

Synthesis of β -octabromocalix[4]pyrroles and conformational diversity in their acetone inclusion complexes

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Abstract

Two β -octabromocalix[4]pyrroles were synthesized using a modified strategy, which provides the advantage of large scale preparation with rapid purification. The acetone inclusion complexes of these compounds show different structural orientations featuring diverse types of novel hydrogen bonding owing to varied *meso*-substitution along with the presence of eight peripheral bromine atoms.
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Calix[4]pyrrole, a long-known¹ versatile class of macrocycles possesses interesting anion,² metal ion,³ and neutral molecule⁴ binding abilities. Since the pioneering synthesis by Baeyer,¹ numerous studies have enriched its synthesis⁵ and uses, including fluorescent,⁶ colorimetric,⁷ and electrochemical sensing.⁸ These macrocycles can adopt a variety of conformations according to the following stability order: 1,3-alternate > partial cone > 1,2-alternate > cone, both in the gas phase and in dichloromethane.⁹ Experimentally, the diverse modes of binding of short-chain alcohols, mono-amides, and other solvent molecules to calix[4]pyrroles have been explored in the solid state by X-ray crystallography and in solution by NMR titration methods.⁴ Recently, we reported thermal behavior on the stability and structural interconvertibility of some neutral host–guest adducts.¹⁰ In a study on anion binding, pyrrole β center modifications were employed to compare their anion binding ability with respect to the β -free analogue.¹¹ It was shown by NMR spectroscopy that β -octabromo substituted derivatives bind with anions more strongly than the corresponding β -free analogue. However, to date no

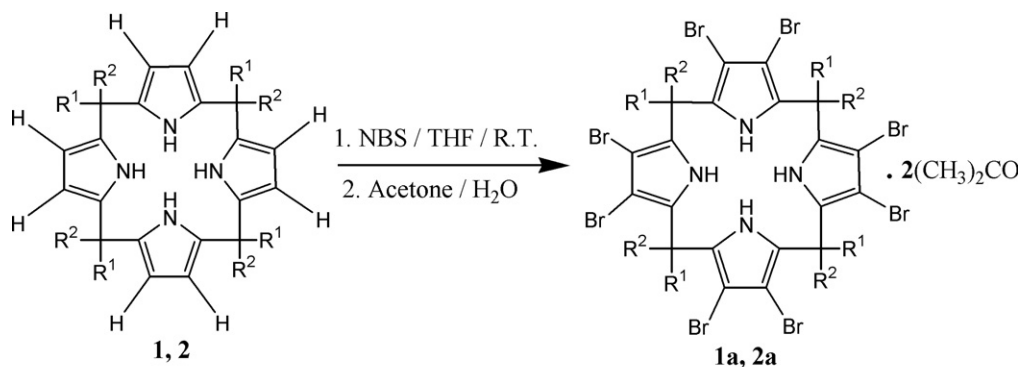
X-ray structural investigation for neutral host–guest binding with such a derivative is available.

Aiming to investigate this aspect, we first targeted an easy synthesis of β -octabromo substituted calix[4]pyrroles using a modified synthetic protocol, which has the advantage of large scale preparation within a short time span avoiding tedious column chromatographic purification.¹¹ We extended our investigation on the adduct formation of these β -octabromo derivatives with a neutral molecule by spectroscopic and by X-ray structure analysis. *meso*-Octamethylcalix[4]pyrrole (**1**) and *meso*-tetraethyltetramethylcalix[4]pyrrole (**2**) were chosen as starting materials for bromination and acetone was utilized as the neutral guest molecule to determine the resulting conformational orientation, which in the presence of peripheral heavy bromine atoms might influence the usual 1,3- or 1,2-geometry prevalent in their β -free analogues.

Compounds **1** and **2** were synthesized using our earlier reported procedure.⁵ Bromination was carried out by a modified version of a previously reported method.¹¹ In general, β -octabromocalix[4]pyrrole was prepared as follows (Scheme 1).^{12,13} Recrystallized[†] *N*-bromosuccinimide

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[†] NBS can be recrystallized by dissolving in hot water followed by rapid cooling.

Scheme 1. Preparation of complexes **1a** and **2a**.

(NBS) was suspended in THF at room temperature. Ligand **1** or **2**, dissolved in THF was added slowly to the NBS suspension with stirring to prevent excess local concentration as the reaction was exothermic. The pale yellow suspension gradually clarified forming a clean yellow-orange solution. After stirring for 15 min, the solution was filtered and evaporated to dryness under reduced pressure. The resulting yellowish mass, when cooled, was washed thoroughly with distilled water (twice) to remove succinimide, generated en route to bromination, followed by washing with hot water (60–70 °C) to remove any unreacted NBS. Finally, the whole mass was shaken with acetone/water mixture (8:1) containing a few drops of triethylamine to neutralize any trace acid, HBr, which might have originated from hydrolysis of the reaction mixture. The product was separated as an off-white powder while the color of the mother liquor became reddish brown. The powder was collected by filtration, washed with acetone/methanol (1:2) mixture, and then with petroleum ether to remove any unreacted free ligand in the case of **2**,[‡] and finally vacuum dried. Recrystallization by dissolving in acetone and precipitating with water led to the isolation of **1a** and **2a** in 77% and 71% yields, respectively, in analytically pure form.

Single crystals suitable for X-ray diffraction were obtained as large colorless rectangular blocks from an acetone/water solution of **1a** or **2a** by standing for 48 h at 4 °C. Complexes **1a** and **2a** were characterized by elemental analyses, NMR, IR, mass spectroscopy, and by single crystal X-ray crystallography (Fig. 1).^{14,15} Selected bond distances and angles are presented in Table 1.

The X-ray structures of **1**·2(CH₃)₂CO and **2**·2(CH₃)₂CO revealed interesting geometry. In **1**·2(CH₃)₂CO, two molecules of acetone were present in a symmetry equivalent manner in the lattice per calix[4]pyrrole molecule, one above and one below the host moiety forming hydrogen bonds with the oxygen atom and N–H of the pyrrole.

The N_{pyrrole}–O_{acetone} distance is 3.09 Å, the corresponding N–H···O distance is 2.283 Å, and the N–H···O angle is 157° (Fig. 1). Unlike normal β-free calix[4]pyrrole analogues, where in most cases all four pyrroles are involved in hydrogen bonding with the guest molecules, here only two pyrroles are involved in H-bonding. The other two alternate pyrroles are not involved in hydrogen bonding as they are situated in a head-on manner with an N–N distance of 4.932 Å and with a dihedral angle of 3.79° indicating that both are nearly coplanar. Some of the *meso* methyl hydrogens form moderately strong hydrogen bonds with the oxygen atom having C–H···O distances of 2.509 Å and 2.498 Å. The C–H···O angles are 132° and 136°, respectively. The other two pyrroles are perfectly coplanar having a dihedral angle of 0°. The overall geometry can be said to be in between 1,2- and 1,3-conformations.

In the case of **2**·2(CH₃)₂CO, two molecules of acetone were found to be present on the same side of the molecule in an asymmetrical manner and were engaged in hydrogen bonding with two alternate pyrrole N–H moieties and oxygen atom forming a distorted 1,3-alternate conformation (Fig. 1). The N–H···O hydrogen bond distances are 2.196 and 2.236 Å with N–H···O angles of 161° and 166°, which indicate strong hydrogen bonds. In addition, there are secondary hydrogen bonding interactions, with the hydrogen of the *meso*-methyl substituents and the oxygen of acetone. The C–H···O distance ranges from 2.420 to 2.665 Å, and the angle C–H···O is in the range of 126–156°. Moreover, a weak π–π stacking interaction was also found to be present with C=O and the planes of two silent pyrrole rings not involved in hydrogen bonding, having a distance of ~4 Å. The two non-interacting pyrroles share a dihedral angle of 17.5°. The other two pyrroles face the opposite side and have a dihedral angle of 83.5°. Interestingly, the ethyl hydrogens do not take part in hydrogen bonding and face away from the oxygen atom. The overall geometry can be considered as 1,3. The structural difference can be accounted for due to the presence of ethyl substitution at the *meso* position in **2**, which may have

[‡] **2** was found to be fairly soluble in petroleum ether.

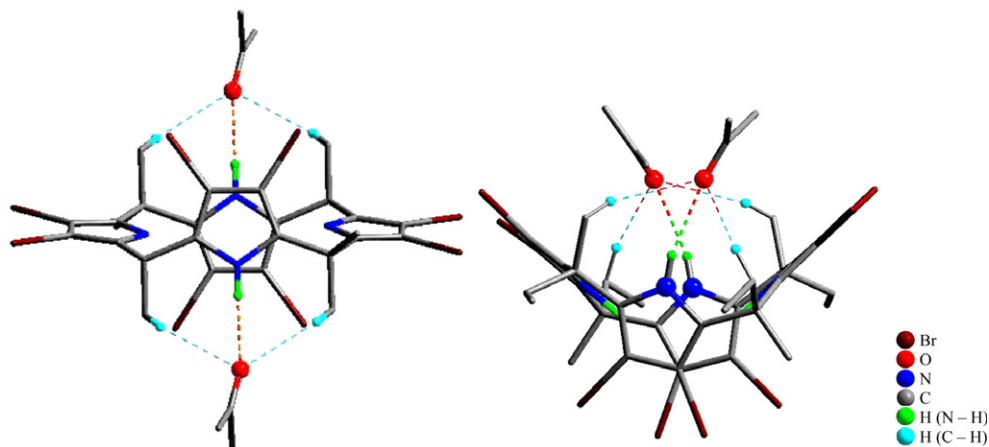


Fig. 1. X-ray crystal structures of complex **1**·2(CH₃)₂CO and **2**·2(CH₃)₂CO showing multi-fashoned hydrogen bonding interactions. Hydrogen atoms of the N–H of pyrroles and hydrogen bonded C–H of methyl groups are shown for clarity. Color code: Brown: Br, Red: O, Blue: N, Grey: C, Green: H of N–H and sky: H of C–H.

Table 1
List of selected bond distances and angles of complexes **1**·2(CH₃)₂CO and **2**·2(CH₃)₂CO

	N _{pyrrole} –H···O _{acetone} (Å)	N _{pyrrole} ···O _{acetone} (Å)	N _{pyrrole} –H···O angle (°)	O–H···C _{meso} (Å)	Dihedral angle (1,2 and 1,3 pyrrole plane) (°)
1 ·2(CH ₃) ₂ CO	2.283/2.283	3.079/3.079	157	2.498/2.501	3.79/0.0
2 ·2(CH ₃) ₂ CO	2.196/2.236	3.021/3.076	160.95/165.75	2.420–2.665	17.5/83.5

hindered the approach of two acetone molecules from the opposite face in a symmetrical manner.

¹³C NMR spectroscopy also revealed that both complexes **1** and **2** retain their respective guest acetone molecules bound in solution. Figure 2 shows the ¹³C NMR of **1**·2(CH₃)₂CO, with an encircled portion (inset picture) where the peak at 205.9 ppm (weak) is due to the C=O of acetone. The ¹H NMR of **1**·2(CH₃)₂CO showed an N–H resonance at 7.72 ppm, a downfield shift of about 0.8 ppm with respect to its β-free analogue **1**. Incorpora-

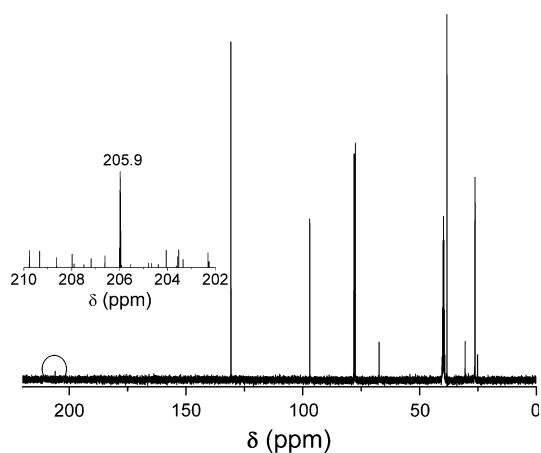


Fig. 2. ¹³C NMR spectrum (100 MHz) of **1**·2(CH₃)₂CO taken in DMSO-*d*₆.

tion of eight bromine atoms in the pyrrole β positions made the N–H proton of the pyrrole ring more acidic owing to the electron withdrawing nature of bromine. In **2**·2(CH₃)₂CO, the N–H protons resonated at 8.22 ppm, about 1.25 ppm downfield compared to free **2** (6.97 ppm) and can be explained as before.

Under mass spectral conditions the host–guest interaction is lost and only the molecular ion peaks of non-coordinated molecules were observed.^{12,13}

The FT-IR spectra of both adducts showed strong bands at 1707 and 1708 cm^{−1}, respectively, due to C=O stretching vibrations indicative of the presence of acetone. The N–H stretching vibrations appeared around 3426–3428 cm^{−1}, about 10 cm^{−1} less, as compared to the β-free analogues. Under prolonged drying, these complexes lose the guest molecules, as observed by FT-IR where the C=O stretching vibrations disappeared. The crystallinity of the compound was also lost with the formation of a powdery material.

Calix[4]pyrroles bearing cyclic substituents do not undergo similar bromination reactions to yield octabromo products, instead they polymerize to form blue solids, which are currently under investigation.

In conclusion, we have reported the bromination of pyrrole at the β position in calix[4]pyrroles. The synthesized octabromo substituted calix[4]pyrroles form adducts with acetone in hitherto unknown bonding fashions involving strong and weak hydrogen bonding and weak π–π interactions as revealed by their X-ray crystal structures.

Acknowledgments

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References and notes

- Baeyer, A. *Ber. Dtsch. Chem. Ges.* **1886**, *19*, 2184–2185.
- (a) Gale, P. A.; Sessler, J. L.; Kral, V. *Chem. Commun.* **1998**, 1–8; (b) Sessler, J. L.; Gross, D. E.; Cho, W.; Lynch, V. M.; Schmidtchen, F. P.; Bates, G. W.; Light, M. E.; Gale, P. A. *J. Am. Chem. Soc.* **2006**, *128*, 12281–12288; (c) Golder, A. J.; Milgrom, L. R.; Nolan, K. B.; Povey, D. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1751–1752; (d) Lee, C. H.; Na, H. K.; Yoon, D. W.; Won, D.; Cho, W.; Lynch, V. M.; Shevchuk, S. V.; Sessler, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 7301–7306; (e) Gale, P. A.; Sessler, J. L.; Kral, V.; Lynch, V. *J. Am. Chem. Soc.* **1996**, *118*, 5140–5141.
- (a) Bhattacharya, D.; Dey, S.; Maji, S.; Pal, K.; Sarkar, S. *Inorg. Chem.* **2005**, *44*, 7699–7701; (b) Floriani, C. *Chem. Commun.* **1996**, 1257–1263; and references cited therein; (c) Bachmann, J.; Nocera, D. G. *J. Am. Chem. Soc.* **2005**, *127*, 4730–4743; (d) Cuesta, L.; Gross, D.; Lynch, V. M.; Ou, Z.; Kajonkijya, W.; Ohkubo, K.; Fukuzumi, S.; Kadish, K. M.; Sessler, J. L. *J. Am. Chem. Soc.* **2007**, *129*, 11696–11697.
- (a) Allen, W. E.; Gale, P. A.; Brown, C. T.; Lynch, V. M.; Sessler, J. L. *J. Am. Chem. Soc.* **1996**, *118*, 12471–12472; (b) Camiolo, S.; Coles, S. J.; Gale, P. A.; Hursthouse, M. B.; Sessler, J. L. *Acta Crystallogr., Sect. E* **2001**, *57*, 816–817; (c) Anzenbacher, P.; Jursikova, K.; Lynch, V. M.; Gale, P. A.; Sessler, J. L. *J. Am. Chem. Soc.* **1999**, *121*, 11020–11021; (d) Camiolo, S.; Coles, S. J.; Gale, P. A.; Hursthouse, M. B.; Paver, M. A. *Acta Crystallogr., Sect. E* **2001**, *57*, 258–260; (e) Inoue, H. K.; Inoue, T.; Ono, N. *Org. Biomol. Chem.* **2003**, *1*, 3857–3865; (f) Lynch, V. M.; Gale, P. A.; Sessler, J. L.; Madeiros, D. *Acta Crystallogr., Sect. C* **2001**, *57*, 1426–1427; (g) Anzenbacher, P.; Jursikova, K.; Shriver, J. A.; Miyaji, H.; Lynch, V. M.; Sessler, J. L.; Gale, P. A. *J. Org. Chem.* **2000**, *65*, 7641–7645; (h) Su, X.; Zhou, Z.; Zhu, S.; Lin, H.; Leng, X.; Weng, L.; Chen, Y. *J. Chem. Res.* **2000**, 538–539; (i) Lehmann, C.; Schweizer, B.; Leumann, C.; Eschenmoser, A. *Helv. Chim. Acta* **1997**, *80*, 1421–1442; (j) Jacoby, D.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *J. Chem. Soc., Chem. Commun.* **1991**, 790–791; (k) Anzenbacher, P.; Try, A. C.; Miyaji, H.; Jursikova, K.; Lynch, V. M.; Marquez, M.; Sessler, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 10268–10272; (l) Nielsen, K. A.; Cho, W. S.; Jeppesen, J. O.; Lynch, V. M.; Becher, J.; Sessler, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 16296–16297.
- (a) Dey, S.; Pal, K.; Sarkar, S. *Tetrahedron Lett.* **2006**, *47*, 5851–5854; and references 12–30 cited therein; (b) Jain, V. K.; Mandalia, H. C. *Heterocycles* **2007**, *71*, 1261–1314.
- Miyazu, H.; Anzenbacher, P., Jr.; Sessler, J. L.; Bleasdale, E. R.; Gale, P. A. *Chem. Commun.* **1999**, 1723–1724.
- Gale, P. A.; Twyman, L. J.; Handlin, C. I.; Sessler, J. L. *Chem. Commun.* **1999**, 1851–1852.
- Gale, P. A.; Hursthouse, M. B.; Light, M. E.; Sessler, J. L.; Warriner, C. N.; Zimmerman, R. S. *Tetrahedron Lett.* **2001**, *42*, 6759–6762.
- Wu, Y.; Wang, D.; Sessler, J. L. *J. Org. Chem.* **2001**, *66*, 3739–3746.
- Dey, S.; Pal, K.; Sarkar, S. *Tetrahedron Lett.* **2007**, *48*, 5481–5485.
- (a) Gale, P. A.; Sessler, J. L.; Allen, W. E.; Tvermoes, N. A.; Lynch, V. *Chem. Commun.* **1997**, 665–666; (b) Sessler, J. L.; Marquez, M.; Anzenbacher, P.; Shriver, J. A. U.S. Patent Application 7,041,819, 2002.
- Synthesis of β -octabromo-meso-octamethylcalix[4]pyrrole* [$C_{28}H_{28}N_4Br_8$] (**1a**): 15 g (85 mmol) of NBS was suspended in THF (70 ml) at room temperature. *meso*-Octamethylcalix[4]pyrrole (5 g, 11.7 mmol) dissolved in 70 ml of THF was added slowly to the NBS suspension with stirring. After completion of the addition, the mixture was stirred for about 15 min, filtered and the solvent was removed under reduced pressure and the residue was dried in vacuo. Distilled water (40 ml) was added to the brownish solid, which was shaken vigorously to dissolve succinimide and the liquor was decanted off. The process was repeated twice and the product finally washed with warm water to remove unreacted NBS. Acetone/water mixture (8:1) was then added dropwise with stirring upon which a white powdery mass separated from the crude brown mass. This was filtered, washed with 90% acetone containing a few drops of triethylamine and finally with hexane. The resultant white product was recrystallized from THF and methanol or from acetone and water. Yield: 9.6 g (77%). Single crystals suitable for X-ray diffraction were grown from a dilute solution of acetone/water upon standing for 2 days at 4 °C. The acetone adduct of the complex was subjected to spectroscopic and other characterizations.
Characterization: Decomposition temperature >100 °C. Anal. Calcd for $C_{28}H_{28}N_4Br_8$: C, 31.70; H, 2.65; N, 5.28%. Found: C, 32.00; H, 2.72; N, 5.38%. FAB-MS: m/z at 1060 due to free **1a**. NMR (400 MHz, DMSO- d_6 , 300 K, ppm): 1H : 7.72 (br s, 4H, N–H, C_4H_2N), 3.17 (s, 3H, C_3H_6O), 2.71 (s, 3H, C_2H_6O), 1.63 (s, 12H, *meso*-CH₃), 1.32 (s, 12H, *meso*-CH₃). Disappearance of the β -H signal confirms complete bromination; ^{13}C NMR (100 MHz, DMSO- d_6 , 300 K, ppm): 205.90 (C, C=O, C_2H_6O), 130.67 (β -C, C_4H_2N), 96.94 (α -C, C_4H_2N), 67.24, 30.43 (*meso*-C), 26.19 (C, *meso*-CH₃, C_2H_6O), 25.11 (C, *meso*-CH₃); FT-IR (KBr, solid, cm^{-1}): 3428 (s, N–H), 2926, 2855 (C–H), 1707 (s, C=O), 1546, 769.
- Synthesis of β -octabromo-meso-tetraethyltetramethylcalix[4]pyrrole* [$C_{32}H_{36}N_4Br_8$] (**2a**): 19 g (107 mmol) of *N*-bromosuccinimide was taken in 70 ml of THF and stirred under ambient conditions. 5.0 g (10.4 mmol) of *meso*-tetraethyltetramethylcalix[4]pyrrole dissolved in 15 ml of THF was slowly added to the stirred NBS suspension avoiding excess addition to avoid enhanced local concentration. The suspension disappeared readily and a clean solution resulted, which gradually turned to a light yellow-brown color. The reaction mixture was stirred for 15 min, filtered, and evaporated under reduced pressure. The resulting mass was cooled, washed thoroughly with distilled water (2 × 40 ml) to dissolve the succinimide, followed by washing with another 40 ml of hot water to dissolve any unreacted NBS. Finally, the brown mass was shaken with 20 ml of 8:1 acetone/water containing a few drops of triethylamine to neutralize any trace acid. The product separated out in the form of an off-white powder and was isolated by filtration, washed with petroleum ether[†] to remove unreacted free ligand, and finally vacuum dried. Recrystallization using acetone/water mixture twice led to the isolation of analytically pure product. Yield: 8.0 g (71%).
Characterization: The compound does not melt rather it decomposes above 200 °C. Anal. Calcd for $C_{32}H_{36}N_4Br_8$: C, 34.40; H, 3.22; N, 5.01%. Found: C, 34.12; H, 3.19; N, 5.09%. 1H NMR: (400 MHz, DMSO- d_6 , 300 K, ppm) 8.22 (br s, 4H, N–H, pyrrole), 3.12 (m, 8H, CH₂), 2.17 (s, 12H, CH₃), 1.40 (m, 12H, CH₃). ^{13}C NMR (100 MHz, DMSO- d_6 , 300 K, ppm): 130.46 (β -C, C_4H_2N), 97.32 (α -C, C_4H_2N), 42.57 (C, CH₂, Et), 29.55 (C, *meso* C), 22.71 (C, CH₃, Me), 9.04 (C, CH₃, Et) FT-IR: (KBr, solid, cm^{-1}) 3426 (s, N–H), 2922, 2855 (C–H, aliphatic stretching), 1708 (s, C=O), 1580, 766. FAB-MS: m/z at 1116 for free **2a**. Also fragment peaks at 1087, 1038 due to removal of 1 Et or 1 Br, respectively.
- Crystal data for 1·2(CH₃)₂CO: Molecular formula $C_{34}H_{40}N_4Br_8O_2$, $M = 1175.90$, colorless prisms, crystal dimensions $0.2 \times 0.2 \times 0.1$ mm³, monoclinic, space group $P2_1/n$, $a = 14.497(5)$, $b = 9.455(5)$, $c = 15.170(5)$ Å; $\alpha = 90$, $\beta = 98.837(5)$, $\gamma = 90^\circ$, $V = 2054.7(15)$ Å³, $Z = 2$, $D_c = 1.901$ mg/m³, $F(000) = 1136$, Bruker SMART APEX, Mo $K\alpha$ radiation ($\lambda = 0.71069$ Å), $T = 100(2)$ K, ($2.11^\circ \leq \theta \leq 28.27^\circ$), 13,197 reflections collected, 5068 unique, final GoF = 1.095, $R_1 = 0.0580$, $wR_2 = 0.1268$, R indices based on 5068 reflections with $I > 2\sigma(I)$, (refinement on F^2), 211 parameters, 0 restraints, absorption corrections empirical, $\mu = 7.841$ mm⁻¹.

15. Crystal data for **2**-2(CH₃)₂CO: Molecular formula C₃₈H₄₈Br₈N₄O₂, $M = 1232.01$, colorless blocks, crystal dimensions $0.2 \times 0.2 \times 0.1 \text{ mm}^3$, monoclinic, space group $P2_1/c$, $a = 20.114(5)$, $b = 11.506(5)$, $c = 19.268(5) \text{ \AA}$; $\alpha = 90$, $\beta = 104.035(5)$, $\gamma = 90^\circ$, $V = 4326(2) \text{ \AA}^3$, $Z = 4$, $D_c = 1.892 \text{ mg/m}^3$, $F(000) = 2400$, Bruker SMART APEX, Mo K α radiation ($\lambda = 0.71069 \text{ \AA}$), $T = 100(2) \text{ K}$, ($2.21^\circ \leq \theta \leq 28.28^\circ$), 28,527 reflections collected, 10,668 unique, final GoF = 1.048, $R_1 = 0.0803$, $wR_2 = 0.2097$, R indices based on 4496

reflections with $I > 2\sigma(I)$, (refinement on F^2), 475 parameters, 0 restraints, absorption corrections empirical, $\mu = 7.454 \text{ mm}^{-1}$. Crystallographic data for **1**-2(CH₃)₂CO and **2**-2(CH₃)₂CO have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 663230 and 663231. Copies of the data can be obtained free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].