

Highly Cooperative Binding of Ion-Pair Dimers and Ion Quartets by a Bis(calix[4]pyrrole) Macrotricyclic Receptor**

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The tendency of ions of opposite sign to associate led to the consideration that single receptors capable of complexation with both a cation and an anion, so-called heteroditopic receptors, should offer significant advantages, in terms of affinity and specificity, compared to monotopic versions.^[1,2] Heteroditopic receptors possess two or more covalently connected binding sites for both the anion and cation. Cooperative effects are claimed to play an important role in the binding of ion pairs by heteroditopic receptors.^[3] Ion-paired complexes derived from heteroditopic receptors exhibit three limiting binding geometries: close-contact, solvent-separated, and host-separated.^[1] The relative arrangement of the bound ions depends on the spatial location of the binding sites, the choice of the ion-pair components, and the fashion in which the binding takes place (sequential/concurrent).^[4–6]

The formation of cascade complexes^[2,7,8] can be considered as an alternative strategy for ion-pair binding providing a bound ion triplet in close-contact mode.^[9,10] Surprisingly, examples of the cooperative complexation of dimers of ion pairs and quartets of ions have not yet been described in the literature, despite the known existence of these species in solution.^[11–14]

Calix[4]pyrroles and their derivatives are known to function as heteroditopic receptors for ion pairs.^[1,5,15,16] On that basis, we envisaged that receptor **1** having two calix[4]-pyrrole binding sites incorporated into a three-dimensional and rigid molecular scaffold could be an ideal candidate for the effective binding of ion-pair dimers through the formation of cascade complexes (Figure 1). Herein, we report the formation in solution of highly thermodynamically and

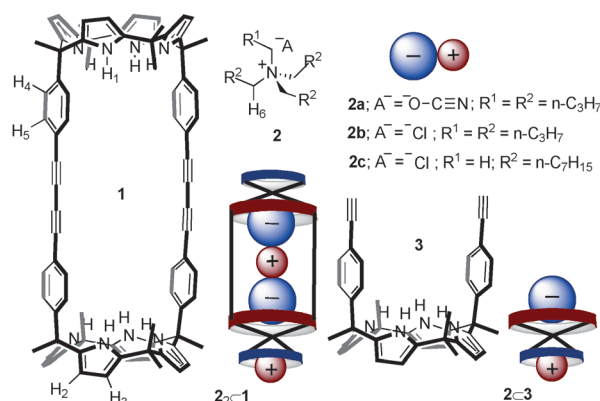


Figure 1. Molecular structures of receptors **1** and **3** and ion-pairs **2** used in this study. Representations (blue/red) of ion-pairs **2**, a cascade complex of receptor **1** with two ion pairs displaying close contacts and host-separated binding modes (**2**₂<**1**), and a complex of receptor **3** with an ion pair in host-separated mode (**2**₂<**3**).

kinetically stable complexes of ion-pair dimers and quartets of ions with receptor **1**. The resulting complexes constitute unprecedented examples of five particle aggregates. The structures of the aggregates proposed in solution are fully supported by X-ray diffraction results of single crystals. Interestingly, both the cooperativity of the assembly process and the binding geometry of the final aggregates can be controlled by the nature of the cations present in the ion-pair components.

The synthesis of the cylindrical homoditopic receptor **1** has been reported previously.^[17] The two 1,3-diynyl linkers in **1** provide conformational rigidity and prevent the collapse of its macrotricyclic structure. These spacers also position the two distal heteroditopic binding sites (calix[4]pyrrole units) at an ideal distance and in an optimal relative orientation to achieve the cooperative binding of two identical or distinct ion pairs.

The initial addition of 1 equiv of **2a** (TBAOCN) to a CDCl₃ solution of **1** (1 mM) resulted in the appearance of a new set of proton signals, which were assigned to bound **1** (Figure 2b). The signal for the bound NH protons (1') is found at $\delta = 11.4$ ppm, indicating their involvement in hydrogen-bonding interactions with the cyanate. The methylene protons alpha to the nitrogen of the TBA cation (6') appear as a broad hump at $\delta = 2.5$ ppm, which is significantly upfield with respect to free TBA (6). The ratio of integral values for the protons signals assigned to free and bound receptor is 1:1. These results indicated that 50 % of the receptor is bound to both components of the ion pair and that the chemical exchange between the free and bound **1** is slow on the ¹H NMR chemical shift timescale. However, they do not

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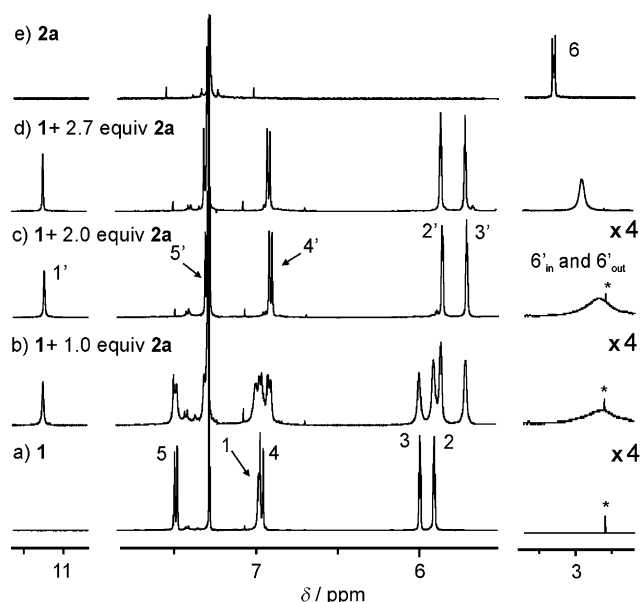


Figure 2. Selected regions of the ^1H NMR spectra (CDCl_3 , 298 K) acquired during the titration of **1** with incremental amounts of **2a**: b) 1.0; c) 2.0; and d) 2.7 equiv of **2a** added. The ^1H NMR spectra of **1** and **2a** are shown in a) and e), respectively. See Figures 1 and 3 for proton assignments. Primed numbers indicate the signals for the $2\text{a}_2\text{c}1$ complex. * = impurity.

allow for an unequivocal assignment of the number of species involved in the bound state of **1**.

The addition of more than 1.0 equiv of **2a** did not induce further changes in the chemical shifts of the signals assigned to bound **1** (primed numbers) but only increased their intensities relative to the signals of free **1**. When 2 equiv of **2a** were added, only the signals assigned to bound **1** were detected. Adding an excess of **2a** (2.7 equiv) only produced sharpening and a moderate downfield shift to the broad signal assigned to the methylene protons ($6'$) α to the nitrogen of the TBA cation.

Taken together, these observations suggest that the new set of signals must correspond to the protons of bound receptor **1** in the $2\text{a}_2\text{c}1$ complex and that the stability constant of the complex can be estimated as $K_{2:1}(2\text{a}_2\text{c}1) > 10^8 \text{ M}^{-2}$. Furthermore, the free and bound TBA cations are involved in a fast chemical exchange on the ^1H NMR chemical shift timescale. A variable-temperature ^1H NMR experiment (Supporting Information, Figure S11) performed on the sample containing 2 equiv of **2a** revealed that at 278 K the broad signal assigned to bound TBA protons ($6'$) splits into two signals of equal intensity. The chemical shift values of these two signals are shifted upfield with respect the same protons in free TBA. Molecular modeling studies (Supporting Information, Figure S8c) advocated for a cascade complex, as depicted in Figure 3, for the probable structure of the $2\text{a}_2\text{c}1$ complex in a solvent of low permittivity, such as chloroform. The modeled structure serves to explain the existence of two chemically non-equivalent TBA cations and the splitting of the N- α methylene signals. At 238 K, the two TBA cations (referred as “in” and “out”) are in chemical exchange, as revealed by the detection of a cross-peak between them in

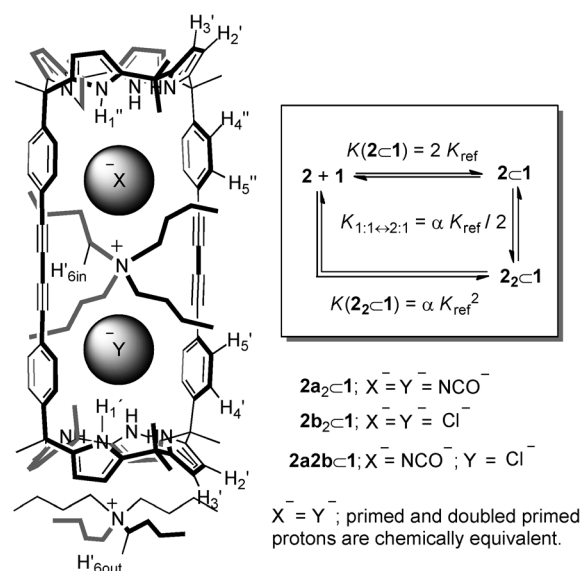


Figure 3. Molecular structure of the homo- and heterodimeric ion-pair complexes derived from the TBA salts. Inset: equilibria involved in the complexation of ion pairs **2a** and **2b** with **1**. The overall binding constant $K(2_2\text{c}1)$ and the stepwise binding constants $K(2\text{c}1)$ and $K(1:1 \leftrightarrow 2:1)$ are shown as well as their relationship with K_{ref} (reference constant), α (cooperativity factor), and statistical corrections.

a ROESY experiment (Supporting Information, Figure S12). At this low temperature, the ROESY experiment allowed the assignment of the more upfield-shifted methylene signal to the TBA_{out} cation, which is included in the electron-rich cup provided by the outer calix[4]pyrrole core in cone conformation. X-ray diffraction of a single crystal grown from a CDCl_3 solution containing **2a** and **1** in a 2:1 molar ratio revealed the formation of the corresponding five-component cascade structure $2\text{a}_2\text{c}1$ in the solid state (Figure 4a).^[24] The high thermodynamic stability estimated for the $2\text{a}_2\text{c}1$ complex ($K_{\text{a}} > 10^8 \text{ L}^2 \text{ mol}^{-2}$) is in striking contrast with the low binding affinity measured for **2a** and the “two wall” calix[4]pyrrole **3** ($K_{1:1}(2\text{a}3) = K_{\text{ref}} = 33 \pm 7 \text{ L mol}^{-1}$) (Supporting Information, Figure S4).^[18,19] Consequently the formation of the $2\text{a}_2\text{c}1$ complex must involve an impressive cooperative effect possibly dictated by the cascade arrangement of the two ion pairs: one bound as an intimate contact ion pair and the other as a host-separated ion pair. The existence of a highly cooperative binding process also explains why the intermediate complex $2\text{a}c1$ (1:1) was not detected during ^1H NMR titration. The binding of ion pairs by **1** is likely to occur in a stepwise fashion.^[20]

To assess the cooperative factor of the binding process, we probed the interaction of **1** with **2a** using isothermal titration calorimetry (ITC) experiments. The stepwise injection of a CHCl_3 solution of macrotricyclic **1** (6 mM) to a solution of **2a** (0.6 mM) in the same solvent resulted in a gradual release of heat owing to the binding process (exothermic process). The normalized integrated data produced a single sigmoidal binding isotherm (Supporting Information, Figure S28). On one hand, the observation of a single inflection point in the binding isotherm at a molar ratio $1/2\text{a} = 0.5$ gave evidence for the formation of the $2\text{a}_2\text{c}1$ complex. On the other hand, the

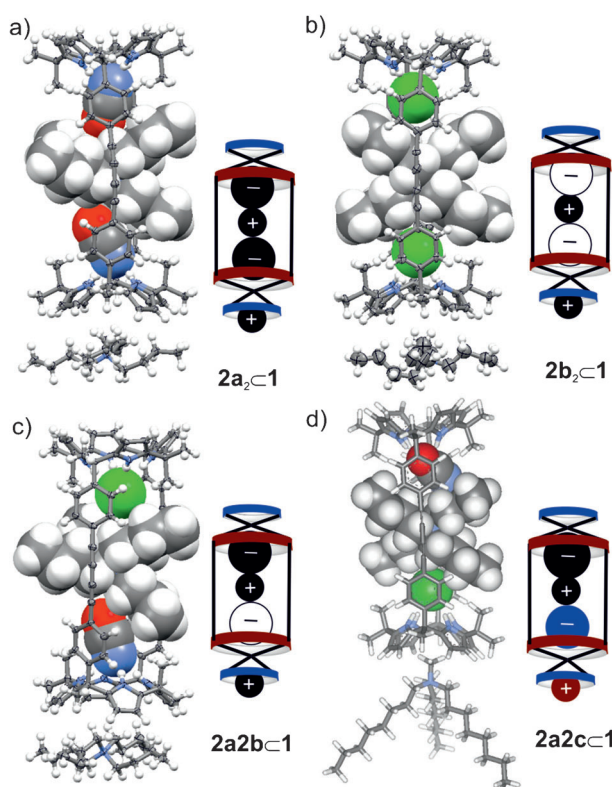


Figure 4. X-ray structures of cascade complexes: a) $2a_2c_1$, b) $2b_2c_1$, c) $2a_2b_1$, and d) energy-minimized structure of $2a_2c_1$ with model representations. Receptor **1** and the “out” cations are shown in ball-and-stick representations. The anions and the “in” TBA cation included in the cavity of **1** are displayed as CPK representations.

lack of a second inflection point at a molar ratio $1/2a=1$, which corresponds to the formation of the $2a_2c_1$ complex, is indicative of either the existence of two almost identical binding events for the two ion-pairs by **1** or, as it is most likely in the present case, that the $2a_2c_1$ complex is formed to a negligible extent during the ITC experiment. For simplicity, the ITC data were fitted to the theoretical isotherm derived from the one set of sites binding model implemented in the Microcal ITC data analysis software.^[21] By using this simple model, the fitting procedure returns averaged enthalpy change ($\Delta H_{\text{average}}$) and microscopic binding constant (K_{average}) values for the two binding events affording the $2a_2c_1$ complex. The values for the overall stability constant and enthalpy change for the $2a_2c_1$ complex are obtained by simply squaring the value of K_{average} and doubling that of $\Delta H_{\text{average}}$. Using this procedure, we determined $K_{2:1}(2a_2c_1) = 1.5 \pm 0.3 \times 10^{11} \text{ L}^2 \text{ mol}^{-2}$ and $\Delta H(2a_2c_1) = -14.6 \pm 0.2 \text{ kcal mol}^{-1}$. When $K(2a_2c_3) = K_{\text{ref}} = 33 \text{ L mol}^{-1}$ is used as reference^[22] for the binding affinity of one of the sites in **1**, the value of the calculated cooperativity factor is $\alpha = K(2a_2c_1)/K_{\text{ref}}^2 = 1.3 \times 10^8$. To the best of our knowledge, this is one of the highest cooperative binding processes reported to date using a synthetic receptor. Analogous results to those described above were obtained during the ^1H NMR studies of the complexation of TBACl, **2b**, by receptor **1** (Figure 4b;^[24] Supporting Information, Figure S14).

ITC titrations revealed that the thermodynamic stability of the cascade complex with the chloride anion, $2b_2c_1$, is reduced by two orders of magnitude with respect to the cyanate analogue $K_{2:1}(2b_2c_1) = 1.9 \times 10^9 \text{ L}^2 \text{ mol}^{-2}$. This result is in agreement with the decrease in binding affinity measured for the calix **3** and **2b** ($K_{1:1}(2b_2c_3) = K_{\text{ref}} = 10 \pm 2 \text{ L mol}^{-1}$) (Supporting Information, Figure S7). Nevertheless, the cooperativity factor value calculated for $2b_2c_1$ is of a similar magnitude than for $2a_2c_1$. Interestingly, the ^1H NMR spectrum of a CDCl_3 solution containing an equimolar mixture of **2a**, **2b**, and **1** showed a set of proton signals that did not coincide either with those assigned to $2a_2c_1$ or $2b_2c_1$ (Figure 5a). Two different and highly downfield shifted

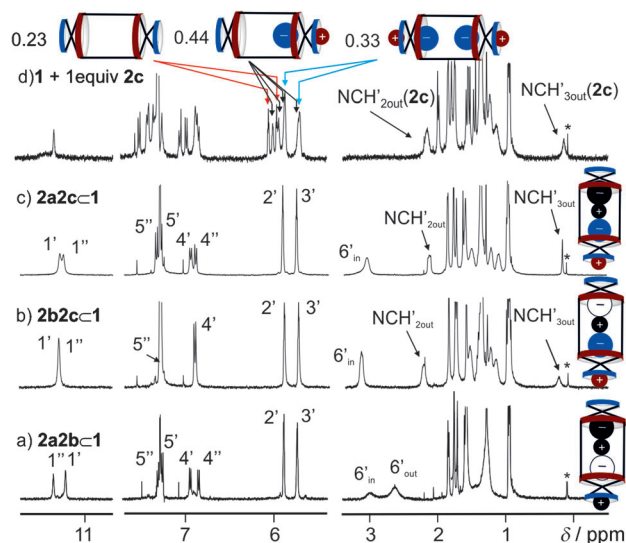


Figure 5. Selected regions of the ^1H NMR spectra (298 K, 500 MHz) of CDCl_3 solutions of **1** (1 mM) containing: a) 1 equiv of **2a** and 1 equiv of **2b**; b) 1 equiv of **2b** and 1 equiv of **2c**; c) 1 equiv of **2a** and 1 equiv of **2c**; and d) 1 equiv of **2c**. See Figure 4 for molecular structures and Figure 3 for proton assignments. The position of the anions in the heterodimeric complexes is interchangeable. The MTOA cation of **2c** is selectively located in the “out” position.

signals for the NH protons ($1'$ and $1''$) of **1** indicated their participation in different hydrogen bonding interactions. Four different set of proton signals for the aromatic protons ($4', 5', 4''$, and $5''$) supported the existence of different interaction in each of the two binding sites of **1**. Clearly, these observations point to the exclusive and quantitative formation of the unsymmetrical assembly $2a_2b_1c_1$. Even at 298 K the methylene protons α to the nitrogen of the TBA cation resonate as separate downfield signals, in complete agreement with the presence of two chemically non-equivalent bound TBA cations in the $2a_2b_1c_1$ complex. Gratifyingly, formation of the ion-pair hetero dimer complex $2a_2b_1c_1$ was also confirmed in the solid state (Figure 4c).^[23,24]

The use of ion pair **2c** containing a methyl triethylammonium cation (MTOA) produced significantly different results. First, in complete agreement with previous reports for the simple octamethylcalix[4]pyrrole,^[15] calix[4]pyrrole **3** shows a remarkable increase in binding affinity for **2c** compared to

2a or **2b** $K_{\text{ref}}(\mathbf{2c} \subset \mathbf{3}) = K_{\text{ref}} = 8.3 \pm 2 \times 10^3 \text{ L mol}^{-1}$ (determined by ITC experiment, $\Delta H_{\text{ref}}(\mathbf{2c} \subset \mathbf{3}) = -5.5 \pm 0.1 \text{ kcal mol}^{-1}$) (Supporting Information, Figure S30). Because the methyl group of the MTOA cation is a better fit than the TBA cation for the shallow cup opposite to the bound anion, this is the expected result for a calix[4]pyrrole unit acting as ion-pair receptor and affording a receptor-separated binding geometry in the ion-paired complex. Second, and more importantly, the complexation process of **2c** by **1** displayed diminished signs of cooperativity, if any (see below). The ^1H NMR spectrum of a CDCl_3 solution containing equimolar amounts of **2c** and **1** shows three different sets of signals for the protons of **1** (Figure 5d). One of the sets corresponds to free **1** while the other two sets, based on the number of proton signals contained and their chemical shifts, are assigned to the protons of **1** in the $\mathbf{2c} \subset \mathbf{1}$ and $\mathbf{2c}_2 \subset \mathbf{1}$ complexes. By integration of selected proton signals in the three different sets, it was possible to determine the ratio of species $\mathbf{1}/\mathbf{2c} \subset \mathbf{1}/\mathbf{2c}_2 \subset \mathbf{1}$ as approximately 0.23:0.44:0.33. This ratio is close to that expected from an equimolar mixture of substrates at 1 mM concentration yielding a 2:1 complex through a noncooperative binding process ($K_{\text{ref}} \approx 10^4 \text{ L mol}^{-1}$). When 2 equiv of **2c** are added a single set of proton signals corresponding to the $\mathbf{2c}_2 \subset \mathbf{1}$ complex were detected. Furthermore, the ITC data for **2c** with **1** returned $K_{\text{average}} = 4.9 \pm 1.0 \times 10^4 \text{ L mol}^{-1}$ and $\Delta H_{\text{average}} = -8.4 \pm 0.2 \text{ kcal mol}^{-1}$ when fitted to the one set of sites model (Supporting Information, Figure S31). The magnitudes of these constants are in very good agreement with the values obtained for **3**. The α value calculated for **1** binding **2c** is only 35 (using the same procedure employed for **2a** and **2b**), which represents a drop in the cooperativity factor of almost six orders of magnitude. Taken together, these results indicate that **1** binds **2c** through a process that is not significantly cooperative and yields a homo-dimeric complex $\mathbf{2c}_2 \subset \mathbf{1}$ having both ion pairs bound in a receptor-separated binding geometry, instead of the cascade arrangement assigned to the homo- and heterodimeric complexes of **2a** and **2b** with **1**.

The separate addition of 1 equiv of **2a** or **2b** to equimolar CDCl_3 solutions of **2c** and **1** induced the quantitative formation of the corresponding heterodimeric $\mathbf{2a2c} \subset \mathbf{1}$, $\mathbf{2b2c} \subset \mathbf{1}$ complexes, respectively (Figure 5b,c). In both heterodimeric complexes, as well as in the homodimer $\mathbf{2c}_2 \subset \mathbf{1}$, the methyl protons for the bound MTOA cation are shifted significantly upfield to $\delta = 0.2 \text{ ppm}$. This observation, together with the existence of exclusive intermolecular contacts between its methylene protons and the β -pyrrole protons of **1**, provides strong support for the selective placement of the MTOA cation in the “out” position of the complexes. The binding processes yielding the complexes $\mathbf{2a2c} \subset \mathbf{1}$ and $\mathbf{2b2c} \subset \mathbf{1}$ are also estimated to be highly cooperative ($\alpha > 10^3$).

In conclusion, we have demonstrated that the bis-(calix[4]pyrrole) macrotricyclic receptor **1** binds two chloride or cyanate TBA ion pairs yielding $(\mathbf{2a/b})_2 \subset \mathbf{1}$ complexes through a highly cooperative process ($\alpha > 10^5$). The complexes have a structure with a cascade-like arrangement of the ion pairs. One ion pair is bound in a close-contact geometry, while the other in a receptor-separated arrangement. The use

of the ion pair **2c** containing a MTOA cation instead of TBA renders the binding process significantly less cooperative. In the homodimeric complex $\mathbf{2c}_2 \subset \mathbf{1}$ both bound ion pairs feature a receptor-separated binding mode. The equimolar combination of TBA and MTOA salts allows the self-assembly of hetero ion-pair dimer (ion quartet) complexes $\mathbf{2a2c} \subset \mathbf{1}$ and $\mathbf{2b2c} \subset \mathbf{1}$ with cascade arrangement of ion pairs and by means of cooperative binding processes. Importantly, in these latter complexes the MTOA cation seems to be selectively located in the “out” position.

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- [18] As indicated in the inset of Figure 3, the value for the stability constant of $\mathbf{2c} \subset \mathbf{1}$ complexes can be statistically estimated as αK_{ref}^2 . Using this relationship, stability constants with different dimensions can be compared and the high magnitude of the cooperativity factor be inferred.
- [19] A binding constant value of $4.3 \times 10^2 \text{ L mol}^{-1}$ was reported for the 1:1 complex of TBACl with octamethylcalix[4]pyrrole in CD_2Cl_2 solution: see Ref. [15].

- [20] The direct complexation of a negatively charged ion triplet followed by TBA binding constitutes a plausible alternative mechanism, which does not involve cooperativity. However, the amount of ion triplet in solution should be very low at millimolar concentrations.
- [21] The use of binding models considering two set of sites or sequential binding sites afforded multiple mathematical solutions providing sensible fits due to the optimization of at least four fitting variables ($K_{1:1}$, $K_{2:1}$, $\Delta H_{1:1}$, $\Delta H_{2:1}$).
- [22] The conformational flexibility of **3** compared to **1** could cause an overestimation in the reported cooperativity factors.
- [23] Based on competitive experiments (Supporting Information, Figures S19 and S20), the thermodynamic stability of the herodimer **2a2b**·**1** lies between that of the two homodimers **2a**₂·**1** and **2b**₂·**1**.
- [24] CCDC 930892 (**2a**₂·**1**), 930893 (**2ab**·**1**), and 930894 (**2b**₂·**1**) 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.
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