Molecular Recognition of *p*-Benzoquinone by a Macrocyclic Host

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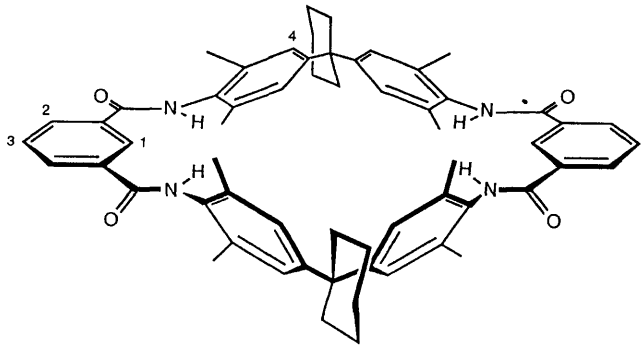
The design, synthesis and molecular recognition properties of a new macrocyclic host which specifically complexes *p*-benzoquinone using four H-bonds and four edge-to-face π–π interactions are reported.

The structure and function of the photosynthetic reaction centres of purple bacteria have been the focus of a major research effort in recent years.[1] Chemical models of the 'special pair' bacteriochlorophyll dimer[2] and the photo-induced electron transfer reactions which constitute the primary charge separation events[3] have made significant contributions to our understanding of these highly complex systems. However, little attention has been paid to the quinone binding domains.[4,5] In this communication, I report the design, synthesis and complexation properties of a new macrocyclic host which specifically binds *p*-benzoquinone. This system mimics some features of the quinone binding domains of the bacterial photosynthetic reaction centres[4] and may lead to insight into the structural relationships which give rise to their novel properties.[4,5]

The X-ray crystal structures of *Rhodopseudomonas viridis* and *Rhodopseudomonas sphaeroides* indicate that recognition of quinones can be achieved *via* a combination of π–π interactions, hydrophobic contacts and H-bonding to the quinone oxygens.[4] The symmetry and size of *p*-benzoquinone make it a more attractive target for molecular recognition than the menaquinone and ubiquinone cofactors found in nature. However, the results obtained for this system should still be relevant to the biological one. The potential sites for recognition of *p*-benzoquinone are illustrated in Fig. 1. The relative merits of the six possible sites for π–π interactions



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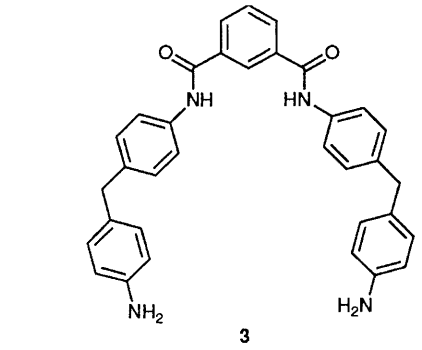

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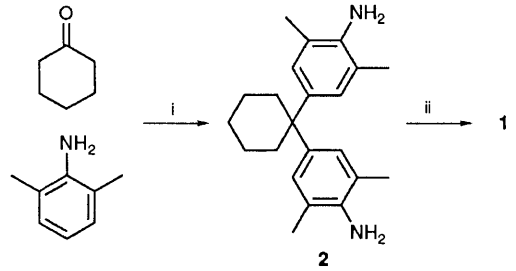

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Scheme 1 *Reagents and conditions*: i, HCl (conc.), reflux (53%); ii, isophthaloyl dichloride, NEt_3, CH_2Cl_2, high dilution (10%)

were assessed using the Hunter–Sanders rules.[6] The polarisation of *p*-benzoquinone makes the four edge-to-face π–π interactions on the quinone periphery particularly favourable. In contrast, edge-to-face interactions at the faces of the quinone π-system should be less favourable. Partially offset π-stacking at these sites is predicted to be attractive. However, this class of π–π interaction is very sensitive to both molecular charge distribution and orientation so that a high degree of precision would be required in host design. Therefore, these sites have not been utilised. The design of the target molecule, **1**, was encouraged by two observations: (*i*) isophthaloyl diamide derivatives are capable of recognising carbonyl oxygens through H-bonding.[7] (*ii*) Diarylmethane derivatives form solid state inclusion complexes with *p*-benzoquinone.[8] The methyl groups were used to hold the isophthaloyl moieties perpendicular to the diarylmethane walls of the cavity, while the cyclohexyl groups provided solubility. The molecule, **1**, is highly preorganised with a cavity perfectly complementary to the molecular surface of *p*-benzoquinone.

The synthesis of **1** is outlined in Scheme 1.† The methyl groups were essential for the success of this procedure. When 4,4′-methylenedianiline was used in place of **2**, the only major product was **3**, which was used as a control in the NMR experiments described below.

The ^1H NMR spectrum of **1** in $CDCl_3$ was broad at room temperature; on addition of an excess of *p*-benzoquinone, the resonances became sharp and well-resolved. Significant changes in the chemical shifts of the **1** signals were also observed.‡ A titration indicated that a 1:1 complex was formed with an association constant of (1.2 ± 0.1) × 10^3 dm^3 mol^{-1}. Equilibration of the free and bound species was rapid on the laboratory timescale and the signals due to the complex were in fast exchange with the signals due to the uncomplexed species on the ^1H NMR timescale. Computer-assisted non-linear curve-fitting was used to calculate the limiting chemical shifts of the signals due to the complex (Table 1). The complexation-induced changes in chemical shift provide strong evidence for the geometry of the 1:1 adduct illustrated in Fig. 2. The 2.4 ppm upfield shift experienced by the quinone signal, coupled with the 0.2 ppm downfield shift experienced by the H-4 signal, implies the formation of edge-to-face π–π interactions with the quinone protons lying over the face of the diarylmethane π-systems. The 1.0 ppm downfield shift of the NH signal is indicative of H-bonding and the 0.3 ppm downfield shift of the H-1 signal suggests that these protons fall in the deshielding zones of the quinone carbonyls.[7] The methyl signals of **1** are not shifted by complexation. This implies that the quinone is buried deep in the heart of the cavity, so far from the methyl groups that its presence does not affect these signals.

† All new compounds gave satisfactory spectroscopic and fast atom bombardment mass spectrometric data.

‡ Addition of an excess of *p*-benzoquinone to a sample of **3** in $CDCl_3$ had no effect on the ^1H NMR spectrum.

Table 1 ^1H NMR chemical shifts (δ)

Proton	Free	Bound
1 signals		
H-1	8.15	8.45
H-2	8.14	8.27
H-3	7.66	7.71
H-4	6.96	7.13
H(Me)	2.16	2.17
NH	7.19	8.22
p-benzoquinone	6.78	4.42

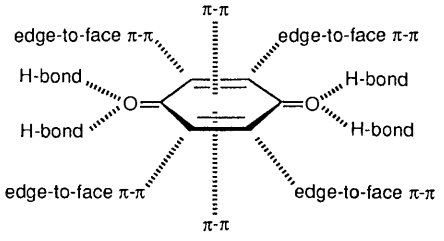

Fig. 1 Interaction sites available for molecular recognition of *p*-benzoquinone

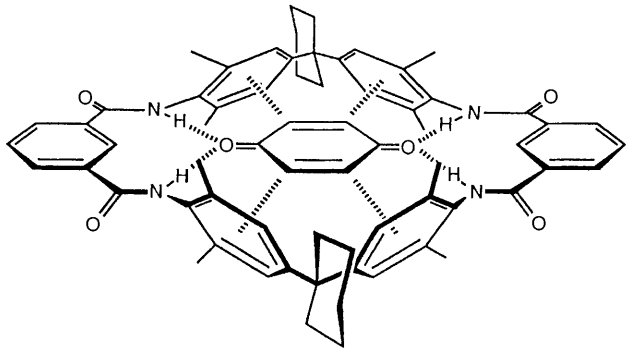

Fig. 2 The **1**·*p*-benzoquinone complex

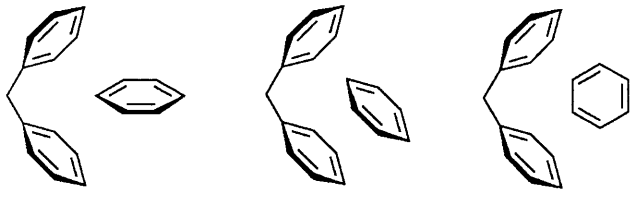

Fig. 3 Orientations of attractive π–π interactions with diarylmethane derivatives: (*a*) see ref. 9; (*b*) see ref. 10; (*c*) the orientation reported here

The complex geometry shown in Fig. 2 was corroborated by the finding that **1** is a specific host for *p*-benzoquinone. No complexation could be detected with large excesses of tetramethylbenzoquinone, tetrachlorobenzoquinone or anthraquinone (binding constants for these compounds are all less than 1 $dm^3\ mol^{-1}$). Corey–Pauling–Koltun models showed that, although these bulkier quinones will fit into the cavity in **1**, they cannot adopt the orientation shown in Fig. 2. The implication is that cooperative formation of 4 H-bonds and 4 π–π interactions is required for complexation in chloroform.

When a titration of **1** with *p*-benzoquinone was carried out in $CDCl_3$–CD_3OD (9 : 1), the association constant fell to 100 ± 10 $dm^3\ mol^{-1}$. This solvent mixture competes for H-bonding sites and so the decrease in association constant confirms that H-bonding plays an important role in complexation. However, the fact that complexation could be detected in a H-bonding solvent suggests that π–π interactions must also make a sizeable contribution to the binding energy.

Despite many studies of complexation between aromatic guests and diarylmethane hosts,[9,10] the geometry of the quinone-diarylmethane π–π interaction reported here has not been observed before. Orientations observed previously are shown schemtically in Fig. 3.[9,10] These results demonstrate the predictive power of the Hunter–Sanders rules in host design.[6]

This work illustrates that a combination of H-bonding and π–π interactions provides an effective method for specific recognition small aromatic molecules, even in the presence of competing solvents. Methods for functionalising **1** so that it more closely resembles the quinone binding domains of the bacterial photosynthetic reaction centres are currently under investigation.

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