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Formation of [5.5]cyclopentadienidophanes by macrocyclization of [3-(methylammonio)propyl]cyclopentadienides under Mannich conditions

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ABSTRACT

2-Acyl-1,4-bis(methoxycarbonyl)-3-[3-(methylammonio)propyl]cyclopentadienides **1** and aqueous formaldehyde can undergo a double Mannich reaction leading to the bisbetainic 2,12-diazonia-[5,5](1,3)cyclopentadienidophanes **2**. The success of this macrocyclization reaction seems to depend on the length of the ω-ammonioalkyl chain and the individual acyl substituent. In the cases of ω-(methylammonio)butyl and ω-(methylammonio)pentyl chains, as well as with ω-ammoniopropyl derivatives bearing particularly electron-rich 4-methoxybenzoyl or 2-furoyl substituents, a mixture of oligomers is formed. On the other hand, DCC-assisted cyclocondensation of **1b**,**d** (acyl=4-methoxybenzoyl and thiophene-2-carbonyl, respectively) occurs only intramolecularly, leading to the bicyclic 6-amino-pentafulvenes **4b**,**d** in good yields.

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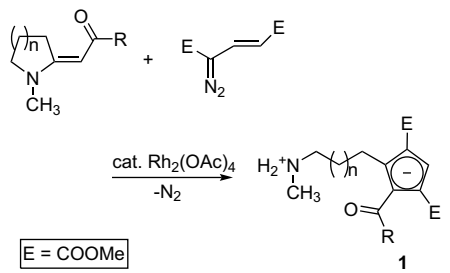
1. Introduction

Benzenoid cyclophanes nowadays represent a well-developed class of aromatic ring systems incorporated in a three-dimensional molecular architecture, offering many interesting properties in terms of structural chemistry, reactivity, and applications.[1,2] In the structural motif of the phanes, the benzene ring can and has been replaced, inter alia, by a large variety of other benzenoid and non-benzenoid entities, one of them being the anionic cyclopentadienide ring system. A particular variety of the phane motif is found in the metallocenophanes.[3,4] Most members of this metallocene family feature a metallocene unit with the two cyclopentadienide rings connected by a single bridge, and some of the research on these compounds has aimed at potential applications in homogeneous catalysis, in particular for stereoselective olefin polymerization.[5] Only a few multiply bridged metallocenophanes, including [4_5](1,2,3,4,5)ferroceno-phane,[6] have been synthesized up to now.

Little is known about metal-free cyclopentadienidophanes. It appears that the first phane of this class was the *ansa*-compound [9](1,3)cyclopentadienidophane.[7] In 1999, Neuenschwander and co-workers[8] described the first doubly bridged cyclopentadienophane, namely a [2.2]cyclopentadienophane; it is likely that this phane resulted from protonation of the corresponding dianionic [2.2]cyclopentadienidophane, which was not isolated nor characterized spectroscopically, however. The dianionic [2.2](2,7)fluorenidophane has also been described.[9]

In previous communications,[10,11] we have reported that (ω-ammonioalkyl)cyclopentadienides **1** result from the rhodium-catalyzed reaction of dimethyl 3-diazo-1-propene-1,3-dicarboxylate with semicyclic enaminoketones (Scheme 1). Betaines **1** are loaded with different functional groups, partly with complementary reactivity. It could be expected that this functional group pattern would allow intra- or intermolecular reactions of the betaines to take place. A twofold reaction of two cyclopentadienide building blocks, i.e., a cyclodimerization reaction, would pave the way to [*n*.*n*]cyclopentadienidophanes. Eventually, the length of the alkyl side chain in **1** (3–5 methylene groups) should decide on whether such reactions would occur intramolecularly or between two



Scheme 1. Synthesis of (ω-ammonioalkyl)cyclopentadienides **1** (*n*=1–3).

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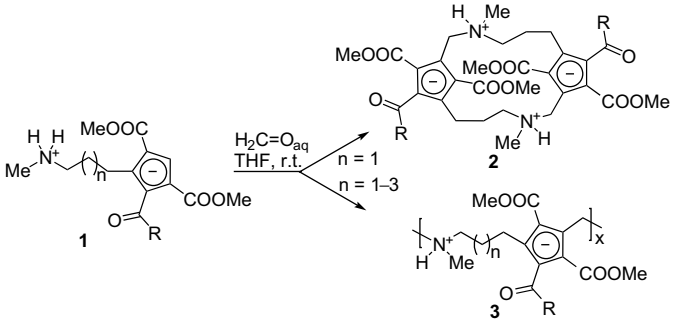
cyclopentadienide molecules. A hint to this issue was obtained from the inspection of the solid-state structures of two betaines **1**:[12] while an (ω-methylammoniopropyl)-substituted derivative forms an intramolecular N–H···O_{acyl} hydrogen bond, an (ω-methylammoniopentyl)-substituted derivative is arranged as a coordination dimer held together by two such hydrogen bonds.

2. Results and discussion

2.1. Reaction of betaines 1 with formaldehyde

The presence of a secondary amine group in betaines **1** suggested its transformation into a methylene iminium function, which could attack the cyclopentadienide ring intra- or intermolecularly. The aminomethylation of a cyclopentadienide ring under Mannich conditions (formaldehyde/*sec*-amine[13]) or by related methods (e.g., $CH_2(NMe_2)_2/H_3PO_4$[14]) is an established method in metallocene chemistry.

The 2-[3-(methylammonio)propyl]-3-(2-thenoyl)cyclopentadienide **1d** was investigated first. From a solution of **1d** and an equimolar quantity of aqueous formaldehyde in THF, a crystalline yellow precipitate separated within 24 h. The water-soluble product was identified as the bisbetainic 2,12-diazonia-[5,5](1,3)cyclopentadienidophane **2d** (Scheme 2) by its spectroscopic and analytical data; a further structural proof was furnished by an X-ray crystal structure determination (see Section 2.2). A field-desorption (FD) mass spectrum showed the molecular ion peak at m/z=750, accompanied only by a lower-intensity peak of the 'monomer' (m/z=376), which probably resulted from a thermal fragmentation. The ^{1}H and ^{13}C NMR spectra, recorded in $CDCl_3$ solution, pointed to a time-averaged symmetrical structure of **2d**, showing only the number of signals expected for the monomeric subunit. The incorporation of the formaldehyde-derived methylene group (i.e., $C_{cp}CH_2N$) was indicated by the disappearance of the cyclopentadienide CH proton signal and by new signals for the methylene group at δ_H=4.30/5.31 ppm and δ_C=54.57 ppm. Further NMR observations are discussed in Section 2.2.

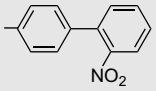


Scheme 2. Reaction of betaines **1** with formaldehyde; see Table 1 for substituents and yields.

Betaines **1a**,**c**,**f** reacted with formaldehyde in the same manner as **1d** and were transformed into bisbetaines **2a**,**c**,**f** (Scheme 2 and Table 1). Obviously, all these bisbetaines result from a twofold Mannich-type aminomethylation reaction, in which two molecules of **1** are combined by a regioselective attack of an in situ formed methylene iminium unit at the cyclopentadienide ring of the second molecule.

The success of the described macrocyclization by a twofold Mannich reaction of betaines **1** seems to depend on the length of the ω-ammonioalkyl chain and the individual acyl substituent (Table 1). In the cases of 3-(methylammonio)propyl betaines **1b** and **1d**, bearing particularly electron-rich 4-methoxybenzoyl or 2-furoyl substituents, solid products were obtained, which are likely to be mixtures of oligomers. The ^{1}H NMR spectra of these products showed ill-defined broad signals, and many signals in the ^{13}C NMR spectra were broadened by the presence of additional closely spaced signals. By the same NMR arguments as given above for **2d**, the presence of a $C_{cp}CH_2N$ moiety can be assumed and therefore, these products are tentatively considered as oligomers **3b** and **3d**. As an accurate integration of the ^{1}H NMR spectra was not possible, it cannot be excluded that these oligomers also contain subunits resulting from an aminomethylation of the anisyl and furyl rings. Considering the deviation from the expected values for the elemental analyses, it is likely that the number of repeating units in the oligomers is small, so that the influence of the (unknown) end groups is no longer negligible. The FAB mass spectra showed, in addition to peaks for the dimer (n=2), several very weak peaks in the measured m/z range up to 2000 Da.

Table 1
Products obtained from betaines **1a**–**h** and formaldehyde

1–3	n	R	Yield of **2** (%)	Yield of **3** (%)
a	1	Ph	52	
b	1	C_6H_4–4-OCH_3		45
c	1		20	
d	1	2-Thienyl	80	
e	1	2-Furyl		45
f	1	1-Adamantyl	79	
g	2	2-Thienyl		74
h	3	2-Thienyl		81

Mixtures of oligomers were also obtained from the reaction of formaldehyde with betaines **1g** and **1h**, which bear ω-(methylammonio)butyl and ω-(methylammonio)pentyl side-chains, respectively. In these cases, the unfavorable entropy factor is likely to prevent the formation of [6,6]- and [7,7]cyclopentadienidophanes. The tentative assignment of the products as oligomers **3g** and **3h**, which in contrast to **3b**,**d** are seemingly insoluble in common organic solvents, is supported by the elemental analyses and a solid-state ^{13}C NMR spectrum of **3h**.

2.2. Structure of [5.5]cyclopentadienidophane 2d

A plot of the solid-state molecular structure of **2d** is shown in Figure 1. One recognizes a cone-shaped molecular framework at which the positions of the two methoxycarbonyl groups at the upper rim, as well as those at the lower rim, have an approximate C_2-symmetrical relationship. In contrast, the two thenoyl groups are arranged differently, with one of the thiophene rings taking the *endo* orientation, the other one the *exo* orientation relative to the macrocyclic scaffold. Two intramolecular N–H···O hydrogen bonds, each involving the carbonyl oxygen atom of an ester group, are present and are likely to stabilize the given conformation in the aliphatic chains.

An inspection of the relevant torsion angles in the structure of **2d** reveals that the thenoyl group with the thiophene ring in *exo* position is perpendicular to the adjacent cyclopentadienide ring, whereas the orientation of the thenoyl group with the thiophene ring in *endo* position is such that a significant amount of π-conjugation is still possible (torsion angle C21–C22–C28–O8=136.1°). Thus, the conformation with the *endo* position of one thiophene ring appears to be energetically more favorable, but an arrangement of both thiophene rings pointing to the interior of the macrocycle is disfavored for steric reasons. In order to corroborate these ideas, we performed a conformation analysis for **2d** using semi-empirical calculations (see Experimental for details). Table 2 summarizes the results for the six structures of lowest energy. In all the

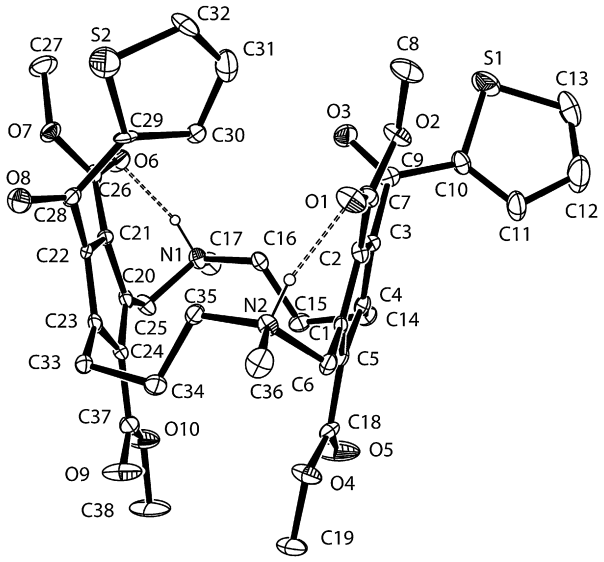


Figure 1. Structure of **2d** in the solid state (ORTEP plot, ellipsoids of thermal vibration shown at the 20% probability level). Selected bond lengths (Å): C1–C2 1.409(8), C2–C3 1.430(8), C3–C4 1.379(8), C4–C5 1.428(8), C5–C1 1.418(8). Hydrogen bonds: N1–H 0.92(7), O6···H 1.79(7), N1···O6 2.684(8) Å, angle N1–H···O6 163(6)°; N2–H 0.88(5), O6···H 1.79(5), N2···O1 2.643(7) Å, angle N2–H···O1 164(5)°. Torsion angles (°): C2–C3–C9–O3 −81.8(9), C21–C22–C28–O8 136.1(7).

Table 2
Calculated (PM3) conformations of lowest energy for **2d**

Entry	E_{rel}[a] (kJ mol^{-1})	Orientation of thiophene ring/O=C–C–S conformation	Orientation of COOMe groups at lower rim
1	0	*endo*/*syn* *exo*/*syn*	Antiparallel
2	3.52	*endo*/*syn* *exo*/*anti*	Antiparallel
3	6.06	*endo*/*syn* *exo*/*syn*	Parallel
4[b]	9.08	*endo*/*syn* *exo*/*syn*	Parallel
5	9.65	*endo*/*syn* *exo*/*anti*	Parallel
6	10.46	*exo*/*syn* *exo*/*syn*	Antiparallel

[a] Corrected for zero-point energy (ZPE).
[b] For entry 4, the carbonyl groups at the lower rim point in the opposite direction compared to entry 3.

conformations, the two five-membered chains connecting the two cyclopentadiene rings are more or less the same, one of the two chains showing a significant deviation from the solid-state structure. The structures listed in Table 2 differ by the conformations at the substituent bonds C_{cp}–COOMe (lower rim), C_{cp}–thenoyl, and C(=O)–$C_{thienyl}$. The results show that in the structure of lowest energy, the conformations around these bonds are the same as in the solid-state structure. Interestingly, the *anti* orientation of the *endo*-positioned thiophene ring is higher in energy than the listed structures (E=13.9 kJ mol^{-1} for the *endo*/*anti*, *exo*/*anti* conformation), although *syn*/*anti* disorder is evident in the solid-state structure. The *exo*, *exo* orientation of the two thiophene rings is clearly less favorable (entry 6) than the structure of lowest energy.

The time-averaged C_2-symmetrical structures of **2a**–**d**, postulated from the number of signals in the ^{1}H and ^{13}C NMR spectra in $CDCl_3$ solution (see Section 2.1), should be achieved easily by equilibration of the six preferred conformations given in Table 2; a significant barrier to rotation around the bonds C3–C7, C7–C10, C5–C18 (and their symmetry-equivalent counterparts in the left-hand part of the molecule, compare Fig. 1) is not expected. Therefore, it was surprising to observe the presence of three sets of

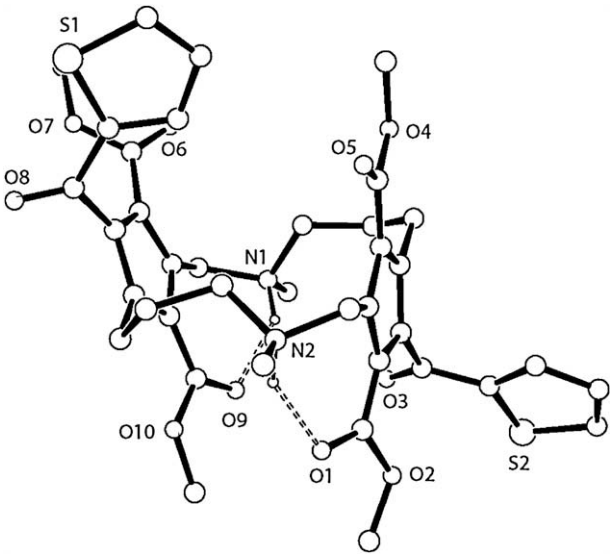
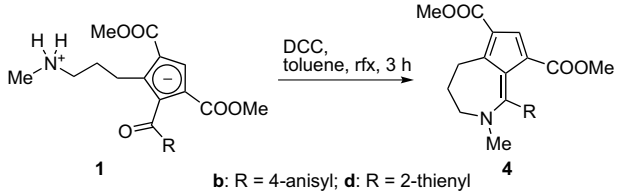


Figure 2. Calculated (PM3) structure of **2d** in the alternate conformation of the macrocyclic framework.

signals when the NMR spectra were recorded in more polar solvents (CD_3CN, CD_3OD, DMSO-d_6). The ^{1}H spectra of **2d** in acetonitrile-d_3 solution at 300 K, for example, showed these signal sets in a 4:1:1 ratio, and in the variable-temperature 200 MHz ^{1}H spectra, (reversible) peak broadening occurred when the temperature was raised to 335 K. A methanol-d_4 solution of **2d** showed three signals for the $COOCH_3$ protons at 300 K, but only one signal at 358 K, which split into three signals again on cooling. These observations suggest a dynamic equilibrium between the species responsible for the different signal sets. We interpret the three signal sets, observed in a 4:1:1 intensity ratio in CD_3CN solution, as belonging to two species. The major component is likely to have the same time-averaged C_2-symmetrical structure as the species observed in $CDCl_3$ solution, while the two minor signal sets of equal intensity are thought to arise from a rather stable unsymmetrical conformer of **2d**, which interconverts with the major conformer only slowly on the NMR time scale. As pointed out above, the unsymmetrical conformers listed in Table 2 are expected to interconvert rather fast by simple bond rotations. We suggest that the unknown conformational isomer has the unsymmetrical structure shown in Figure 2. PM3 calculations place this isomer at $E_{rel(ZPE)}$=18.0 kJ mol^{-1} with respect to the global minimum structure (Table 1, entry 1). It can be seen that this conformer has an 'up, down' arrangement of the two cyclopentadienide rings; it is still stabilized by two intramolecular N–H···O hydrogen bonds, but in contrast to the structure shown in Figure 1, two chemically different ester groups participate in these hydrogen bonds (one adjacent to a thenoyl group, the other one between the aliphatic bridges). Interconversion between the cone conformation shown in Figure 1 and the alternate conformation is reminescent of the conformational isomerism so well known in calixarene chemistry (for energy differences between several conformations in [4]calixarenes, see lit.[15]). In the case of phanes **2**, this interconversion requires at least one intramolecular



Scheme 3. Cyclocondensation of betaines **1b**,**d**.

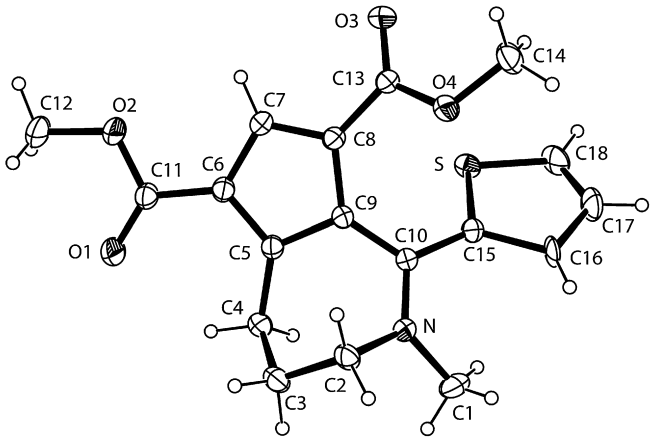


Figure 3. Structure of **4d** in the solid state (ORTEP plot, ellipsoids of thermal vibration shown at the 30% probability level). Selected bond lengths (Å): C5–C6 1.395(2), C6–C7 1.423(2), C7–C8 1.369(2), C8–C9 1.449(2), C9–C10 1.414(2), C5–C9 1.428(2), C10–N 1.336(2), N–C1 1.455(2), N–C2 1.467(2); C8–C13 1.463(2), C13–O3 1.205(2), C6–C11 1.451(2), C11–O1 1.210(2). Torsion angle: C5–C9–C10–N −35.4(2)°.

N–H···O hydrogen bond to be broken temporarily, and this should be facilitated in rather polar solvents such as acetonitrile, methanol, and dimethyl sulfoxide.

2.3. Cyclocondensation of betaines 1b,d

It was expected that the *sec*-amine group in betaines **1** under appropriate conditions would react with one of the carbonyl functional groups. By analogy with the formation of cyclopentadienidophanes **2**, a cyclodimerization reaction could lead to macrocyclic bis-lactams (reaction with an ester group) or bis-enamines (reaction involving the keto function). However, when betaines **1b**,**d** were treated with dicyclohexylcarbodiimide, only an intramolecular cyclocondensation involving the keto function took place, and the bicyclic 6-aminopentafulvenes **4b**,**d** were obtained in 80–85% yield (Scheme 3).

The constitution of **4d** was confirmed by a crystal structure determination (Fig. 3). The bond lengths in the aminofulvene moiety, the deviation from coplanarity at the formal double bond C9–C10, and the presence of a trigonal-planar coordinated nitrogen atom (sum of valence angles=360.0°) all indicate the strong contribution of an iminio-cyclopentadienide resonance structure. This is typical for 6-aminofulvenes; see for example, the structure of methyl 6-dimethylamino-6-ethylfulvene-2-carboxylate.[16]

3. Conclusion

We have presented here a novel access to the barely known [*n*.*n*]cyclopentadienidophanes. 2-Acyl-1,4-bis(methoxycarbonyl)-3-[3-(methylammonio)propyl]cyclopentadienides, easily prepared from semicyclic enaminoketones and a 3-diazopropene-1,3-dicarboxylate by a carbenoid reaction, and formaldehyde can undergo a bimolecular macrocyclization through a twofold Mannich reaction to yield [5.5](1,3)cyclopentadienidophanes. The success of this transformation seems to depend on the length of the ω-(methylammonio)alkyl side chain. With (ω-methylammonio)butyl and -pentyl side-chains, a controlled macrocyclization does not take place and mixtures of oligomers are formed instead. On the other hand, a simple intramolecular cyclocondensation rather than a macrocyclization occurs, when the same (3-methylammoniopropyl)cyclopentadienides are treated with DCC: the reaction of the *sec*-amine group with the adjacent acyl function yields bicyclic 6-aminopentafulvenes.

4. Experimental

4.1. General information

NMR spectra: Bruker AMX 500 spectrometer (^{1}H: 500.14 MHz; ^{13}C: 125.77 MHz). TMS was used as the internal standard; δ values are reported in part per million (m_c=centered multiplet). When necessary, ^{13}C signal assignments were derived from C,H COSY, HSQC and gradient-selected HMBC spectra. A solid-state CP-MAS ^{13}C NMR spectrum was recorded on a Bruker DSX 400 instrument (100.62 MHz, glycine as external reference). IR spectra: Perkin–Elmer IR spectrophotometer 883; wavenumbers [cm^{-1}] are given. Elemental analyses: Perkin Elmer EA 240. Mass spectra: Varian MAT 711 (FD spectra) and SSQ 7000 (EI spectra). Column chromatography was performed under hydrostatic pressure (silica gel Si 60, Macherey-Nagel, 0.063–0.2 mm) and under medium-pressure conditions [Merck Lobar columns, Lichroprep Si 60, particle size 40–63 μm, two columns (240×10 mm and 310×25 mm) connected; gradient pump Merck-Hitachi L6200].

4.2. Materials

Betaines **1a**,**b**,**d**,**e**,**g**,**h**[10] and **1c**,**f**[11] were prepared as described previously.

4.3. Synthesis of bisbetaines 2

*4.3.1. 3,12-Dimethyl-9,18,19,20-tetrakis(methoxycarbonyl)-8,17-dibenzoyl-3,12-diazoniatricyclo[14.2.1.1^{7,10}]-eicosa-1(18),7,9,16-tetraene-19,20-diylide (**2a**)*

To a suspension of betaine **1a** (231 mg, 0.65 mmol) in THF (1 mL) was added aqueous formaldehyde (35%, 0.057 mL, 0.72 mmol), and the resulting solution was stirred at rt for 24 h. After concentration of the solution to half of the volume, the precipitated yellow product was isolated by centrifugation and washed with a small volume of cold THF, then dried at 20 °C/0.008 mbar. Yield: 128 mg (52%); mp 161 °C. IR (KBr): ν=3250–2400 (several bands, br, m), 1648 (vs), 1625 (vs), 1596 (s), 1469 (vs), 1265 (s), 1233 (vs), 1215 (vs), 1104 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=1.59 and 2.20 (br m_c, 2×1H, NCH_2CH_2), 2.76 and 3.16 (m_c, 2×1H, NCH_2CH_2), 2.87 (d, J=5.1 Hz, 3H, NCH_3), 2.93 (m_c, 2H, $C_{cp}CH_2CH_2$), 2.97 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 4.43 (d, ^2J=12.0 Hz, 1H, $C_{cp}CH_2N$), 5.28 (dd, ^2J=12.1 Hz, ^3J=9.0 Hz, 1H, $C_{cp}CH_2N$), 7.36 (m_c, 3H, H_{Ph}), 7.55 (d, J=7.1 Hz, 2H, H_{Ph}), 9.34 (br, 1H, N^+H). ^{13}C NMR (DMSO-d_6): δ=22.93 ($C_{cp}CH_2CH_2$), 24.97 (NCH_2CH_2), 39.92 (NCH_3), 49.58 (OCH_3), 49.77 (OCH_3), 50.52 (NCH_2CH_2), 53.19 (NCH_2C_{cp}), 112.00, 112.97, 120.47, 127.54, 128.42, 129.26, 130.81, 141.87, 166.11 and 167.99 ($COOCH_3$), 196.10 (C=O). Anal. Calcd for $C_{42}H_{46}N_2O_{10}\times 1H_2O$ (738.83+18.02): C 66.65, H 6.39, N 3.70. Found: C 66.87, H 6.27, N 3.50.

*4.3.2. Betaine **2c** (R=2′-nitrobiphenylyl)*

To a suspension of betaine **1c** (103 mg, 0.21 mmol) in THF (1 mL) was added aqueous formaldehyde (35%, 0.019 mL, 0.24 mmol) and a few drops of water to obtain a clear solution. After stirring the solution for 7 days, the solvent was evaporated and the residue was dissolved in ethyl acetate/methanol at 50 °C. After several days in a refrigerator (−18 °C), a yellow powder precipitated (22 mg, 20%); mp 209 °C (dec). The product decomposed partially on standing in $CDCl_3$ solution and in hot solvents. IR (KBr): ν=3434 (br, m), 3050–2400 (little structured series of weak bands), 1678 (vs), 1619 (vs), 1532 (m), 1468 (vs), 1442 (s), 1267 (vs), 1238 (vs), 1221 (vs), 1105 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ=1.51 and 1.95 (br m_c, 2×1H, NCH_2CH_2), 2.93 (d, J=4.8 Hz, 3H, NCH_3), 2.98 and 3.16 (m_c, 2×1H, NCH_2CH_2), 3.11 (m_c, 2H, $C_{cp}CH_2CH_2$), 3.18 (s, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 4.29 (d. ^2J=12.4 Hz, 1H, $C_{cp}CHN$), 5.02 (dd, ^2J=12.4 Hz, ^3J=8.7 Hz, 1H, $C_{cp}CHN$), 7.28–7.90 (m, 4H, H_{aryl}), 8.93 (br, 1H, N^+H). ^{13}C NMR

($CDCl_3$): δ=22.64 ($C_{cp}CH_2CH_2$), 23.52 (NCH_2CH_2), 39.69 (NCH_3), 49.53 (OCH_3), 50.05 (OCH_3), 50.32 (NCH_2CH_2), 51.44 (NCH_2C_{cp}), 111.36, 115.34, 121.26, 124.22, 127.40, 127.52, 128.40, 128.48, 128.90, 131.80, 132.32, 132.39, 136.05, 149.02, 166.31 and 167.08 ($COOCH_3$), 196.81 (C=O). Anal. Calcd for $C_{54}H_{52}N_4O_{14}\times 3H_2O$ (981.02+54.06): C 62.66, H 5.65, N 5.41. Found: C 62.14, H 5.45, N 5.12.

*4.3.3. Bisbetaine **2d** (R=2-thienyl)*

To a suspension of betaine **1d** (200 mg, 0.55 mmol) in THF (1 mL) was added aqueous formaldehyde (35%, 0.045 mL, 0.57 mmol), and the resulting solution was stirred at rt for 24 h. The precipitated yellow product was isolated by centrifugation and washed with a small volume of cold THF, then dried at 20 °C/0.008 mbar. Yield: 169 mg (80%); mp 186 °C (dec). IR (KBr): ν=3486 (br m), 2945 (s), ~2870–2400 (little structured series of weak bands), 1679 (vs), 1610 (vs), 1459 (br, vs), 1414 (vs), 1274 (vs), 1211 (br, vs), 1101 (vs), 1040 (s), 1016 (s) cm^{-1}. ^1H NMR ($CDCl_3$, 303 K): δ=1.62 and 2.14 (br m_c, 2×1H, NCH_2CH_2), 2.81 (d, J=4.9 Hz, 3H, NCH_3), 2.92 (m_c, 2H, NCH_2CH_2), 3.16 (m_c, 2H, $C_{cp}CH_2CH_2$), 3.22 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.30 and 5.31 (broad unstructured signal and t, 2×1H, $C_{cp}CH_2N$), 6.98 (dd, ^3J=3.8 and 4.7 Hz, 1H, 4-$H_{thienyl}$), 7.10 (br, 1H, 3-$H_{thienyl}$), 7.45 (d, ^3J=4.7 Hz), 9.34 (br, 1H, N^+H). ^1H NMR (CD_3CN, 300 K): three sets of signals with the intensity ratio 4:1:1 are observed, which coincide in the case of the $N(CH_2)_3$ protons; δ (signals of the three sets are separated by a slash, the major signal is given first)=1.40 and 2.05 (br m_c, 2×1H, NCH_2CH_2), 2.77 and 3.12 (br m_c, 2×1H, $C_{cp}CH_2CH_2$), 2.81–2.88 (m_c, 2H, NCH_2CH_2), 2.81/2.85/2.88 (3×d, J=5.2, 5.2, 5.5 Hz, 3H, $NHCH_3$), 3.17/3.02/3.16 (3×s, 3H, OCH_3), 3.76/3.78/3.81 (3×s, 3H, OCH_3), 4.02 (dd, J=12.8 and 2.4 Hz) and 5.18 (dd, J=12.8 and 9.1 Hz)/4.14 (d) and 5.02 (dd)/4.29 (d) and 4.95 (dd) ($C_{cp}CH_2N$), 7.02/6.94/6.98 (3×dd, 1H, 4-$H_{thienyl}$), 7.05–7.10 (br m, 1H, 3-$H_{thienyl}$), 7.56/7.53/7.55 (3×d, 1H, 5-$H_{thienyl}$), 9.00/9.2 (br, NH). ^{13}C NMR ($CDCl_3$): δ=22.93 ($CH_2CH_2C_{cp}$), 24.99 (NCH_2CH_2), 39.57 (NCH_3), 49.99 (OCH_3), 50.68 (OCH_3), 51.29 (NCH_2CH_2), 54.57 (NCH_2C_{cp}), 112.41 and 113.29 (both C–$COOCH_3$), 120.91 (O=C–$C_{thienyl}$), 127.18 (C_{cp}), 127.64 (4-$C_{thienyl}$), 128.58 (C_{cp}), 131.53 (3-$C_{thienyl}$), 132.09 (5-$C_{thienyl}$), 150.04 (C-$2_{thienyl}$), 167.31 and 169.66 (both $COOCH_3$), 187.6 (C=O). MS (FD, 8 kV): m/z=750 (100) [M^+], 376 (18). Anal. Calcd for $C_{38}H_{42}N_2O_{10}S_2\times 1H_2O$ (750.89+18.02): C 59.36, H 5.77, N 3.64. Found: C 59.3, H 5.9, N 3.7.

*4.3.4. Betaine **2f** (R=1-adamantyl)*

To a suspension of betaine **1f** (165 mg, 0.39 mmol) in THF (1 mL) was added aqueous formaldehyde (35%, 0.04 mL, 0.51 mmol), and the resulting solution was stirred for 24 h. The colorless precipitate was isolated by centrifugation and washed with a small volume of cold THF, then dried at 20 °C/0.008 mbar. Yield: 138 mg (79%); mp 197 °C. IR (KBr): ν=~3500–3400 (very br m), 2903 (s), 1657 (vs, br), 1454 (vs), 1409 (s), 1355 (s), 1313 (s), 1267 (vs), 1191 (vs), 1160 (vs), 1104 (vs), 1087 (vs) cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.61 (m_c, 6H, $H_{adam.}$), 1.81 (m_c, 6H, $H_{adam.}$), 1.94 (m_c, 3H, $H_{adam.}$), 2.07 and 2.28 (m_c, 2×1H, NCH_2CH_2), 2.91 (t, J=11.6 Hz, 2H, NCH_2CH_2), 3.03 (d, J=3.0 Hz, 3H, NCH_3), 3.38 (t, J=12.5 Hz, 2H, $C_{cp}CH_2CH_2$), 3.48 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 4.22 and 5.04 (br m_c, 2×1H, $C_{cp}CH_2N$), 9.31 (br, 1H, N^+H). ^{13}C NMR $CDCl_3$, 125.77 MHz): δ=22.64 ($C_{cp}CH_2CH_2$), 23.52 (NCH_2CH_2), 39.69 (NCH_3), 49.53 (OCH_3), 50.05 (OCH_3), 50.32 (NCH_2CH_2), 51.44 (NCH_2C_{cp}), 111.36, 115.34, 121.26, 124.22, 127.40, 127.52, 128.40, 128.48, 128.90, 131.80, 132.32, 132.39, 136.05, 149.02, 166.31 and 167.08 ($COOCH_3$), 196.81 (C=O). Anal. Calcd for $C_{50}H_{66}N_2O_{10}\times 2H_2O$ (855.08+36.04): C 67.39, H 7.92, N 3.14. Found: C 66.93, H 7.65, N 3.30.

4.4. Reaction of betaines 1b,e,g,h with formaldehyde; general procedure

To a suspension of the appropriate betaine **1** (0.27–0.64 mmol) in THF (1 mL) was added an equimolar amount (0.021–0.05 mL) or a small excess of aqueous formaldehyde (35%), and the mixture was stirred at rt for 1–3 days. The precipitate was isolated by centrifugation and washed with cold THF, then dried at 20 °C/0.01 mbar. Products **3b**,**e**,**g**,**h** were insoluble in water, and **3g**,**h** were also insoluble in common organic solvents.

*4.4.1. Oligomer **3b** (n=1, R=4-anisyl)*

Reaction time: 3 days. A beige powder was isolated in 45% yield; mp 138–144 °C (dec). IR (KBr): ν=3439 (br, m), 2948 (s), 1728 (s), 1678 (vs), 1599 (vs), 1458 (vs), 1303 (s), 1251 (vs), 1166 (vs), 1108 (s), 1027 (s) cm^{-1}. ^{13}C NMR ($CDCl_3$; many of the following signals, in particular those in the aliphatic region, appear as the most intense ones in a group of peaks with very close chemical shifts): δ=22.8 ($C_{cp}CH_2CH_2$), 24.3 (CH_2), 30.6 (NCH_3), 39.5 (NCH_2), 50.3 (OCH_3), 50.5 (OCH_3), 55.3 ($C_{cp}CH_2N$), 113.0, 113.2, 113.6, 120.7, 128.8, 130.6, 134.6, 161.7, 162.1, 167.2. Anal. Calcd for $(C_{22}H_{25}NO_6)_n$ (n×399.44): C 66.15, H 6.31, N 3.51. Found C 60.46, H 6.11, N 3.35.

*4.4.2. Oligomer **3f** (n=1, R=2-furyl)*

The reaction was carried out with 163 mg (0.47 mmol) of betaine **1f**. After a reaction time of 3 days, a white precipitate (24 mg), which was practically insoluble in organic solvents, was filtered off and discarded. The filtered solution was concentrated to dryness, and the solid residue was triturated with THF (1 mL) for 30 min. After filtration, a beige-brownish powder remained (83 mg, 45% yield); mp 164–166 °C (dec). IR (KBr): ν=3448 (br, m), 2946 (s), ~2850–2400 (little structured series of weak bands), 1676 (vs), 1619 (vs), 1563 (s), 1469 (vs), 1395 (s), 1267 (vs), 1221 (vs), 1161 (s), 1119 (vs), 1015 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ=1.88 and 2.25 (br m, 2×1H, NCH_2CH_2), 2.7–3.2 (several br m, 7H, NCH_3 NCH_2CH_2, $C_{cp}CH_2CH_2$), 3.3 (m, OCH_3), 3.7 (m, OCH_3), 4.7–5.0 ($C_{cp}CH_2N$), 6.4/6.7/7.5 (each: br m, 3×H_{furyl}), 9.15 (br s, N^+H). ^{13}C NMR ($CDCl_3$; many of the following signals, in particular those in the aliphatic region, appear as the most intense ones in a group of peaks with very close chemical shifts): δ=22.1 ($C_{cp}CH_2CH_2$), 27.7 (CH_2), 40.1 (NCH_3), 50.0 (NCH_2), 50.3 (OCH_3), 50.8 (OCH_3), 55.3 ($C_{cp}CH_2N$), 111.6 (C-4_{furyl}), 115.4, 116.9, 119.9 (C-3_{furyl}), 121.1, 124.9, 144.4, 145.1 (C-5_{furyl}), 155.7 (C-2_{furyl}), 170.0 ($COOCH_3$), 190.0 (C=O). Anal. Calcd for $(C_{19}H_{21}NO_6)_n$ (n×359.38): C 63.50, H 5.89, N 3.90. Found: C 55.39, H 5.73, N 3.45.

*4.4.3. Oligomer **3g** (n=2, R=2-thienyl)*

Yellow powder. Yield: 74%; mp 195–197 °C (dec). IR (KBr): ν=3460 (m, very broad), 3050–2400 (little structured series of weak bands), 1675 (vs), 1633 (vs), 1513 (w), 1466 (vs), 1420 (m), 1398 (m), 1370 (w), 1346 (w), 1306 (w), 1277 (m), 1247 (s), 1229 (vs), 1188 (m), 1142 (w), 1102 (vs), 1060 (w), 1044 (w) cm^{-1}. Anal. Calcd for $(C_{20}H_{23}NO_5S)_n$ (n×389.47): C 61.68, H 5.95, N 3.59. Found: C 61.7, H 6.2, N 3.5.

*4.4.4. Oligomer **3h** (n=3, R=2-thienyl)*

Yellow powder. Yield: 81%; decomposition at ≥250 °C. IR (KBr): ν=3460 (m, very broad), 3050–2400 (little structured series of weak bands), 1674 (s), 1633 (s), 1601 (s), 1468 (vs), 1277 (m), 1248 (s), 1229 (vs), 1187 (m), 1101 (s) cm^{-1}. Solid-state ^{13}C NMR (CP-MAS): δ=22–34 (several signals), 40.7, 41.7, 50.5, 52.8, 53.5 (broadened by additional signals), 113.1, 116.6, 121.7, 126.9, 128.0, 129.0, 132.3, 134.2, 150.4, 166.6, 170.9, 187.6. Anal. Calcd for $(C_{21}H_{25}NO_5S)_n$ (n×403.49): C 62.51, H 6.24, N 3.47. Found: C 62.4, H 6.5, N 3.6.

4.5. Dimethyl 2-methyl-1-(4-methoxyphenyl)-2,3,4,5-tetrahydrocyclopenta[*c*]azepine-6,8-dicarboxylate (4b)

A magnetically stirred mixture of betaine **1b** (213 mg, 0.55 mmol), dicyclohexylcarbodiimide (114 mg, 0.55 mmol), and

toluene (10 mL) was heated at reflux for 3 h. After cooling, the solvent was evaporated in vacuo, and **4b** was separated from also formed dicyclohexylurea by column chromatography (elution with methanol). The product was dissolved in ethyl acetate and precipitated as a yellow powder by addition of ether (162 mg, 80% yield); mp 205 °C. IR (KBr): ν=1700 (sh), 1679 (vs), 1603 (s), 1540 (s), 1508 (m), 1478 (s), 1437 (vs), 1407 (m), 1320 (m), 1305 (m), 1253 (vs), 1220 (s), 1206 (vs), 1186 (s), 1144 (s), 1057 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ=2.54 (quin, 2H, NCH_2CH_2), 3.23 (t and s, 5H, $NCH_2CH_2CH_2$ and $COOCH_3$), 3.41 (s, 2H, NCH_3), 3.78 (s, 3H, $COOCH_3$), 3.80 (t, 2H, NCH_2), 3.85 (s, 3H, aryl-OCH_3), 6.90/7.30 (AA′BB′ system, 4H, H_{aryl}), 7.38 (s, 1H, CH_{cp}). ^{13}C NMR ($CDCl_3$, 125.77 MHz): δ=23.00 ($NCH_2CH_2CH_2$), 35.04 (NCH_2CH_2), 40.87 (NCH_3), 50.45 (2×$COOCH_3$), 55.43 (aryl-OCH_3), 56.74 (NCH_2), 113.46 (CH_{aryl}), 116.71 (CH_2C=C), 119.44 and 120.02 (2×C–$COOCH_3$), 127.98 (C_{aryl}), 129.16 (CH_{cp}), 133.30 (CH_{aryl}), 143.06 (NC=C), 162.28 (C_{aryl}–OCH_3), 165.52 (C=O), 166.66 (C=O), 172.81 (NC=). MS (EI, 70 eV): m/z (%)=369 (100) $[M]^+$, 354 (19), 338 (24), 310 (31), 148 (31).

4.6. Dimethyl 2-methyl-1-(2-thienyl)-2,3,4,5-tetrahydrocyclopenta[*c*]azepine-6,8-dicarboxylate (4d)

Prepared from **1d** (200 mg, 0.55 mmol) as described for **4b** (Section 4.5). The product obtained after column chromatography was dissolved in ethyl acetate and exposed to diffusion of ether vapor to furnish red needles (167 mg, 85% yield); mp 162 °C. IR (KBr): ν=1677 (br, vs), 1520 (m), 1476 (m), 1439 (s), 1408 (m), 1390 (m), 1250 (s), 1215 (s), 1141 (m), 1094 (m), 1058 (s) cm^{-1}. ^1H NMR ($CDCl_3$): δ=2.53 (quin, 2H, NCH_2CH_2), 3.21 (broadened t, J=7.4 Hz, 2H, $NCH_2CH_2CH_2$), 3.33 (s, 3H, OCH_3), 3.55 (s, 3H, NCH_3), 3.74 (t, J=5.9 Hz, 2H), 3.78 (s, 3H, OCH_3), 7.14 (dd, J=5.0 and 3.8 Hz, 1H, 4-$H_{thienyl}$), 7.35 (dd, ^3J=3.8 Hz, $|^4J|$=1.2 Hz, 1H, 3-$H_{thienyl}$), 7.39 (s, 1H, CH_{cp}), 7.68 (dd, ^3J=5.0 Hz, $|^4J|$=1.3 Hz, 1H, 5-$H_{thienyl}$). ^{13}C NMR ($CDCl_3$): δ=22.94 ($NCH_2CH_2CH_2$), 35.14 (NCH_2CH_2), 40.87 (NCH_3), 50.48 and 50.53 (2×OCH_3), 56.83 (NCH_2), 117.28 and 119.93 (2×C–$COOCH_3$), 120.20 (CH_2C=), 127.58 C-$4_{thienyl}$), 129.53 (C-$3_{thienyl}$), 137.61 (C-$2_{thienyl}$), 143.42 (NC=C), 163.95 (NC=), 165.52, 166.66 (2×C=O). MS (EI, 70 eV): m/z (%)=347 (7), 345 (100) $[M]^+$, 336 (16), 314 (20) $[M-CH_3O]^+$, 286 (37). Anal. Calcd for $C_{18}H_{19}NO_4S$ (345.42): C 62.59, H 5.54, N 4.06. Found: C 62.18, H 5.73, N 4.50.

4.7. Crystal structure determination for compounds 2d and 4d

Data collection was performed at ambient temperature with an image-plate diffraction system (IPDS, Stoe) using monochromated Mo Kα radiation (λ=0.71073 Å). The structures were solved with direct methods and refined with a full-matrix least-squares procedure using F^2 values. Software for structure solution and refinement: SHELX-97;[17] molecule plots: ORTEP-3.[18] CCDC-717015 (**2d**) and 717016 (**4d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

4.7.1. Data for *2d*

Crystal data: $C_{38}H_{42}N_2O_{10}S_2$, M=750.9, monoclinic, space group $P2_1/n$, a=12.254(2), b=19.970(2), c=15.607(3) Å, β=104.61(2)°; V=3695.7(10) $Å^3$, Z=4, D_c=1.349 g cm^{-3}, μ=0.21 cm^{-1}. Data collection: crystal size 0.35×0.32×0.22 mm, 19,211 reflections in the range θ=1.69–24.14°, 5769 unique reflections (R_{int}=0.2045). Structure refinement results: refinement of 475 parameters using all 5769 data gave final R indices of R_1=0.2220, wR_2=0.1721 (0.0790 and 0.1411 for 1910 reflection data with ($I>2\sigma(I)$). Residual electron density between 0.54 and −0.39 e $Å^{-3}$. The positions of the N–H hydrogen atoms were refined freely. All other hydrogen atoms were treated as riding on their bond neighbors. The thiophene ring containg atom S2 appears to be disordered over two positions (rotation by 180 °C about the C28–C29 bond). Efforts to include this disorder in the refinement resulted in unreasonable geometries, probably due to the low occupancy factor of the second ring position.

4.7.2. Data for *4d*

Crystal data: $C_{18}H_{19}NO_4S$, M=345.4, orthorhombic, space group $Pbca$, a=12.906(1), b=9.921(1), c=26.645(4) Å, $\alpha=\beta=\gamma$=90°, V=3411.4(7) $Å^3$, Z=8, D_c=1.345 g cm^{-3}, μ=0.211 mm^{-1}. Data collection: crystal size 0.57×0.23×0.15 mm, 19,916 reflections in the range θ=2.70–28.02°, 4023 unique reflections (R_{int}=0.0445). Structure refinement: refinement of 261 parameters using all data gave final R indices of R_1=0.0597, wR_2=0.1070 (0.0405 and 0.0992 for 2902 reflection data with ($I>2\sigma(I)$). Residual electron density between 0.21 and −0.19 e $Å^{-3}$. Hydrogen atoms were treated as riding on their bond neighbors. The thiophene ring is disordered over two positions (rotation by 180 °C about the C10–C15 bond). This disorder was included in the refinement procedure, yielding occupancy factors of 0.74 and 0.26.

4.8. Computational conformation analysis of 2d

The calculations were performed using the semiemperical PM3 method as implemented in the SPARTAN 06 program package.[19] Starting with the atom position coordinates from the solid-state structure of **2d**, 256 conformations were generated automatically and optimized. The 12 structures with lowest energy were characterized as minimum-potential structures by frequency calculations. In Table 2, the six structures with lowest energy (ZPE corrected) are listed.

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