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Neutral guests complexation with calix[4]arenes preorganised by intramolecular McMurry reaction

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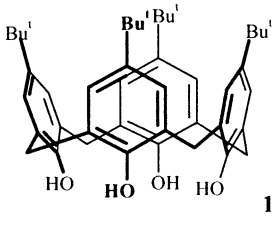
Abstract—The introduction of two aromatic aldehyde moieties into the lower rim of calix[4]arenes led to the precursors that were intramolecularly bridged in the presence of low-valent titanium agents (the McMurry reaction). These compounds, preorganised in the *cone* conformation, represent novel receptors with good complexation ability towards suitable neutral guest molecules both in solution and in the solid state. The influence of preorganisation and overall rigidity of receptor to the complexation process has been studied.

Cyclic oligomers of *p*-substituted phenols and formaldehyde, known as calix[*n*]arenes,[1] have found many applications in supramolecular chemistry[2] due to their simple one-pot preparation and their unique structural properties. The easily tuneable shape of the molecule, together with almost unlimited possibilities of chemical transformation, make calix[*n*]arenes useful building blocks in the construction of more sophisticated molecular systems. Calix[4]arene **1** especially is widely used as a molecular scaffold for the design and synthesis of a wide range of receptors with recognition ability towards both neutral and charged molecules.[3]



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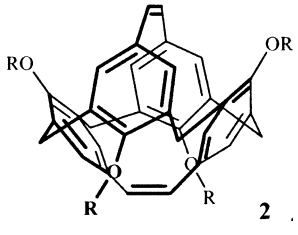

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As already demonstrated, intramolecular McMurry reactions[4] of calix[4]arene derivatives bearing formyl groups on the upper rim[5,6] leads to systems with highly strained structures. Thus, compound **2** possesses a molecular cavity preorganised for possible complexation. On the other hand, the usage of this derivative as a receptor is rather restricted by the small size of the inner cavity. In this paper we report a simple strategy leading to receptors with preorganised cavities based on the McMurry reaction of suitable formyl-substituted[7] calix[4]arene derivatives.

Starting *tert*-butylcalix[4]arene **1** was diametrically dialkylated with *p*-cyanobenzyl bromide in refluxing acetone using K_2CO_3 as a base to yield derivative **3** in 58% yield (Scheme 1). The cyano groups were then reduced to aldehydes using DIBAL in chlorobenzene in 81% yield. Unfortunately, *p*-cyanobenzyl bromide is accessible only in low yield by the radical bromination of *p*-methylbenzonitrile and proved to be a very strong lachrymator. Hence, another synthetic pathway was finally employed using methyl 4-bromomethylbenzoate which is much easier to handle. The dialkylation of **1** with methyl 4-bromomethylbenzoate gave derivative **5** in 69% yield. All our attempts at the direct transformation of ester **5** to the formyl derivative **4** have failed and gave only inseparable mixtures of starting compound and several products. On the other hand, an indirect route via reduction of ester **5** to benzyl alcohol **6** and subsequent oxidation[8] to aldehyde **4** was accomplished in an overall yield of 55%.

The McMurry reaction was carried out[9] by stirring **4** with a mixture of Zn and $TiCl_3$·1.5DME complex. Slightly better results (42% versus 35% yield) were obtained using the Zn/$TiCl_4$·2THF complex (commercially available from Aldrich) in refluxing THF. This so called 'instant procedure'[4] led exclusively to the product of intramolecular coupling reaction **7**, bridged by a

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cis-double bond in the cone conformation. Neither the formation of possible intermolecular products nor the corresponding *trans* isomer were observed.

The structures of the novel compounds were confirmed by ^{1}H NMR spectroscopy. All compounds **3**–**7** possess typical features of distally disubstituted calix[4]arenes being immobilised in the *cone* conformation. Thus, the ^{1}H NMR ($CDCl_3$) spectrum of compound **7** exhibited two doublets at 4.39 and 3.39 ppm with geminal coupling ($J=13$ Hz) corresponding to axial and equatorial protons of Ar-CH_2-Ar groups, respectively. The formation of a double bond in **7** was supported by the disappearance of IR stretching for carbonyl groups originally present in the starting compound **6** (1701 cm^{-1}).

The structure of **7** was unequivocally proved by X-ray crystallography.[10] Suitable single crystals were grown by slow evaporation of an ethyl acetate solution. The molecule of calixarene **7** adopts a slightly *pinched cone* conformation (aromatic part of the molecule exhibits almost C_{4v} symmetry, see Figure 1) the cavity of which is held by intramolecular hydrogen bonds between two phenolic OH functions and the neighbouring OCH_2 groups. Obviously, the whole arrangement is reinforced by the presence of the corresponding alkene bridge on the lower rim. Interestingly, the cavity is filled by the methyl group of ethyl acetate, held by the CH-π interactions[11] of hydrogen atoms with the aromatic walls of the calixarene (Figs. 1 and 2). The methyl group is situated almost exactly in the middle of the cavity as indicated by the corresponding distances from the centres of the aromatic rings (from 3.59 to 3.91 Å). It is known that suppression of the conformational flexibility of the *cone* conformation is an important prerequisite for efficient formation of CH-π interactions in calix[4]arenes. It was demonstrated that bridging of lower rim with two short diethylene glycol units[12] or fixation of C_{4v} symmetry via metal coordination[13] leads to calix[4]arenes capable of forming inclusion complexes with neutral guest molecules[14,15] possessing acidic CH_2 or CH_3 groups. During our study of the solid-state behaviour of **7** we found that almost identical types of complexes could be obtained with several other solvents, such as acetonitrile or acetone. In all cases, the methyl group (possessing relatively acidic

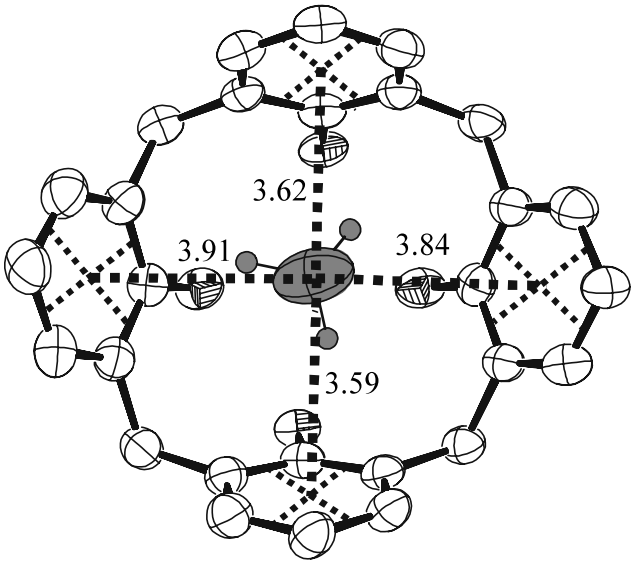
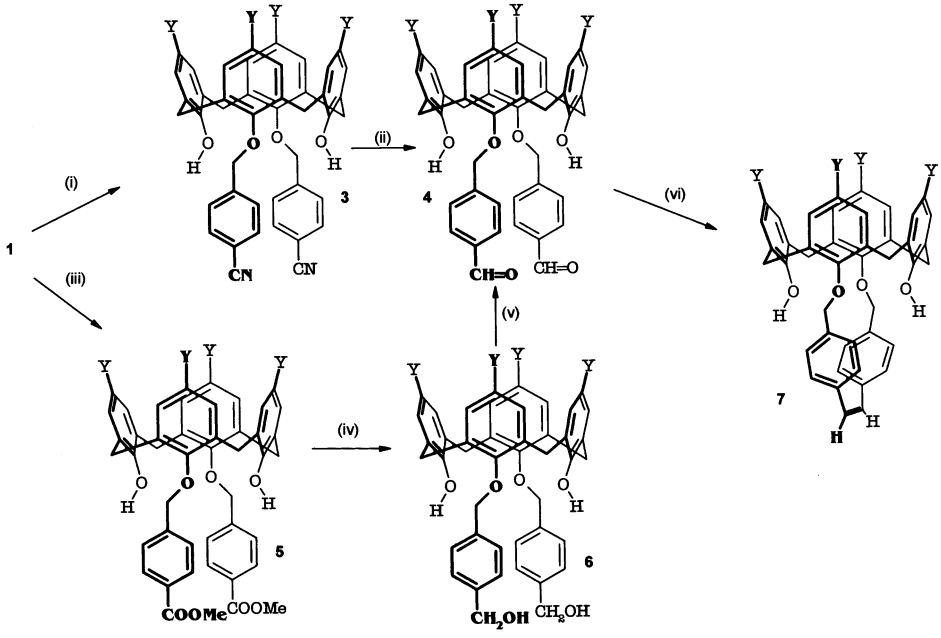


Figure 1. ORTEP drawing of complex **7** with ethyl acetate (for clarity only aromatic part of the calixarene and the CH_3 group of acetate are depicted). All distances are in Å.



Scheme 1. Synthesis of derivative **7** (Y = Bu^t). *Reagents and conditions*: (i) *p*-NC-$C_6H_4CH_2Br/K_2CO_3$/acetone, reflux 1 week (58%); (ii) DIBAL, chlorobenzene, 0°C (81%); (iii) *p*-MeOOC-$C_6H_4CH_2Br/K_2CO_3$/acetone, 5 days reflux (69%); (iv) $LiAlH_4$, rt (94%); (v) PCC/CH_2Cl_2, 4 h, rt (59%); (vi) $TiCl_4$·2THF/Zn/THF, reflux (42%).

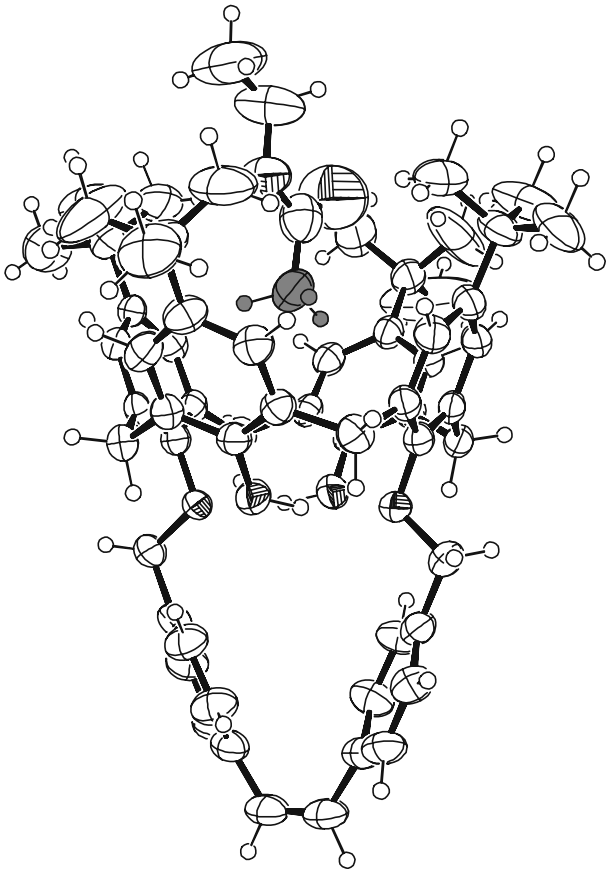


Figure 2. ORTEP drawing of complex **7** with ethyl acetate (for clarity the CH_3 group is shaded).

hydrogen atoms) is immersed deep in the cavity via strong CH-π interactions. This indicates that intramolecular bridging leads to a relatively rigid cavity, which is suitably preorganised for the CH-π interactions.

To gain deeper insight into the complexation phenomenon, the complexation ability of compound **7** was also measured in solution ($CDCl_3$) by standard ^1H NMR titrations with suitable neutral guest molecules. As shown in Figure 3, the addition of 1 equiv. of **7** to a solution of acetonitrile in $CDCl_3$ leads to a dramatic upfield shift (ca. 1 ppm). This strongly suggests that the methyl group is shielded by magnetic anisotropy due to the aromatic units being in a close proximity. This is fully consistent with the assumption that the structure of the complex in the solution is the same as that found by X-ray crystallography in the solid state. Titration curves were obtained using a constant calixarene concentration (1–3 mM) and increasing concentrations of the appropriate guest to obtain different host/guest ratios (0.1–20).[16] All titration curves were constructed from the CIS of the aromatic signals (Δ ppm $\approx$ 50 Hz) and they reflect the 1:1 stoichiometry of binding. The corresponding complexation constants are collected in Table 1. It is evident that the preorganisation of the molecule (alkene bridge together with hydrogen bonds) enables efficient CH-π interactions in solution with

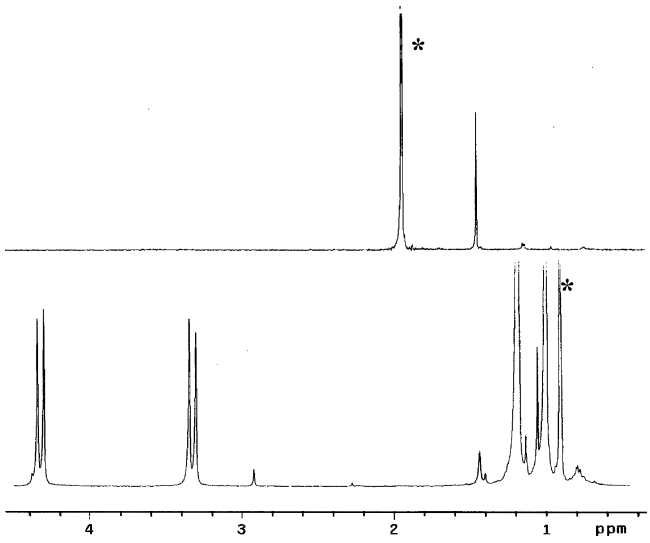


Figure 3. Partial ^1H NMR spectrum ($CDCl_3$, 300 MHz, 298 K): (a) free CH_3CN; (b) the same sample after addition of 1 equiv. of **7**.

Table 1. Complexation constants of compound **7** with selected neutral guests ($CDCl_3$, 298 K, 300 MHz)

Guest	K [M^{-1}]
CH_3CN	19±2
CH_3COCH_3	4±2
CH_3COOEt	0[a]
$NCCH_2CN$	113±12
$ClCH_2CN$	19±3

[a] No shifts upon addition of the guest molecule.

highest affinity ($K = 113$ M^{-1}) towards malondinitrile, which is obviously the most acidic. On the other hand, addition of ethyl acetate did not produce any measurable changes in the receptor molecule (<5 Hz).

In conclusion, we have demonstrated that the intramolecular bridging of calix[4]arenes via the McMurry reaction leads to derivatives with a rigidified *cone* conformation. The suppression of conformational motion results in an enhanced ability to include neutral guests inside a cavity suitably preorganised for the binding via CH-π interactions. The design and synthesis of other receptors of this type are currently under investigation.

Acknowledgements

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References

1. For books on calixarenes, see: (a) Asfari, Z.; Böhmer, V.; Harrowfield, J.; Vicens, J., Eds.; *Calixarenes 2001*;

Kluwer Academic Publishers: Dordrecht, 2001; (b) Mandolini, L.; Ungaro, R. *Calixarenes in Action*; Imperial College Press: London, 2000; (c) Gutsche, C. D. *Calixarenes Revisited*: Monographs in Supramolecular Chemistry; Stoddart, J. F. Ed.; The Royal Society of Chemistry: Cambridge, 1998; Vol. 6.

2. Lhoták, P.; Shinkai, S. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 963–974.
3. For review on calixarenes, see for instance: (a) Shinkai, S. *Tetrahedron* **1993**, *49*, 8933–8968; (b) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713–745; (c) Pochini, A.; Ungaro, R. In *Comprehensive Supramolecular Chemistry*; Vögtle, F., Ed.; Elsevier Science Ltd.: Oxford, 1996; Vol. 2, p. 103; (d) Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713–1734.
4. (a) Fürstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. *J. Org. Chem.* **1994**, *59*, 5215–5229; (b) Fürstner, A.; Hupperts, A. *J. Am. Chem. Soc.* **1995**, *117*, 4468–4475; (c) Ephritikhine, M. *Chem. Commun.* **1998**, 2549–2554; (d) Fürstner, A.; Bogdanovic, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2442–2468.
5. Arduini, A.; Fanni, S.; Pochini, A.; Sicuri, A. R.; Ungaro, R. *Tetrahedron* **1995**, *51*, 7951–7958.
6. Lhoták, P.; Shinkai, S. *Tetrahedron Lett.* **1996**, *37*, 645–648.
7. Sukwattanasinitt, M.; Rojanathanes, R.; Tuntulani, T.; Sritana-Anant, Y.; Ruangpornvisuti, V. *Tetrahedron Lett.* **2001**, *42*, 5291–5293.
8. Preparation of compound **4** (from **6**): A mixture of **6** (0.3 g, 0.34 mmol), pyridinium chlorochromate (0.44 g, 2.04 mmol) and 30 ml of dried dichloromethane was stirred for 4 h at rt under nitrogen. The mixture was then poured into water (50 ml) and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated to dryness. The crude product was purified by column chromatography on silica gel using a mixture of ethyl acetate/petroleum ether = 1:10 as eluent to yield 0.17 g (59%) of **4** as a white solid. Mp: 226–228°C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 10.05 (s, 2H, -CH=O), 7.86 (m, 8H, H-arom), 7.14 (s, 2H, -OH), 7.06 (s, 4H, Ar-H), 6.80 (s, 4H, Ar-H), 5.13 (s, 4H, -O-CH_2-Ar), 4.26 (d, 4H, J = 12.4 Hz, Ar-CH_2-Ar ax.), 3.32 (d, 4H, J = 12.4 Hz, Ar-CH_2-Ar eq.), 1.29 (s, 18H, But), 0.94 (s, 18H, But). IR ($CHCl_3$) ν_{max}: 1701 cm^{-1} (C=O), 3432 cm^{-1} (OH). EA calcd for $C_{60}H_{68}O_6$: C, 81.41; H, 7.74. Found: C, 81.18; H, 7.90%.
9. Preparation of compound **7**: A mixture of **4** (0.525 g, 0.23 mmol), zinc dust (0.230 g, 1.84 mmol) and titanium(IV) chloride·2THF complex (Aldrich, 0.596 g, 1.37 mmol) was stirred at reflux in 50 ml of dry THF under argon. The reaction mixture was refluxed for 20 h, then cooled to rt and the solvent was removed under a reduced pressure. The resulting solid was dissolved in $CHCl_3$ and filtered through the short column of silica gel to remove all inorganic materials. The crude product was purified using preparative TLC (20×20 cm) on silica gel (chloroform:petroleum ether = 1:3) to yield 0.075 g (42%) of **7**. Mp: >360°C ($CHCl_3$–MeOH, white crystals), ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 10.34 (s, 2H, -OH), 7.60 (d, 4H, J = 7.8 Hz, H-arom), 7.06 (brs, 8H, Ar-H), 6.99 (s, 2H, -CH=CH-), 6.91 (d, 4H, J = 6.4 Hz, H-arom), 4.85 (s, 4H, -O-CH_2-Ar), 4.39 (d, 4H, J = 12.6 Hz, Ar-CH_2-Ar ax.), 3.39 (d, 4H, J = 12.6 Hz, Ar-CH_2-Ar eq.), 1.28 (s, 18H, But), 1.04 (s, 18H, But). ^{1}H NMR ($CDCl_3$:CD_3OD = 4:1 v/v, 300 MHz) δ (ppm): 7.42 (d, 4H, J = 8.2 Hz, H-arom), 6.88 (s, 4H, H-arom), 6.86 (s, 4H, H-arom), 6.82 (s, 2H, -CH=CH-), 6.74 (d, 4H, J = 8.2 Hz, H-arom), 4.63 (s, 4H, -O-CH_2-Ar-), 4.23 (d, 4H, J = 13.2 Hz, Ar-CH_2-Ar ax.), 3.23 (d, 4H, J = 13.2 Hz, Ar-CH_2-Ar eq.), 1.04 (s, 18H, But), 0.92 (s, 18H, But). IR (KBr) ν_{max}: 3377 cm^{-1} (OH), 1629 cm^{-1} (C=C). MS-FAB: m/z (rel. %): 853.0 [M+] (100). EA calcd for $C_{60}H_{68}O_4$: C, 84.47; H, 8.03. Found: C, 84.20; H, 8.10%.
10. X-Ray data for $C_{60}H_{68}O_4 \cdot C_4H_8O_2$, M = 941.3 g/mol, monoclinic system, space group $P2_1/n$, a = 12.679(1), b = 27.979(1), c = 15.990(1) Å, β = 100.56(1), Z = 4, V = 5576.7(5) Å^3, D_{calcd} = 1.12 g cm^{-3}, μ(Cu Kα) = 5.5 mm^{-1}, crystal dimensions of 0.2×0.2×0.3 mm. Data were measured at 293 K on an Enraf–Nonius CAD4 diffractometer with graphite monochromated Cu-Kα radiation. The structure was solved by direct methods.[17] The whole structure was refined anisotropically by full matrix least-squares on F values[18] to final R = 0.087 and R_w = 0.091 using 5332 independent reflections (θ_{max} = 68°). Hydrogen atoms were located from a Fourier map and expected geometry and were not refined. Psi scan was used for the absorption correction. The crystallographic data were deposited in CSD under CCDC registration number 205696.
11. See for instance: (a) Ribas, J.; Cubero, E.; Luque, F. J.; Orozco, M. *J. Org. Chem.* **2002**, *67*, 7057–7065; (b) Iwamoto, H.; Hirakata, M.; Usui, S.; Haino, T.; Fukazawa, Y. *Tetrahedron Lett.* **2002**, *43*, 85–87; (c) Suezawa, H.; Yoshida, T.; Umezawa, Y.; Tsuboyama, S.; Nishio, M. *Eur. J. Inorg. Chem.* **2002**, 3148–3155; (d) Kunsagi-Mate, S.; Bitter, I.; Grün, A.; Nagy, G.; Kollar, L. *Anal. Chim. Acta* **2001**, *443*, 227–234; (e) Takahashi, H.; Tsuboyama, S.; Umezawa, Y.; Honda, K.; Nishio, M. *Tetrahedron* **2000**, *56*, 6185–6191; (f) Umezawa, Y.; Tsuboyama, S.; Takahashi, H.; Uzawa, J.; Nishio, M. *Tetrahedron* **1999**, *55*, 10047–10056.
12. (a) Arduini, A.; McGregor, W. M.; Paganuzzi, D.; Pochini, A.; Secchi, A.; Ugozzoli, F.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1996**, 839–846; (b) Smirnov, S.; Sidorov, V.; Pinkhassik, E.; Havlicek, J.; Stibor, I. *Supramol. Chem.* **1997**, *8*, 187–196.
13. Arduini, A.; Giorgi, G.; Pochini, A.; Secchi, A.; Ugozzoli, F. *Tetrahedron* **2001**, *57*, 2411–2417.
14. For review on the recognition of neutral guests by calixarenes, see: Arduini, A.; Pochini, A.; Secchi, A.; Ugozzoli, F. In *Calixarenes 2001*; Ref. 1a, pp. 457–475.
15. Arena, G.; Contino, A.; Magri, A.; Sciotto, D.; Arduini, A.; Pochini, A.; Secchi, A. *Supramol. Chem.* **2001**, *13*, 379–386.
16. The complexation constants were calculated using the computer program OPIUM (Kyvala, M.). This software is freely available at http://www.natur.cuni.cz/~kyvala/opium.html.
17. Altomare, A.; Cascarano, G.; Giacovazzo, G.; Guagliardi, A.; Burla, M. C.; Polidori, G.; Camalli, M. SIR92—a program for automatic solution of crystal structures by direct methods *J. Appl. Cryst.* **1994**, *27*, 435.
18. Watkin, D. J.; Prout, C. K.; Carruthers, J. R.; Betteridge, P. W.; Cooper, R. I. CRYSTALS, Issue 11. Chemical Crystallography Laboratory: Oxford, UK, 2001.