. Sidebands are marked with an asterisk.

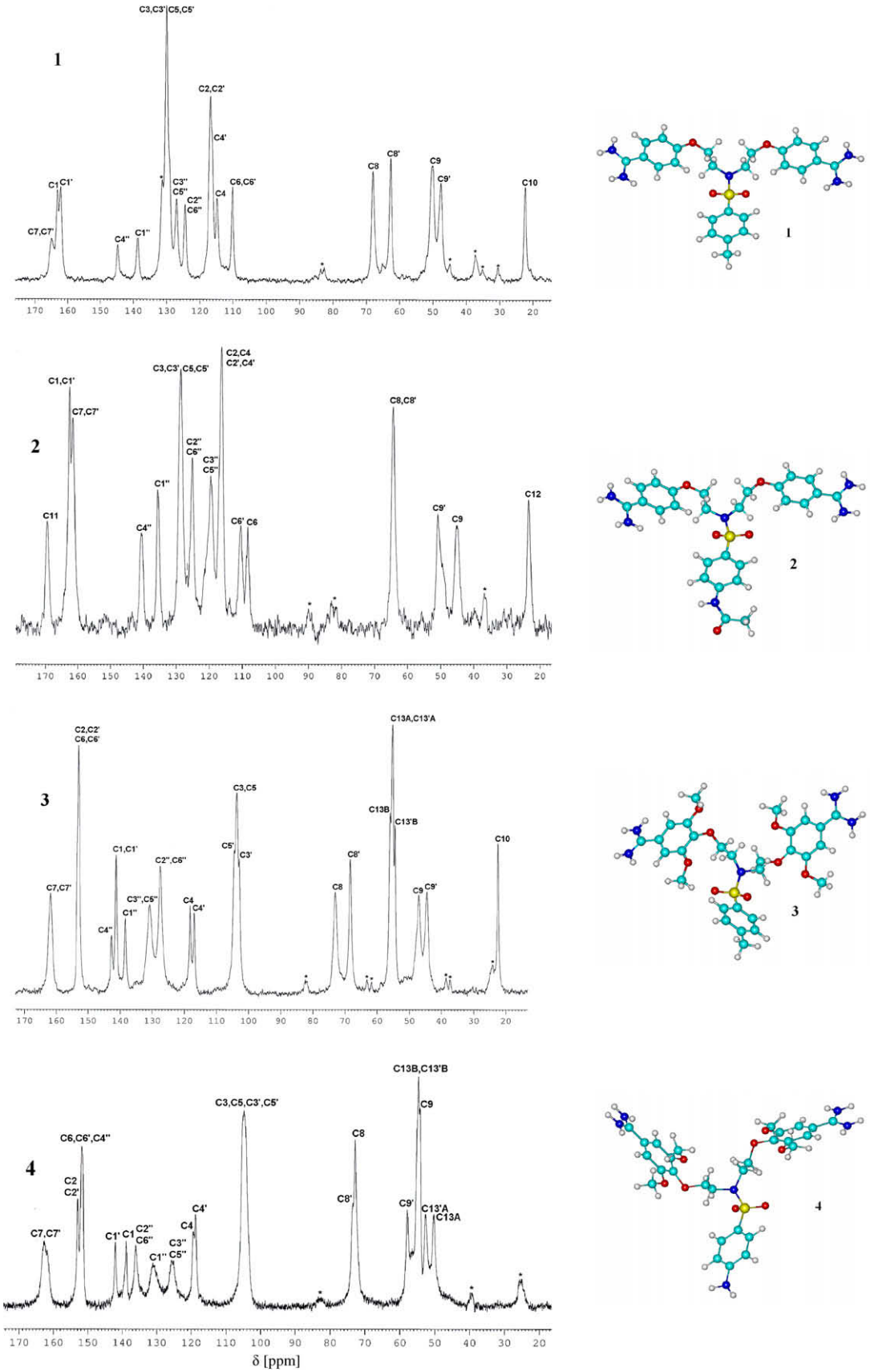


Fig. 3. The ^{13}C CP/MAS NMR spectra of *bis*-amide dihydrochlorides **1**–**4** in the solid-state together with hypothetical conformations in the solid shown on the right-hand side. Sidebands are marked with an asterisk.

3. Results and discussion

3.1. ^{13}C CP/MAS NMR spectra in solid-state and computational analysis

^{13}C CP/MAS NMR spectra of the *bis*-amidines **1**–**4** and the *bis*-nitriles **1c**–**4c**, the key intermediates in their syntheses, are shown in Figs. 2 and 3. Detailed assignments given in the spectra (see Table 1) were made from dipolar-dephased spectra, which revealed resonances from quaternary and methyl carbon atoms, by comparison with the spectra of structurally related compounds [14,15,19], and using theoretical computations of shielding constants of ^{13}C atoms. To perform these calculations, it is necessary to determine the preferred conformations in solid-state. The orientations of the benzene rings with respect to the linking 3-azapentanediyl chain and also those of the methoxy or acetamide substituents with respect to the appropriate rings are difficult to define because several conformations are of nearly the same energy. The starting geometries were obtained on the basis of crystallographic coordinates of 1,5-*bis*(4-cyanophenoxy)-*N*-methyl-3-azapentane [14] and 1,5-*bis*(4-cyano-2,6-dimethoxyphenoxy)-3-oxapentane [15] by modifications of suitable structural elements. After energy minimization at PM3 level of theory, different conformers were generated by changing the dihedral angles specific for methoxy groups: C10–O–C2–C1, C13–O–C6–C1, C8–O–C1–C2, C8′–O–C1′–C2′, and acetyl substituent C3″–C4″–N–C11. The various orientations of amidine groups relative to benzene ring planes were also analyzed. For the structures corresponding to local energy minima (at PM3 level of theory), the theoretical shielding constants were calculated at DFT level of theory with B3LYP/6-31(2d,p) hybrid functional using the GIAO CPHF method.

In the ^{13}C CP/MAS NMR spectra, the peak multiplicities and intensities of the resonances showed the structures with a single molecule in the crystallographic asymmetric unit. We observed different values of the ^{13}C chemical shifts in the alkyl range in solid-state spectra as compared with the solution ones. In the solution spectra methylene groups in the linker were found to be pairwise equivalent and only single resonances of atoms C8,8′ (in proximity 70 ppm) and atoms C9,9′ (in proximity 48 ppm) were observed. In the solid-state spectrum of compound **1c** the same resonance pattern was found to exist, but the majority of spectra of *bis*-nitriles and *bis*-amidines revealed double resonances of C8,8′ and C9,9′ pair of atoms with the exception of C8,C8′ resonances in the spectra of **2** and **4**. The splitting of methylene carbon signals could be explained in terms of conformation variability of all CH_2 groups in the aliphatic linker. Taking into consideration the calculated isotropic ^{13}C shielding constants σ *(ppm)* for different conformations of the analyzed compounds and the experimental ^{13}C chemical shifts δ *(ppm)* we were able to propose stable solid-state structures of the studied *bis*-nitriles and *bis*-amidines. In Figs. 2 and 3 we present (next to respective spectrum) the most probable conformations, for which we obtained the best linear dependence (i.e. the highest correlation coefficient R^2) between the calculated σ and the experimental δ values. Exemplary linear correlation for compound **1** is shown in Fig. 4. The alkyl chains in

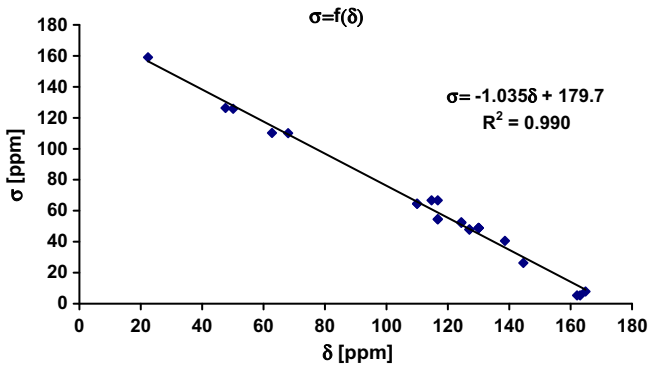


Fig. 4. A linear correlation between calculated shielding constants σ and experimental chemical shifts δ values for compound **1**.

Table 1
The ^{13}C CP/MAS NMR chemical shifts in the solid-state for compounds **1c**–**4c** and **1**–**4**.

Numbers of atoms	^{13}C chemical shifts in solid-state (ppm)							
	1c	**2c**	**3c**	**4c**	**1**	**2**	**3**	**4**
C1	160.8	161.6	136.4	138.0	163.1	132.4	141.2	138.7
C1′		161.1	137.4	136.3	162.1			141.9
C2	117.8	118.5	151.4	152.7	116.7	116.1	152.9	152.9
C2′			152.3	153.3				
C3	132.4	134.7	109.4	108.2	130.1	128.5	103.6	104.8
C3′			105.3				102.8	
C4	100.7	104.0	105.3	106.7	116.7	116.1	118.1	118.7
C4′	102.2	102.6	104.1	106.0	114.7		116.8	119.3
C5	132.4	132.3	108.2	107.6	130.1	128.5	103.6	104.8
C5′			105.3				104.4	
C6	111.1	111.9	152.3	152.3	110.0	108.2	152.9	151.8
C6′			151.4	153.3		110.3		
C7,C7′	118.8	122.0	118.6	121.0	164.8	161.5	161.7	162.5
C8	64.7	67.3	64.2	71.1	68.0	64.3	73.0	72.8
C8′		69.1	66.8	65.7	62.7		68.3	
C9	46.6	49.9	45.6	43.4	50.1	45.3	47.0	54.2
C9′		50.5	42.2	47.6	47.6	50.8	44.5	57.8
C10	20.5	–	21.0	–	22.4	–	22.4	–
C11	–	169.6	–	170.8	–	169.4	–	–
C12	–	26.0	–	25.1	–	23.4	–	–
C13A	–	–	55.0	55.0	–	–	55.2	50.0
C13B	–	–	53.5	55.9	–	–	56.0	54.7
C13′A	–	–		56.5	–	–	55.2	52.6
C13′B	–	–		57.4	–	–	54.4	54.7
C1″	138.5	129.5	134.9	134.2	138.6	135.5	138.3	131.0
C2″	126.9	130.9	124.7	128.0	124.4	125.0	127.4	136.0
C6″		128.2	125.9	129.6				
C3″,C5″	127.7	118.6	130.1	120.3	127.0	119.4	130.7	125.6
C4″	142.4	144.0	144.2	143.6	144.6	140.5	142.6	151.8

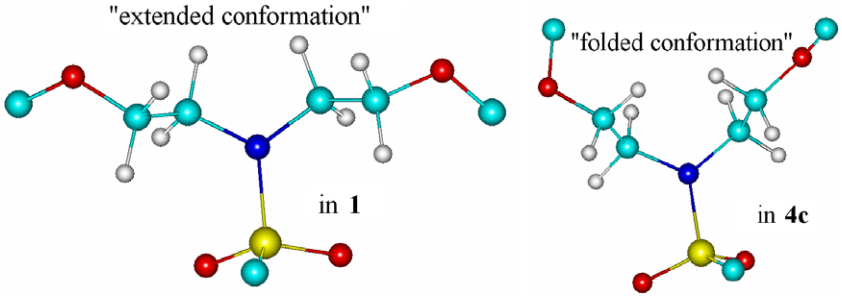


Fig. 5. Examples of extended and folded conformations of the aliphatic linker.

compounds **1**, **2** and **1c, 2c** have extended conformation, whereas the remaining derivatives, bearing methoxy substituents at benzene rings, adopt more folded conformations (see the examples in Fig. 5). The distances between C1–C1′ atoms in both conformations are equal on average 8.2 and 7.0 Å, respectively.

The spectra in the aromatic region reveal resonances associated with each carbon of the three benzene rings. Single resonances represent atoms of C3,3′, C5,5′ (in the spectra of **1c**, **1**, **2**, **4**), and atoms of C2″,6″ (in the spectra of **1c**, **1–4**) as well as atoms of C3″,5″ in all spectra. The doublets represent atoms of C2,6 and C2′,6′ (in **1c–4c**, **1**, **4**), and the quaternary atoms of C1,1′ and C4,4′. The differences in chemical shifts of the pairs of atoms of C1,1′, C2,2′, C4,4′, C6,6′ could be explained by the presence of slightly different torsion angles between the methylene C8 and C8′ atoms and benzene ring planes in both parts of the molecule. The diversity of intermolecular short contacts, as was shown by X-ray diffraction experiment before [14,15], is also expected to be responsible for the measured resonance pattern. Very often only one of two analogical functional groups is engaged in the intermolecular interactions (for example only one N atom of two C≡N groups forms hydrogen bonds).

In all spectra the values of carbon resonances *ortho* to amidine and nitrile substituents correspond to coplanarity of those substituents with benzene rings. The four methoxy substituents in compounds **3c**, **4c** and **3**, **4** are also generally located in benzene ring plane with methyl groups oriented so that they face the C3,3′ and C5,5′ atoms, respectively. Each methoxy group forms the slightly distinct torsion angle with respect to the *ortho* carbons. This appears to be reflected in small differences of the chemical shifts of C3,3′ and C5,5′ pairs of atoms, which are represented by separated signals shifted upfield as compared with the solution resonances. As a result, the four methoxy groups are also represented as separated resonances.

The computed structural parameters are similar to these observed for related molecules in X-ray diffraction experiments [14,15,19,22,23]. This can be illustrated by comparison of data for the nitrile and the amidine substituents. X-ray results showed, that the C–N bonds in both the nitrile groups are different, and are in the range 1.136–1.159 Å, but the C–N bonds in the amidine groups are almost equivalent, and the mean value is 1.318 Å. The computed values of the C–N bonds are equal on average 1.159 Å for nitriles and 1.311 Å for amidine groups, and are situated closely to above data.

4. Conclusions

Four sulfonamide-based pentamidine analogs and four key intermediates leading to them were synthesized with satisfactory yields. Their most stable solid-state conformations were proposed on the basis of the solid-state NMR studies and theoretical calculations. Two main conformations of aliphatic linker were determined, extended (length of 8.2 Å) and folded (length of 7.0 Å). In all studied structures the molecular packing appears to be dictated by an incompatibility between the packing motifs of two parts of the molecules. Additionally, the structure of compounds **3c**, **4c** and **3**, **4** is affected by the methoxy groups at the phenyl rings. The four methoxy substituents in these compounds are generally located in benzene ring plane with methyl groups oriented so that they face the C3,3′ and C5,5′ atoms, respectively. The ^{13}C CP/MAS NMR spectra did not show a polymorphism of the examined sulfonamides in solid-state.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2009.02.015.

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