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2,4-Dithiouracil: the reproducible H-bonded structural motifs in the complexes with 18-membered crown ethers

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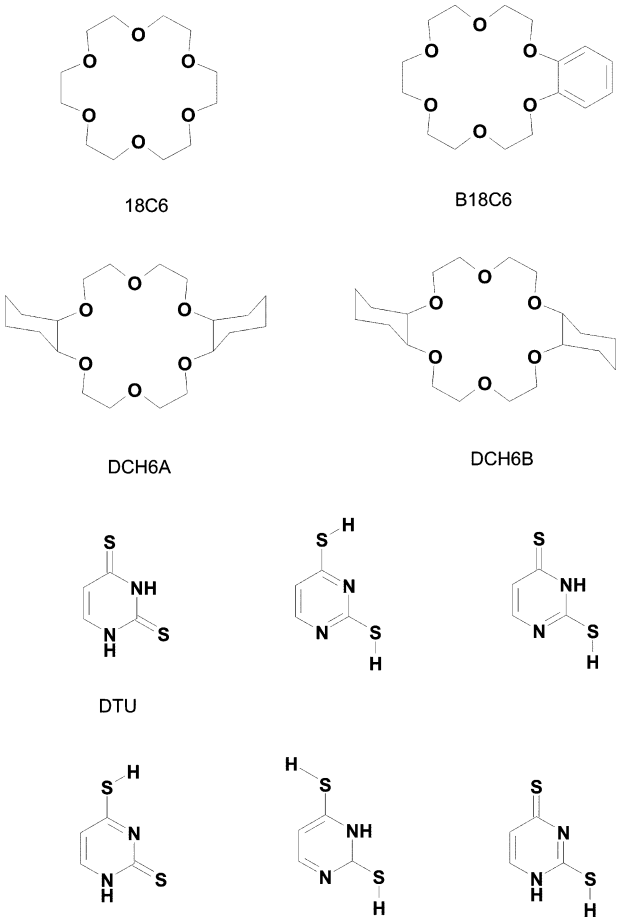
2,4-Dithiouracil (DTU) forms in the crystals the H-bonded monohydrates of a 1 : 1 : 1 ratio with 18-crown-6 (18C6) **1**, *cis*,*syn*,*cis*-isomer of dicyclohexano-18-crown-6 (DCH6A) **2**, and benzo-18-crown-6 (B18C6) **3**, while the anhydrous adduct with *cis*,*anti*,*cis*-isomer of dicyclohexano-18-crown-6 (DCH6B) **4** is of a 2 : 1 ratio. In **1**–**3** the components reproducibly alternate in the chains, while in **4** the chains are built of the alternative centrosymmetric dimers of 2,4-dithiouracil and the molecules of the *cis*,*anti*,*cis*-isomer of dicyclohexano-18-crown-6.

The mimicry of natural recognition processes is one of the challenging research topics of supramolecular chemistry. In biological receptors, the recognition sites offer a precise stereochemistry and exhibit very efficient recognition processes. However, this is achieved at the expense of a high molecular weight. The development of artificial receptors for neutral molecules is an important challenge in modern bioorganic chemistry. A possible strategy for the development of synthetic receptors comprises the combination of medium-sized organic building blocks to which functional groups for molecular recognition can be attached. In addition to compatibility of shape and size, effective molecular recognition requires a precise alignment of binding groups on the receptor with complementary regions on the substrate.[1,2] On the other hand, the traditional widely explored receptors, *e.g.*, macrocyclic crown ether molecules, could give a new insight into the binding of biologically important small molecules.[3,4]

The 1*H*-pyrimidine-2,4-dione ring system plays a significant role in traditional duplex formation, associated with complementary base pairing through hydrogen bonding involving NH and CO functionalities which have been studied in detail.[5,6] Essentially, fewer efforts have been made to examine the interactions involving the divalent sulfur atom with its partners.[7] Cambridge Structural Database studies of the divalent sulfur as acceptor for the system C=S, carried out by Allen *et al.*,[8] described the geometry based on van der Waals cut-off definition $d < 2.9$ Å for O–H and N–H donors.

The sulfur derivatives of pyrimidines and purines are widely used as antitumor agents in clinical treatment.[9] The tautomerism of purine and pyrimidine bases naturally occurring in nucleic acids, nucleotides, and enzymes may play a role in mutagenesis.[10] In recent years, much effort, both experimental and theoretical, has been devoted to the study of their structural properties and stabilities. The *ab initio* and spectroscopic studies for 2-thiouracil, 4-thiouracil, and 2,4-dithiouracil[11–16] revealed that oxothione and dithione tautomers are the most stable forms in crystal, solution and in the gas phase. In the crystalline state the agreement between theory and experiment is fairly good because of the crystal forces and hydrogen-bonding interactions. So far available are the crystallographic data for the pure 2-thiouracil,[17] 2,4-dithiouracil,[16] and the complex of 2-thiouracil with DCH6B.[18]

The present study was undertaken to follow the binding mode of 2,4-dithiouracil with the 18-membered crown ethers shown in Scheme 1 with the aim of finding any reproducible similarities



Scheme 1 Structural formulas of the crown ethers used and possible tautomers of 2,4-dithiouracil.

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Table 1 Bond lengths and angles for the DTU molecule in **1**–**4**

	1	2	3	4
Bond distances/Å				
S1–C1U	1.665(2)	1.642(4)	1.664(4)	1.665(3)
S2–C2U	1.662(2)	1.649(4)	1.654(4)	1.652(3)
N1U–C1U	1.370(2)	1.370(4)	1.352(5)	1.365(4)
N1U–C2U	1.382(2)	1.379(4)	1.383(5)	1.379(4)
N2U–C1U	1.355(2)	1.356(4)	1.368(5)	1.363(4)
N2U–C4U	1.354(3)	1.354(4)	1.361(5)	1.349(4)
C2U–C3U	1.420(3)	1.414(4)	1.409(5)	1.421(4)
C3U–C4U	1.337(3)	1.343(4)	1.319(6)	1.334(4)
Bond angles/deg				
C1U–N1U–C2U	126.1(1)	127.7(3)	127.1(3)	127.8(3)
C1U–N2U–C4U	123.2(2)	123.6(4)	122.4(4)	123.6(3)
N2U–C1U–N1U	114.6(2)	113.1(4)	114.2(4)	113.3(3)
N2U–C1U–S1	122.5(1)	122.9(3)	122.5(3)	123.8(2)
N1U–C1U–S1	123.0(1)	124.1(3)	123.3(3)	123.0(2)
N1U–C2U–C3U	115.0(2)	114.3(3)	114.1(4)	113.6(3)
N1U–C2U–S2	121.0(1)	121.7(3)	121.2(3)	120.6(2)
C3U–C2U–S2	124.0(1)	124.0(3)	124.7(3)	125.8(3)
C4U–C3U–C2U	119.6(2)	119.7(4)	120.8(4)	120.5(3)
C3U–C4U–N2U	121.6(2)	121.5(4)	121.3(4)	121.1(3)

in the organization of the structural units of the macrocyclic receptor, 2,4-dithiouracil, and in the supramolecular architecture.

2,4-Dithiouracil,[16] forms monohydrates in a 1 : 1 : 1 ratio with 18C6, DCH6A and B18C6 (complexes **1**, **2** and **3**), whereas its anhydrous adduct with DCH6B (complex **4**) is in a 2 : 1 ratio. For 2,4-dithiouracil,[16] six possible tautomers are known, which differ by the positions of two hydrogens in the vicinity of either the ring nitrogens or the exocyclic sulfur atoms. From six tautomeric forms only one form, the 2,4-dithione, denoted as DTU[11,12] is registered in complexes **1**–**4** (Scheme 1). It is confirmed by the equal (within the cut-off of 2σ) C=S distances that correspond to the double bond and by the location of the hydrogen atoms on the ring nitrogens. The bond distances and angles in the DTU molecule in **1**–**4** are given in Table 1. Fig. 1 shows the ORTEP diagrams for **1**–**4** with the atomic numbering schemes.

In **1**–**3** the ternary complexes are organized in a similar way, so that DTU mediates crown ether and water molecules *via* N–H···O and C–H···O hydrogen bonds with participation of its acidic H-donor centers. The hydrogen bonding data of **1**–**4** are summarized in Table 2. In **1** the DTU and 18C6 molecules are held together by one N–H···O hydrogen bond, between N2U and O16 atoms with an N···O distance of 2.810(2) Å and N2U–H1···O16 angle of 170(2)°, and one CH···O hydrogen bond, between C3U and O7 atoms with C···O distance of 3.260(2) Å and C3U–H1···O4 angle of 129°. In **2** the DTU and DCH6A molecules are held together only by one NH···O hydrogen bond, between atoms N2U and O16 with the N···O distance of 2.862(4) Å and N2U–H2U···O16 angle of 171°. Similar to **1**, the H4U hydrogen atom of the neighboring CH group is directed just in the center of the macrocyclic ring with H4U···O(crown) distances that all exceed the cut-off limit of the hydrogen bonding (<2.6 Å). Similar to **1**, in **3** the DTU and B18C6 are held together also by one NH···O and one CH···O hydrogen bonds, although different CH groups of uracil ring are involved in these interactions, The N–H···O hydrogen bond involves N2U and O13 atoms, with N···O distance of 2.970(4) Å and N2U–H2U···O13 angle of 153(4)°, and CH···O hydrogen bond involves C4U and O7 atoms with C···O separation of 3.550(5) Å and C4U–H4U···O7 angle of 168°. The difference is that the neighboring NH and CH groups of DTU molecule are involved in these contacts. The mutual arrangement of the crown ether and DTU molecules approaches to the orthogonal one and is characterized by the dihedral angle between the pyrimidine and crown ether rings (least-squares-planes were calculated through atoms O1/O4/O7/O10/O13/O16 and C1U/C2U/C3U/C4U/N1U/N2U) equal to 84.4(1)° in **1**, 86.8(1)° in **2**, whereas in **3** this angle is decreased to 53.8(1)°. The pronounced deviation from orthogonality in **3** is defined by the aromatic ring in the B18C6 molecule that is responsible for the π–π stacking interactions between the off-set overlapping phenyl and uracil rings with the dihedral angle between these aromatic systems equal to 15.9(2)° and the deviations of the atoms of uracil ring from the plane of the phenyl ring (C17/C18/C19/C20/C21/C22) being in the range 3.04–3.73 Å. The water molecule acts in a reproducible way in **1**–**3**. It blocks the second aminogroup of the DTU ring, thus precluding the typical nucleic bases pairing[17–19] *via* $R_2^2(8)$ NH···S synthon.[20] Strong intermolecular H-bonding, N1U–H1U···O1w is described by the N1U···O1w separation of 2.826(2) Å and N1U–H1U···O1w angle of 175(2)° in complex **1**, by N1U···O1w separation of 2.911(4) Å and N1U–H1U···O1w angle of 175° in **2**, and by N1U···O1w separation of 2.974(2) Å and N1U–H1U···O1w angle of 166(4)° in **3**. Our search of the Cambridge

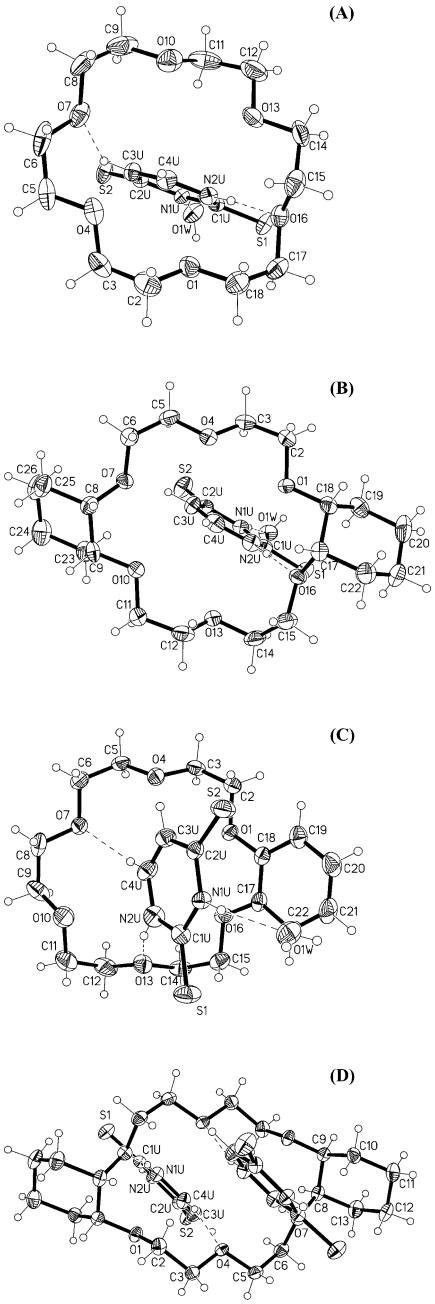


Fig. 1 (A)–(D) ORTEP view for **1**–**4** in projection on the plane of crown ether oxygen atoms. Ellipsoids for non-hydrogen atoms are drawn at the 30% probability level.

Table 2 Hydrogen bonding geometry in **1**–**4**

D–H···A	*r*(D–H)/Å	*r*(H···A)/Å	*r*(D···A)/Å	∠D–H···A/deg	Symmetry transformation for H-acceptor
1					
N2U–H2U···O16	0.84(2)	1.98(2)	2.810(2)	170(2)	*x*, *y*, *z*
N1U–H1U···O1W	0.80(2)	2.03(2)	2.826(2)	175(2)	*x*, *y*, *z*
C3U–H3U···O7	0.93	2.60	3.260(2)	129	*x*, *y*, *z*
O1W–H1W···O10	0.84(2)	2.37(2)	3.124(3)	150(2)	$x + 1/2, -y + 1/2, z - 1/2$
O1W–H1W···O13	0.84(2)	2.47(2)	3.158(2)	139(2)	$x + 1/2, -y + 1/2, z - 1/2$
O1W–H2W···O4	0.84(2)	2.12(2)	2.955(2)	174(3)	$x + 1/2, -y + 1/2, z - 1/2$
2					
N2U–H2U···O16	0.86	2.01	2.862(4)	171	*x*, *y*, *z*
N1U–H1U···O1W	0.86	2.05	2.911(4)	175	*x*, *y*, *z*
O1W–H1W···O10	0.83(2)	2.21(2)	2.990(4)	159(4)	$x + 1/2, -y + 3/2, z - 1/2$
O1W–H2W···O1	0.83(2)	2.60(3)	3.267(4)	138(4)	$x + 1/2, -y + 3/2, z - 1/2$
O1W–H2W···O4	0.83(2)	2.44(3)	3.145(4)	143(3)	$x + 1/2, -y + 3/2, z - 1/2$
3					
N1U–H1U···O1W	0.85(2)	2.14(2)	2.974(4)	166(4)	*x*, *y*, *z*
N2U–H2U···O13	0.86(2)	2.18(3)	2.970(4)	153(4)	*x*, *y*, *z*
C4U–H4U···O7	0.93	2.63	3.550(5)	168	*x*, *y*, *z*
O1W–H1W···O7	0.86(1)	2.34(2)	3.171(4)	164(4)	$-x - 3/2, -y - 1, z + 1/2$
O1W–H2W···O1	0.86(2)	2.40(3)	3.191(4)	155(5)	$-x - 3/2, -y - 1, z + 1/2$
O1W–H2W···O16	0.86(2)	2.47(4)	3.179(4)	141(5)	$-x - 3/2, -y - 1, z + 1/2$
4					
N1U–H1N···S1	0.85(2)	2.61(2)	3.430(3)	163(3)	$-x - 1, -y - 1, -z$
N2U–H2N···O7	0.85(3)	2.10(3)	2.939(3)	167(3)	$-x, -y - 1, -z - 1$
C4U–H4U···O4	0.93	2.37	3.273(4)	163	*x*, *y*, *z*

Structural Database[21] revealed the similar type of water binding in 2,4-dithio-5-fluoro-2′-deoxyuridine monohydrate, 6-amino-2-thiouracil monohydrate (two independent determinations), tris(5-carboxymethylaminomethyl-2-thiouridine) tetrahydrate, and in 2-thioxo-5,6-dimethyl-1*H*,3*H*-thieno(2,3-d)pyrimidin-4-one monohydrate with N···O separations of 2.917, 2.848(2.850), 2.838 and 2.729 Å, correspondingly.[22]

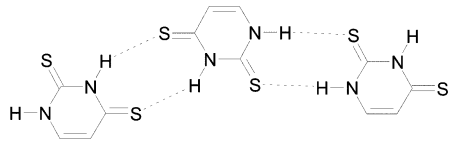
The anhydrous complex **4** differs in composition from **1–3**. The DCH6B molecule imposes on the inversion center, thus providing the 1 : 2 ratio of the components (Fig. 1d). The mode of interaction of DTU with DCH6B molecule absolutely coincides with that found in **3**; the neighboring N2U and C4U atoms of DTU molecule are involved in these interactions. The DTU and DCH6B molecules are held together by one NH···O and one CH···O hydrogen bonds, between atoms N2U and O7($-x$, $-y$ + 1, $-z$ + 1) with an N···O distance of 2.939(3) Å and an N2U–H2U···O16 angle of 167(3)°, and the CH···O hydrogen bond, C4U–H4U···O4 with a C···O distance of 3.273(4) Å and a C4U–H4U···O4 angle of 163°. The angle between the pyrimidine and crown ether rings is 88.0(1)°.

The packing diagrams (Fig. 2a–c) for **1–3** reveal the very similar organization of the complexes in the chains *via* an intermolecular O(water)···O(crown) hydrogen bonding, where the water molecule donates both of its hydrogen atoms to the symmetry-related macrocycle with the formation of one single and one bifurcated O1w–H···O(crown) hydrogen bonds, the O···O separations for the single hydrogen bond neatly increasing from 2.955(2) to 3.171(4) Å, and for the bifurcated hydrogen bond from 2.990(4) Å up to 3.267(4) Å. A water molecule is displayed at 1.864(2), 1.904(3), and 1.983(3) Å from the mean plane defined by the six crown ether's oxygen atoms in **1**,**2**,**3** correspondingly.

Only in **4** is the intermolecular H-bonding of the type N–H···S (typical for nucleic bases between the N1U and S1($-x$ − 1, $-y$ + 1, $-z$) atoms) with an N···S separation of 3.430(3) Å and an N1U–H1U···S1 angle of 163(3)° pairing two DTU molecules into a centrosymmetric dimer. The DCH6B molecules and DTU dimers alternate in the chains running along *c* direction in the unit cell (Fig. 2d).

In the four complexes described above, the hydrogen-bonded DTU : CE unit is supported by three different types of mutual interactions. Only in **1** due to high flexibility of 18C6 molecule the cross-cavity coordination occurs that results in the participation of N2U and C3U atoms of uracil ring, separated by CH_2–methylene group, in hydrogen bonding. In **2** the space obstacles, arising from the dicyclohexyl rings oriented in the DCH6A molecule in the same direction, provide the participation of only one NH group of DTU molecule in the hydrogen bonding with the CE. In **3** and **4** the neighboring NH and CH groups of uracil ring are involved in two hydrogen bonds with the crown oxygens separated by the –CH_2–O–CH_2– fragment, the similar type of hydrogen bonding was previously found in the complex of DCH6B with 2-thiouracil.[18] **1**–**4** reveal two supramolecular motifs: **1**–**3** represent the 1 : 1 : 1 alternative chains, where crown molecules behave as different-faced ligands, and coordinate on their two faces two different molecules, DTU and water, and only **4** represents the chain of 1 : 2 composition due to the equal-face symmetry of DCH6B.

Only in **4** do we observe the preservation of the centrosymmetric dimer of DTU as the fragment of the supramolecular architecture typical for its pure form. In the crystalline DTU itself[5] the molecules are associated in the chains sustained by two similar alternating $R_2^2(8)$ synthons[19] (Scheme 2) built on the NH···S hydrogen bonds.



Scheme 2 Association of the DTU molecules in the crystal *via* NH···S hydrogen bonds.

These chains are further aggregated into ladder-like layers due to ability of sulfur to participate in the multiple short contacts (in this case weak CH···S).

The interaction with DCH6B results in the breakage of the weakest CH···S interactions and their substitution by the interactions with the crown oxygens as H-acceptors. These contacts occur in the plane of the planar skeleton of DTU and are decisive for chain organization. This chain motif was previously found in the crystal structure of DCH6B·2(2-thiouracil),[18] where the centrosymmetric dimer of 2-thiouracil is sustained by the $R_2^2(8)$ NH···O base-pairing supramolecular

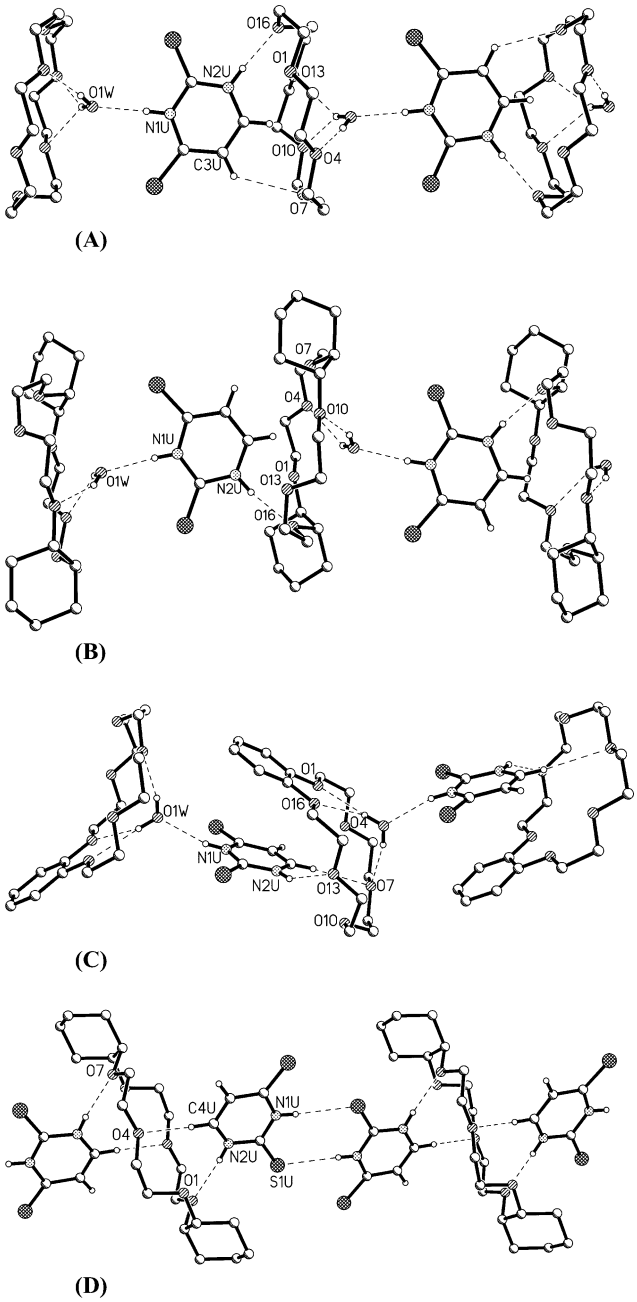


Fig. 2 (A)–(D). Fragment of chain in **1**–**4**. C-bound hydrogen atoms of crown molecules are omitted for clarity.

synthon instead of $R_2^2(8)$ NH···S supramolecular synthon in **4**.

Conclusion

Four complexes of 2,4-dithiouracil (DTU) with 18-membered crown ethers (CE) were synthesized in approximately the same conditions and characterized by X-ray diffraction analysis. From six possible tautomeric forms of DTU, only 2,4-dithione form was registered in all crystalline products. The crystal structures revealed two 1D structural motifs, ···CE···water···DTU···CE··· and ···CE···$(DTU)_2$···CE···, both sustained by diverse hydrogen bonding. In the first motif all the hydrogen bonding interactions typical for pure DTU itself were substituted by the interactions with the oxygen atoms of water and crown ether, as the stronger hydrogen acceptors. In the second motif the only $R_2^2(8)$ NH···S base-pairing supramolecular synthon responsible for the centrosymmetric dimer of DTU remains, as the part of self-assembling DTU molecules in its pure form.

Experimental

All the chemicals used (crown ethers, and 2,4-dithiouracil) were purchased from Aldrich Chemical Co .and were not purified prior to use. In all the experiments a 1 : 1 mixture of DTU (0.144 g, 1 mmol) and 0.1 mmol of the corresponding crown ether was dissolved in a mixture of methanol (20 ml) and ethyl acetate (40 ml), and the solution was stored for 3–4 d at 20–25 °C in an open flask. Crystals suitable for the X-ray diffraction experiments were isolated from the mass of crystals obtained.‡ Suitable microanalyses were obtained for all compounds. ^{1}H spectra were obtained in DMSO-d_6 on a 300−MHz Bruker instrument. Unit cell dimension and intensity data collection for **1**–**4** were performed at room temperature on a Philips PW1100 diffractometer equipped with graphite monochromated Mo Kα radiation. The lattice parameters were obtained by least-square fit to 25 reflections ($13.22° < \theta < 17.90°$) for complex **1**, 39 reflections ($4.69° < \theta < 12.61°$) for complex **2**, 39 reflections ($5.37° < \theta < 15.30°$) for complex **3**, 24 reflections ($7.04° < \theta < 16.39°$) for complex **4**, respectively. All the data sets were collected by ω-2θ scan mode. There was no significant intensity decay. Structure solutions were performed by direct methods (SHELXS-97) and refinements by full-matrix least-squares methods on F^2 (SHELXL-97). All non-hydrogen atoms were refined anisotropically. In all the structures H atoms attached to carbons were included in idealized positions in a riding model with isotropic temperature factors (1.2 times the carbon temperature factor), whereas those on N and O(water) atoms were found from difference Fourier maps at an intermediate stage of the refinement and were constrained by distance only (N–H and O–H = 0.86 Å) and were refined with isotropic temperature factors (1.5 times the parent N(O) temperature factor).

Transparent yellow crystals of **1**, soluble in methanol, ethanol, acetone, mp 265 °C (decomp). Found, %C, 45.02, H, 7.13, N, 6.65, S, 15.09 required for $C_{16}H_{30}N_2O_7S_2$: C, 45.05, H, 7.09, N, 6.57, S, 15.03%. ^{1}NMR: δ = 3.50 s (24H, 18C6), 6.49 d, 7.25 d (2H, CH–DTU).

Crystal data for **1**, monoclinic, $P2_1/n$, a = 7.707(2), b = 17.374(4), c = 16.622(3)Å, β = 92.17(3)°, V = 2224.1(8) Å^3, Z = 4, D_x = 1.274 g cm^{-3}, λ(Mo Kα) 0.71073 Å, μ = 2.76 cm^{-1}, $F(000)$ = 912, GooF = 1.088, R indices (all data) $R1$ = 0.0667, $wR2$ = 0.1320 for 4380 reflections and 256 parameters and R indices $R1$ = 0.0452, $wR2$ = 0.1237 for 3152 reflections obeying $I > 2\sigma(I)$ criterion of observability.

Transparent yellow crystals of **2**, soluble in methanol, ethanol, acetone, mp 260 °C (decomp). Found, %C, 53.82, H, 7.88, N, 5.28, S, 12.04 required for $C_{24}H_{42}N_2O_7S_2$: C, 53.90, H, 7.92, N, 5.24, S, 12. ^{1}NMR: δ = 1.19–1.71 m and 3.49 m (36H, DCH6A), 6.50 d, 7.23 d (2H, CH–DTU).

Crystal data for **2**, monoclinic, $P2_1/n$, a = 7.988(2), b = 21.627(4), c = 16.439(3)Å, β = 93.17(3)°, V = 2835.6(10) Å^3, Z = 4, D_x = 1.253 g cm^{-3}, λ(Mo Kα) 0.71073 Å, μ = 2.30 cm^{-1}, $F(000)$ = 1152, GooF = 0.709, R indices (all data) $R1$ = 0.2645, $wR2$ = 0.0929 for 5555 reflections and 322 parameters and R indices $R1$ = 0.0556, $wR2$ = 0.0668 for 1556 reflections obeying $I > 2\sigma(I)$ criterion of observability.

Transparent yellow crystals of **3**, soluble in methanol, ethanol, acetone, mp 250 °C (decomp.). Found, %C, 50.68, H, 6.41, N, 5.99, S, 13.48% required for $C_{20}H_{30}N_2O_7S_2$: C, 50.61, H, 6.37, N, 5.90, S, 13.51. ^{1}NMR: δ = 3.59 m, 3.73 m, 4.05 m (20H, CH_2) and 6.89 m (4H, CH–B18C6), 6.49 d, 7.25 d (2H, CH–DTU).

Crystal data for **3**, orthorhombic, $P2_12_12_1$, a = 7.973(2), b = 16.918(3), c = 17.566(4)Å, V = 2369.4(8) Å^3, Z = 4, D_x = 1.330 g cm^{-3}, λ(Mo Kα) 0.71073 Å, μ = 2.67 cm^{-1}, $F(000)$ = 1008, GooF = 0.881, R indices (all data) $R1$ = 0.1051,

‡ CCDC reference numbers 268384–268387. See http://dx.doi.org/10.1039/b505807d for crystallographic data in CIF or other electronic format.

$wR2 = 0.0922$ for 2644 reflections and 292 parameters and R indices $R1 = 0.0446$, $wR2 = 0.0805$ for 1493 reflections obeying $I > 2\sigma(I)$ criterion of observability.

Transparent yellow crystals of **4**, soluble in methanol, ethanol, acetone, mp > 250 °C (decomp). Found, %C, 50.90, H, 6.74, N, 8.54, S, 19.43 required for $C_{28}H_{44}N_4O_6S_4$ C, 50.87, H, 6.71, N, 8.48, S, 19.41. ^{1}NMR: δ = 1.19–1.70 m and 3.53 m (36H, DCH6B), 6.49 d, 7.25 d (4H, CH–DTU).

Crystal data for **4**, monoclinic, $P2_1/n$, $a = 11.624(2)$, $b = 12.698(3)$, $c = 12.093(2)$Å, $\beta = 109.69(3)°$, $V = 1680.6(6)$ Å^3, $Z = 2$, $D_x = 1.306$ g cm^{-3}, λ(Mo Kα) 0.71073 Å, $\mu = 3.27$ cm^{-1}, $F(000) = 704$, GooF = 0.853, R indices (all data) $R1 = 0.1279$, $wR2 = 0.1316$ for 3302 reflections and 196 parameters and R indices $R1 = 0.0536$, $wR2 = 0.1129$ for 1669 reflections obeying $I > 2\sigma(I)$ criterion of observability.

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