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ORIGINAL ARTICLE

Silica-attached molecular receptor complexes for benzoates and naphthoates

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Abstract A series of cyclen (1,4,7,10-tetraazacyclododecane) derived molecular receptors for aromatic oxoanions, that are activated by complexation with Cd(II), have been covalently linked to 3-(glycidoxy)propyl-functionalised silica gel (70–230 mesh). These immobilised receptor complexes are highly effective for the sequestration of *o*-hydroxybenzoates and 2-naphthoate from aqueous solution, achieving a >80% saturation level by stirring the material in the aqueous solution for 1 h at pH 7.00 and 298 K. Examination of the uptake levels of a variety of different benzoates and naphthoates suggests that the retention mechanism involves a combination of classical hydrogen bonding and non-classical, water mediated, O–H···π hydrogen bonding. Contrary to expectations, attachment of hydroxy terminated polyether chains to the periphery of the receptor complex diminished the level of uptake.

Keywords Inclusion complex · Hydroxybenzoates · Naphthoates · Cyclen derivatives · Silica attachment

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Introduction

In earlier work we have described a range of pendant arm macrocyclic ligands which when complexed to an eight-coordinating metal ion, such as Cd(II), form receptor complexes that contain a hydrophobic pocket suitable for the sequestration of aromatic oxoanions through the formation of receptor host–guest complexes [1–5]. Examples can be seen in Fig. 1a and b where the guest molecules are, respectively, *p*-aminobenzoate and 2,6-dihydroxybenzoate, and the walls of the pocket are defined by four or three phenoxy moieties. In each case the anion is primarily retained by four classical O–H hydrogen bond forming donor groups that converge from the base of the pocket and serve to capture any appropriately hydrophobic, hydrogen bond acceptor guest molecule that moves into their vicinity. We have also found that in certain instances, such as when *ortho*-substituted benzoates are retained, this classical hydrogen bonding may be augmented by water mediated non-classical hydrogen bonding to the walls of the pocket, as shown in Fig. 1b [5, 6]. In cases where both hydrogen bonding mechanisms can operate association constants have been determined that exceed 10^7 M^{-1} [5].

Modification of the receptor complexes shown in Fig. 1 so that one arm carries an anthracenyl [5], or dansyl [7], fluorescent probe has enabled us, with some guests, to elicit an observable fluorescence perturbation when the guest molecule moves into the receptor pocket, for which the aromatic fluorophore now forms one of the walls. This has taken us some way towards producing useful sensor materials for aromatic oxoanions [5]. However, until now we have conducted these sequestration reactions with both the receptor complex and the guest molecule in the same solution, thereby unavoidably contaminating the sequestration medium with the receptor complex. We have now

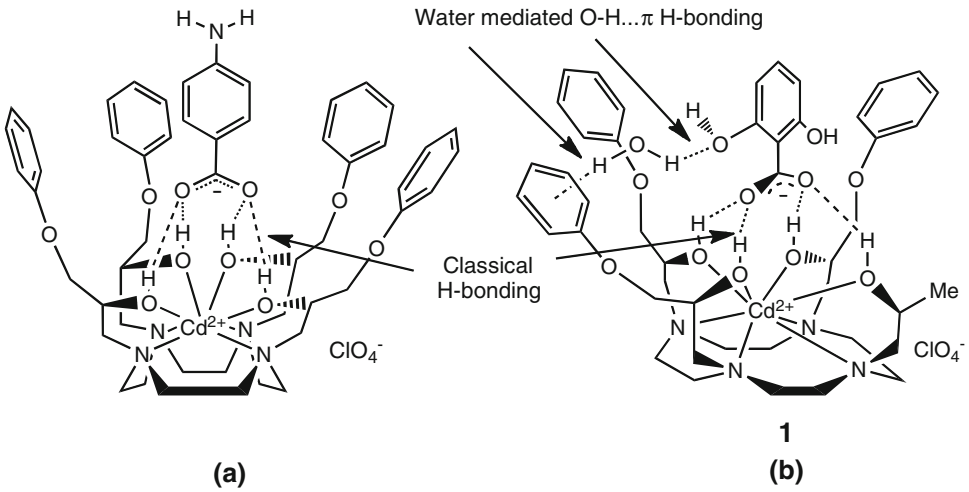


Fig. 1 **a** X-ray determined structure of a four walled receptor host–guest complex where the guest is retained by classical H-bonding alone [3]. **b** Presumed structure of a three walled receptor host–guest complex, with a guest capable of water mediated O–H···π hydrogen bonding (for clarity, shown for only one O–H group) as well as classical H-bond acceptance [6]

turned our attention towards immobilizing these receptor complexes by covalently attaching them to silica gel. Immobilisation in this way has been used in the past for macrocyclic ligands designed to remove metal ions from aqueous solution [8–13]. It allows isolation of the receptor from the guest-containing solution without preventing sequestration, even though in these circumstances it must occur across a solid–liquid interface. In this paper we report on the consequences for aromatic oxoanion uptake from water of modifying and using our receptor complexes in this way.

The materials used for the investigation are those shown as **8**–**10** in Scheme 1. Receptor complex **8** is an adaptation of receptor complex **1**, shown in Fig. 1b, and some of the guest anion uptake levels obtained using it under aqueous conditions will be discussed in terms of the solution association constant values previously measured using **1**, which serves as a soluble model, in aqueous acetonitrile [6]. Receptor complexes **9** and **10** are similar to **8**, but carry hydroxy terminated polyether (HTPE) chains at their periphery. These were added to allow for an investigation of their ability to improve anion uptake across the solid–liquid interface by improving the contact between the receptor complex and the aqueous phase [14–17], compared to **8**.

Results and discussion

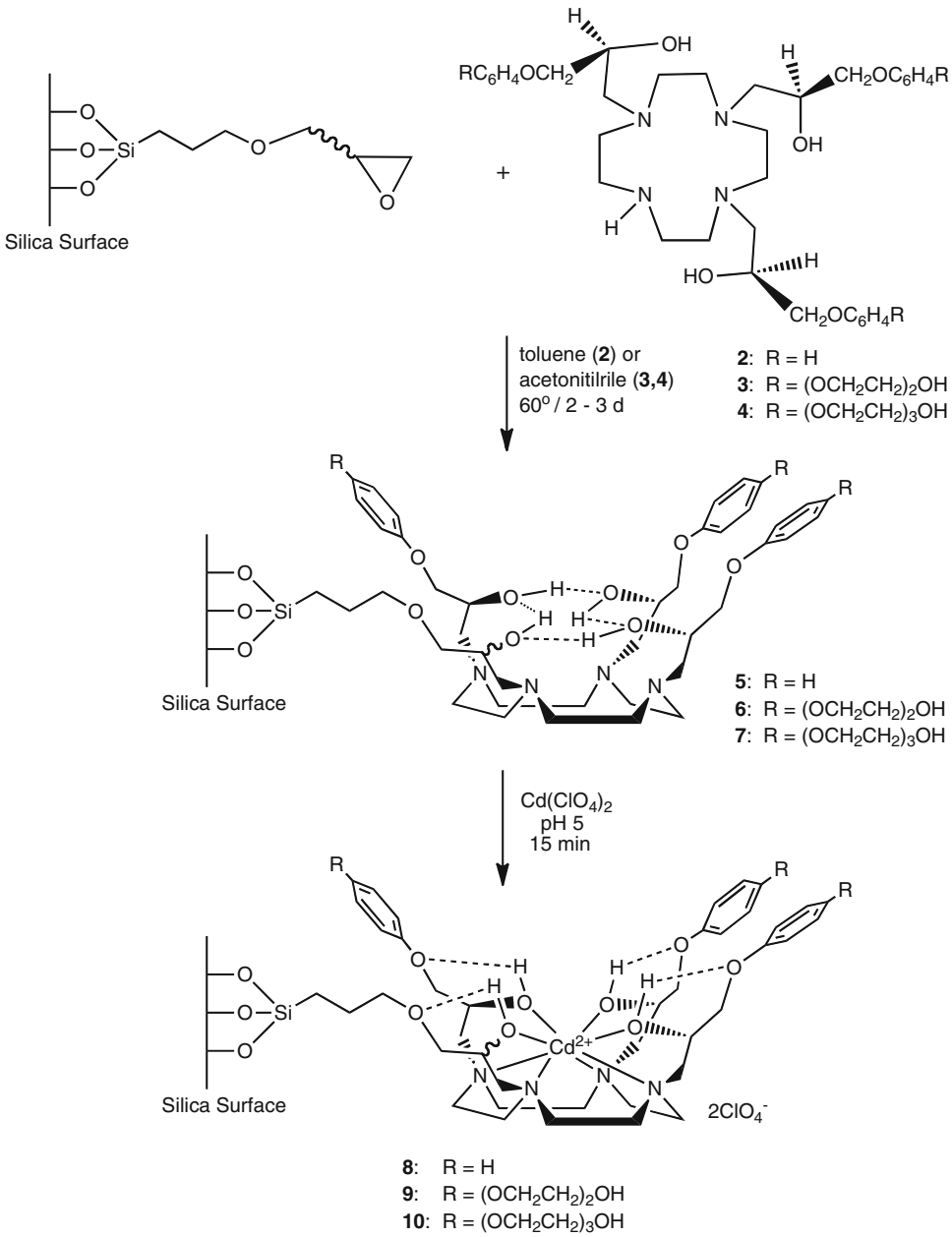
Synthesis of the silica-attached receptor complexes

Synthesis of the silica-attached receptor complexes was achieved using racemic 3-(glycidoxy)propyl-functionalised silica gel (70–230 mesh), prepared according to an established method [10, 18, 19], in conjunction with the previously reported three-armed macrocycle, **2** [5], or a hydroxy terminated polyether variant of it (**3** or **4**) as shown in Scheme 1.

Characterisation of **5**–**7**, following Soxhlet extraction of the siliceous product with MeOH, to remove any residual, adsorbed macrocycle, was performed qualitatively by both ^{13}C solid state NMR spectroscopy and DRIFT (infrared) spectroscopy. In both cases, signals associated with the aromatic moieties, in particular, belonging to the macrocycle, were clearly evident indicating that covalent attachment of the receptor ligand had occurred. The loading of the receptor ligand on the silica was quantified by microanalysis of the carbon and nitrogen content [8, 10], and confirmed by thermal decomposition [20], as being 0.31, 0.17 and 0.10 mmol g^{-1} ± 5% for **5**–**7**, respectively. A comparison of these loadings with the loading of the 3-(glycidoxy)propyl linker moiety on the silica, which was determined in the same way to be 1.1 ± 3% mmol g^{-1}, shows that the more bulky the receptor ligand becomes the fewer the number of linker moieties that are accessible to it. Loadings of receptor ligand **2** on two higher surface area forms of silica, namely 230–400 mesh silica gel and MCM-41, with the 3-(glycidoxy)propyl linker covalently attached at loadings of 0.88 and 1.70 mmol g^{-1} ± 3%, respectively, were also investigated. In both cases these were inferior, being 0.27 and 0.22 mmol g^{-1} ± 5%, respectively and consequently the following work was conducted using the 70–230 mesh silica gel derived materials.

For receptor ligands such as **5**–**7** to behave as receptors they must first be activated by complexation with an eight-coordinating metal ion [1]. This causes the receptor ligand to develop a partially rigid three-dimensional structure in which the binding pocket is formed from the juxtaposed aromatic moieties on the coordinated pendant arms, as shown in Fig. 1 and Scheme 1. Metal ion uptake was investigated with the potentially eight-coordinating metal

Scheme 1 Synthesis of the silica-attached receptor complexes **8–10**



ions Cd(II), Pb(II) and Ca(II) as well as Cu(II) and Zn(II) by suspending 100 mg of **5**, **6** or **7** in 10 cm^3 of an aqueous solution 2×10^{-2} mol dm^{-3} in the appropriate metal nitrate at pH 5 (HEPES), and then periodically measuring the reduced concentration of the free metal ion by atomic absorption spectroscopy. The results of this investigation were similar for **5**, **6** and **7** and are shown for **5** in Fig. 2. There it can be seen that whilst the uptake of Ca(II) is somewhat slower, 100% uptake of all the other metal ions is complete in 1 h or less. Accordingly, receptor ligands **5–7** were loaded with Cd(II) by treatment with $Cd(ClO_4)_2 \cdot 6H_2O$ to form the silica-attached receptor complexes **8–10** for use in aromatic oxoanion binding studies.

Aromatic oxoanion uptake studies

Aromatic oxoanion uptake studies were conducted using the collection of sodium benzoates and naphthoates listed in Table 1. These were chosen since they were mostly known from earlier studies of related, but non-silica attached receptor complexes, to show good affinity in solution for this class of receptor [1–6]. In each case 100 mg of receptor complex material (<0.03 mmol of receptor complex) was suspended in 10 cm^3 of a 5×10^{-3} mol dm^{-3} aqueous solution of the guest (0.05 mmol) at pH 7.00 (0.01 mol dm^{-3} HEPES) and stirred for 1 h at 298 K. After filtering off the expended receptor complex material the concentration of

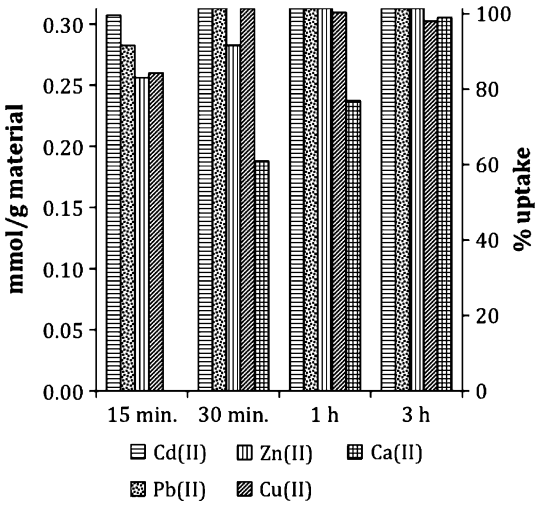


Fig. 2 Metal ion uptake by receptor **5** from metal(II) nitrate solutions

residual guest was determined by UV spectroscopy and the uptake calculated as the percentage of the available receptor complex sites filled, on the basis of there being one guest molecule per receptor complex, as demonstrated in earlier work through the construction of Job's plots [6]. In cases where the guest uptake exceeded 60% the ^{13}C solid state NMR spectrum of the thoroughly washed, expended receptor complex displayed easily seen resonances attributable to both the receptor complex and the guest, thus qualitatively confirming the uptake and that the Cd(II) is not lost from the receptor complex during the uptake process. A typical montage is displayed as Fig. 3, the remainder are provided as supplementary information.

The uptake of the series of hydroxybenzoates identified as Group A in Table 1 has been of interest to us for some time owing to the observation that in aqueous conditions, with this class of receptor, the association constant increases quite markedly as the hydroxy substituent moves from the *para*- to the *ortho*-position [5, 6]. This was initially unexpected since the diminishing basicity of the anions along this progression should diminish the strength of the hydrogen bonding between the benzoate and the hydroxy groups at the base of the binding pocket and consequently lower the association constant. We have explained this trend by suggesting that non-classical hydrogen bonding of the O–H···π type [22], shown in Fig. 1b, increasingly comes into play as the O–H group(s) on the benzoate moves closer to the carboxylate, and hence deeper into the binding pocket, where interaction of the O–H group(s) with the aromatic moieties that constitute the pocket wall becomes geometrically possible, especially if mediated by water (as seems likely since this phenomenon is not seen in anhydrous solvents [6]). In the present study we see that the uptake trend for these guests mirrors the association constant trend seen with the model receptor complex, **1**, with very high uptakes occurring for *o*-hydroxybenzoates where water mediated O–H···π hydrogen bonding could be expected to be most effective. Further evidence for the existence of O–H···π hydrogen bonding, and its importance to the uptake process, can be seen from the data for the Group B guests. Here the hydroxy group has been replaced with a methoxy group to eliminate all possibility of O–H···π hydrogen bonding and not only is there now a much lower level of uptake for the *o*-substituted compounds, but also the ordering of the uptake follows the decline in basicity of the guest, as expected if only the classical hydrogen bonding retention mechanism is operative. Interestingly for the *p*-methoxy and to a lesser extent the *m*-methoxy benzoates there is an increase in uptake compared to the corresponding hydroxy-guests. This is probably a manifestation of the hydrophobic effect [23], whereby the methoxy guests are excluded from the aqueous phase and retreat into the pocket whilst the hydrophilic hydroxy guests tend to be extracted from it by the solvent. The uptake of the Group C guests (Table 1) support the same dual retention mechanism: It can be seen that as the number of *o*-OH groups (those in the 2 or 6-positions) increases the uptake goes up, whilst 3,4,5-trihydroxybenzoate (gallate) has a lower uptake despite it being more basic.

The effect on the guest uptake level of attaching the HTPE chains to the periphery of the receptor complex, to improve its hydrophilicity, was investigated with the group A guests using **9** and **10**. It can be seen from the Table that for the four guests examined there was no improvement in their uptake. In fact the general pattern was one of diminishment, with a clear deterioration as the length of the HTPE chain increased. We interpret this as evidence of the HTPE chain inserting itself into the binding pocket of the receptor complex and hydrogen bonding to the O–H groups at its base, thereby blocking access to it and thwarting the objective of HTPE attachment.

The Group D guests provide another opportunity to examine a group some of which, the amines, can potentially N–H···π hydrogen bond to the cavity wall, compared to a group that cannot, the nitro compounds. The group of amines again show higher uptake when the amine is *ortho* to the carboxylate, but the level of uptake is much less than for the corresponding class A compound, consistent with much weaker N–H···π hydrogen bonding [22]. It is nonetheless interesting to note that the least basic amine still has the highest uptake, supporting the presence of N–H···π hydrogen bonding, whereas the uptake trend for the nitro compounds simply follows their basicity.

Amongst the Group E guests the 1- and 2-naphthoates are particularly interesting since they have high and very high uptakes, respectively. This again suggests that a second type of retention force is operating that augments

Table 1 % Uptake (±7%) by receptors **8–10** of sodium benzoates and naphthoates from aqueous solution at pH 7.00 (HEPES) and 298 K

Group	Benzoate or naphthoate	% Uptake by **8**	% Uptake by **9**	% Uptake by **10**	Log(K_{assoc}/M^{-1}) in 20% D_2O/CD_3CN using **1**[a]	pK_a[b]
A	Benzoate	30			3.1	4.19
	p-OH	32	50	31	3.2	4.54
	m-OH	48	45	30	3.5	4.30
	3,5-di-OH	50				4.04
	o-OH	81	76	45	3.7	2.97
	2,6-di-OH	95	92	46	4.6	1.05
	p-OMe	60				4.47
B	*m*-OMe	55				4.09
	o-OMe	29				3.90
	2,6-di-OMe	23				3.44
	2,5-di-OH	82				2.95
C	2,4,6-tri-OH	94				1.68
	3,4,5-tri-OH	73				4.41
	p-NH_2	22				2.38
	m-NH_2	12				3.07
D	*o*-NH_2	43				2.14
	p-NO_2	16				3.44
	m-NO_2	23				3.46
	o-NO_2	12				2.47
	p-CH_3	43				4.37
	p-F	33				4.14
E	*p*-Cl	38				3.98
	p-CHO	19				3.77
	1-naphthoate	76				3.60
	2-naphthoate	98				4.17

[a] Data taken from [6]

[b] pK_a of the acid conjugate to the benzoate or naphthoate, data taken from [21]

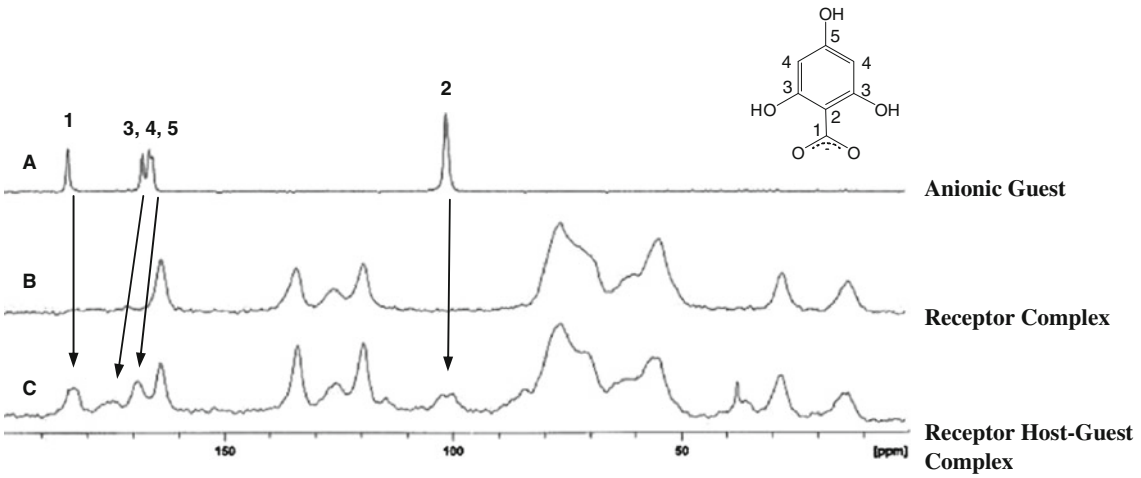


Fig. 3 ^{13}C CPMAS NMR spectra for (*top*) sodium 2,4,6-trihydroxybenzoate (*middle*) receptor complex **8**, and (*bottom*) receptor complex **8** with 94% loading of 2,4,6-trihydroxybenzoate

hydrogen bonding at the base of the cavity, since benzoate, which has a similar basicity to 2-naphthoate but lacks the second aromatic ring, shows less than one-third the level of uptake. The high level of uptake for both naphthoates may be due to an enhanced hydrophobic effect compared to benzoate, but this should be more pronounced for 1-naphthoate, which on spatial grounds, as shown in Fig. 4, should sit lower in the binding pocket than 2-naphthoate. It is also possible a similar type of non-classical hydrogen bonding interaction to that seen when O–H···π hydrogen

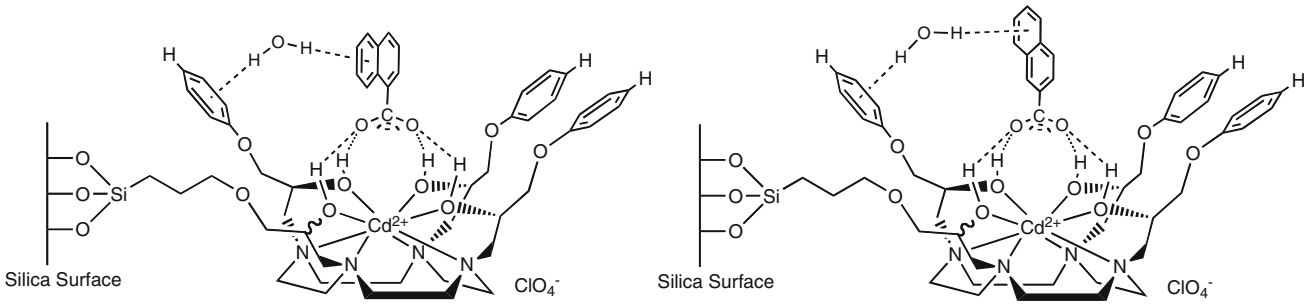


Fig. 4 Representation of the possible hydrogen bonding interactions responsible for the high level of uptake of 1- (*left*) and 2-naphthoate (*right*)

bonding was first substantiated by X-ray crystallography occurs [24], whereby a water molecule bridges between two aromatic rings, engaging in O–H···π hydrogen bonding with each of them. This is suggested in Fig. 4, however, on spatial grounds again this would appear to favour 1-naphthoate over 2-naphthoate where the additional aromatic ring, compared to benzoate, is in closer proximity to the walls of the pocket. It appears that whilst either or both of these two factors must contribute significantly to the binding strength of both naphthoates, since neither is likely to favour 2-naphthoate it is ultimately the higher basicity of 2-naphthoate that is the determining factor responsible for its higher uptake level.

Conclusion

We have demonstrated that it is possible to attach our metal ion activated receptor complexes to silica in a manner that retains their ability to sequester benzoates from aqueous solution. In cases where the guest benzoate has two hydroxy moieties both *ortho* to the carboxylate the uptake level exceeds 90 or 80% if there is just one. For 2-naphthoate the impressively high level of sequestration, and hence selectivity over most of the other guests examined, of 98% was measured.

Experimental

General

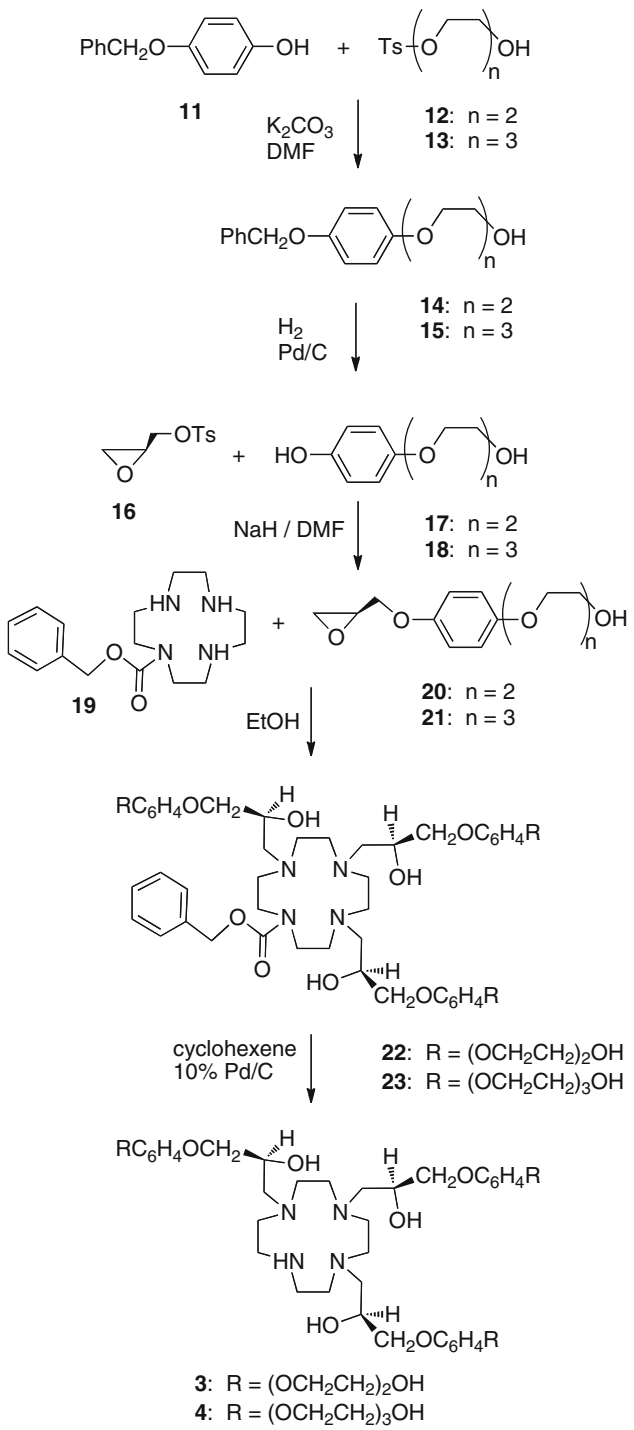
All reactions were performed under an atmosphere of nitrogen. Solvents were pre-dried and purified using known literature methods. Microanalyses and high resolution mass spectra acquisition were carried out at the University of Otago, New Zealand. ^{1}H and ^{13}C NMR solution spectra were obtained using a Bruker Avance 400 MHz spectrometer. Referencing of the ^{13}C NMR chemical shifts was to the central resonance of the solvent multiplet: δ 77.00 for $CDCl_3$, 118.10 for CD_3CN and δ 49.00 for CD_3OD. ^{1}H NMR chemical shifts were referenced to the residual non-deuterated solvent peak at δ 7.26 for $CDCl_3$. ^{13}C CPMAS NMR spectra were recorded on a Bruker 400 Avance spectrometer at an operating frequency of 100.61 MHz with TOSS (TOtal Suppression of Spinning Side-bands) software in a 4 mm zirconium oxide rotor with a Kel-F end-cap. The samples were spun at 5 kHz and a contact time of 1 ms with a recycle delay time of 4 s. Chemical shift values were referenced to external glycine. DRIFT spectra were recorded using finely ground mixtures of the compound and KBr held in aluminium sample cups on a Nicolet Nexus 8700 FTIR Spectrophotometer fitted with a Smart Collector DRIFT accessory. Optical rotations were measured using a PolAAr polarimeter. Thermal combustion determinations of receptor ligand loading levels on silica gel were conducted in 15 cm^3 crucibles at 1073 K in a C muffle furnace (H. B. Selby and Co.).

Synthesis of compounds **3** and **4**

Ligands **3** and **4** were prepared by the procedure outlined in Scheme 2. 4-Benzyloxyphenol, **11**, and *S*-glycidyl tosylate, **16**, were purchased from Sigma-Aldrich. Compounds **12** and **13** were prepared following the literature procedure [25], as was **19** [26].

1-[2-(2-hydroxyethoxy)ethoxy]-4-benzyloxybenzene·0.5H_2O, **14**

This compound was synthesised by a procedure modified from Amabilino and co-workers [27]. A solution of 4-(benzyloxy)phenol, **11** (2.34 g, 11.70 mmol), dissolved in anhydrous DMF (10 cm^3) was added slowly over 10 min to a stirring suspension of finely ground anhydrous K_2CO_3 (4.04 g, 29.30 mmol), in anhydrous DMF (5 cm^3). The mixture was stirred at 80 °C for 1 h in an atmosphere of nitrogen. A solution of the tosylate **12** (3.10 g, 11.90 mmol), dissolved in dry DMF (10 cm^3) was then added dropwise and the mixture stirred for 4 days at 80 °C. The mixture was diluted with water (200 cm^3), and extracted with CH_2Cl_2 (5 × 100 cm^3). The CH_2Cl_2 extracts were



Scheme 2 Synthesis of receptor ligands **3** and **4**

combined and washed with 1 mol dm^{-3} $KHSO_4$ (3 × 100 cm^3), brine (3 × 100 cm^3), and water (3 × 100 cm^3), and then dried over $MgSO_4$. The solvent was removed in vacuo to yield a brown oil which was purified by column chromatography on silica (eluent 40% EtOAc/DCM, rf: 0.35), and concentrated in vacuo to obtain **14** as an off-white oil that solidified overnight into a white waxy solid (2.6 g, 76%). ^{1}H NMR ($CDCl_3$): δ 7.38–7.30 (5H, m, Bn–*H*); 6.92–6.85 (4H, m, Ar–*H*); 5.01 (2H, s, Bn–CH_2–); 4.10–3.84 (2H, m, –OCH_2); 3.78–3.76 (2H, m, –OCH_2); 3.76–3.66 (4H, m, –OCH_2); 2.10 (1H, br s, –OH). ^{13}C NMR ($CDCl_3$): 153.19 (1C, Ar, *para*); 152.94 (1C, Ar, *ipso*); 137.18 (1C, Bn, ipso);128.48 (2C, Bn, *meta*); 127.83 (1C, Bn, *para*); 127.41 (2C, Bn, *ortho*); 115.80 (2C, Ar, *ortho*); 115.59 (2C, Ar, *meta*); 72.52 (1C, –*C*H_2–OAr); 70.60 (2C, –*C*H_2–Bn); 69.72 (1C, –*C*H_2–CH_2–OAr); 68.03 (1C, –*C*H_2–OAr); 61.71 (1C, –*C*H_2–OH). (Found: C, 70.54; H, 7.56. $C_{17}H_{20}O_4{\cdot}0.5H_2O$ requires C, 70.57; H, 7.32%).

1-[2-(2-(2-hydroxyethoxy)ethoxy)ethoxy]-4-benzyloxybenzene, **15**

Preparation of this compound was by a method analogous to that used for the preparation of **14** from 4-(benzyloxy)phenol, **11** (3.25 g, 16.23 mmol), K_2CO_3 (5.6 g, 40.60 mmol), and **13** (5.01 g, 16.45 mmol) (rf: 0.18), to obtain **15** as an off-white oil which solidified overnight into a white, waxy solid (4.6 g, 85%). ^{1}H NMR ($CDCl_3$): 7.44–7.31 (5H, m, Bn–*H*); 6.92–6.84 (4H, m, Ar–*H*); 5.01 (2H, s, Bn–CH_2–); 4.10–4.07 (2H, m, –OCH_2–); 3.86–3.82 (2H, m, –OCH_2–); 3.75–3.70 (6H, m, –OCH_2–); 3.63–3.60 (2H, m, –OCH_2–); 2.52 (1H, br s, OH). ^{13}C NMR ($CDCl_3$): δ 153.12 (1C, Ar, *para*); 153.01 (1C, Ar, *ipso*); 137.21 (1C, Bn, *ipso*); 128.46 (2C, Bn, *meta*); 127.79 (1C, Bn, *para*); 127.39 (2C, Bn, *ortho*); 115.75 (2C, Ar, *ortho*); 115.57 (2C, Ar, *meta*); 72.43 (1C, –*C*H_2–CH_2OH); 70.72 (1C, –*C*H_2OCH_2CH_2OH; 70.59 (1C, –CH_2–Bn); 70.32 (1C, –*C*H_2OCH_2CH_2OAr); 69.79 (1C, –*C*H_2–CH_2OAr); 67.97 (1C, –*C*H_2–OAr, 61.69 (1C, –*C*H_2–OH). (Found: C, 68.60; H, 7.24. $C_{19}H_{24}O_5$ requires C, 68.66; H, 7.28%).

1-[2-(2-hydroxyethoxy)ethoxy]-4-hydroxybenzene, **17**

A solution of **14** (2.5 g, 8.67 mmol), dissolved in anhydrous DCM (25 cm^3) was added to a suspension of Pd/C (10%, 0.30 g), in anhydrous MeOH (25 cm^3) and stirred at ambient temperature under an atmosphere of H_2 for 2 days. The catalyst was removed by filtration through Celite. The solvent was removed in vacuo to yield **17** as a brown oil in quantitative yield. ^{1}H NMR ($CD_3OD/CDCl_3$): 6.68–6.61 (4H, m, Ar–*H*); 4.06 (2H, br s, 2 x –OH); 3.95–3.93 (2H, m, –OCH_2); 3.70–3.67 (2H, m, –OCH_2); 3.62–3.59 (2H, m –OCH_2); 3.53–3.50 (2H, m, –OCH_2). ^{13}C NMR ($CD_3OD/CDCl_3$): 151.42 (1C, Ar, *para*); 150.56 (1C, Ar, *ipso*); 115.32 (2C, Ar, *meta*); 115.31 (2C, Ar, *ortho*); 72.10 (1C, –*C*H_2–CH_2OH); 69.12 (1C, –*C*H_2–CH_2OAr); 68.11 (1C, –*C*H_2–OAr); 61.08 (1C, –*C*H_2–OH); (m/z) HRMS (ESI^+): calculated 221.0784 for $C_{10}H_{14}NaO_4$ $(M + Na)^+$, found 221.0774.

1-[2-(2-(2-hydroxyethoxy)ethoxy)ethoxy]-4-hydroxybenzene, **18**

Deprotection of this compound was analogous to the preparation of **17** using **15** (3.6 g, 10.83 mmol), and Pd/C (10%, 0.40 g), to obtain **18** as a brown oil in quantitative yield. ^{1}H NMR ($CD_3OD/CDCl_3$): 6.70–6.64 (4H, m, Ar–*H*); 4.68 (2H, br s, 2x –O*H*); 3.95–3.93 (2H, m, –OCH_2–); 3.75–3.72 (2H, m, –OCH_2–); 3.69–3.64 (4H, m, –OCH_2–); 3.62–3.60 (2H, m, –OCH_2–); 3.55 (2H, m, –OCH_2–) ^{13}C NMR ($CD_3OD/CDCl_3$): 152.37 (1C, Ar, *para*); 150.14 (1C, Ar, *ipso*); 116.07 (2C, Ar *meta*); 115.66 (2C, Ar, *ortho*); 72.50 (1C, –*C*H_2–CH_2OH); 70.73 (1C, –*C*H_2–OCH_2CH_2OH); 70.21 (1C, –*C*H_2–CH_2CH_2OAr; 69.88 (1C, *C*H_2–CH_2OAr; 67.85 (1C, –*C*H_2–OAr; 61.68 (1C, –*C*H_2–OH); (m/z) HRMS (ESI^+): calculated 265.1052 for $C_{12}H_{18}NaO_5$ $(M + Na)^+$, found 265.1059.

(*2S*)-(+)-3-(phenoxy-4-[2-(2-hydroxyethoxy)ethoxy]-1,2-epoxypropane, **20**

A solution of **17** (2.00 g, 10.1 mmol), was added slowly over 20 min to a stirring suspension of anhydrous K_2CO_3 (3.5 g, 25.3 mmol), in anhydrous DMF (10 cm^3). The mixture was stirred at 50 °C for 2 h. (*2S*)-(+)-glycidyl tosylate, **16** (2.30 g, 10.0 mmol), dissolved in anhydrous DMF (10 cm^3) was then added dropwise and the mixture was stirred at 50 °C for 4 days. The reaction was quenched with saturated NH_4Cl (10 cm^3) and then diluted with water (200 cm^3). The product was extracted with CH_2Cl_2 (4 × 150 cm^3). The organic extracts were combined and then washed with brine (2 × 100 cm^3) and water (1 × 100 cm^3), concentrated in vacuo and purified by column chromatography on silica (eluent 40% EtOAc/DCM, rf: 0.20). The pure product was concentrated in vacuo to yield **20** (1.73 g, 68%) as a pale yellow oil. ^{1}H NMR ($CDCl_3$): δ 6.81 (4H, s, Ar–*H*); 4.13 (1H, dd, $J = 3.0$, 11.5 Hz, –CH_2OAr); 4.03 (2H, m, –OCH_2–); 3.84 (1H, dd, $J = 5.7$, 11.5 Hz, –CH_2OAr); 3.78 (2H, m, –OCH_2–); 3.70 (2H, br s, –OCH_2–); 3.61 (2H, m, –OCH_2–); 3.29 (1H, m, –C*H*O–); 2.90 (1H, br s, –O*H*); 2.85 (1H, t, $J = 4.5$ Hz, –HC*H*O–); 2.70 (1H, dd, $J = 2.7, 4.8$ –*H*CHO–). ^{13}C NMR ($CDCl_3$): δ 153.04 (1C); 152.75 (1C); 115.52 (2C); 115.47 (2C); 72.48 (1C); 69.55 (1C); 69.29 (1C); 67.87 (1C); 61.53 (1C); 50.09 (1C, epoxide); 44.48 (1C, epoxide). $[\alpha]_D^{25} = +4.21°$ (c 2.19, MeOH); (m/z) HRMS (ESI^+): calculated 277.1052 for $C_{13}H_{18}NaO_5$ $(M + Na)^+$, found 277.1049.

(*2S*)-(+)-3-(phenoxy-4-[2-(2-(2-hydroxyethoxy)ethoxy)ethoxy]-1,2-epoxypropane, **21**

The preparation of this compound was by the same method as for **20** using **18** (4.21 g, 17.40 mmol), K_2CO_3 (6.01 g, 43.5 mmol), and **16** (3.97 g, 17.39 mmol), to yield **21** as a pale yellow oil (3.71 g, 74%), rf: 0.21. ^{1}H NMR ($CDCl_3$): δ 6.82 (4H, s, Ar–*H*); 4.14 (1H, dd, $J = 3.2$, 11.04 Hz, –CH_2OAr); 4.05 (2H, m, –OCH_2–); 3.86 (1H, dd, $J = 5.7$, 11.04 Hz, –CH_2OAr); 3.81 (2H, m, –OCH_2–); 3.71–3.64 (6H, m, –OCH_2–); 3.58 (2H, m, –OCH_2–); 3.30 (1H, m, –C*H*O–); 2.87 (1H, t, $J = 4.48$ Hz, –HC*H*–O–); 2.71 (1H, dd, $J = 2.68, 4.91$ Hz, –*H*CHO–); 2.15 (1H, br s, O*H*). ^{13}C NMR ($CDCl_3$): δ 153.15 (1C, Ar); 152.75 (1C, Ar); 115.53 (2C, Ar); 115.48 (2C, Ar); 72.39 (1C); 70.66 (1C); 70.24 (1C); 69.71 (1C); 69.35 (1C); 67.87 (1C); 61.61 (1C); 50.14 (1C, epoxide); 44.56 (1C, epoxide). $[\alpha]_D^{25} = +2.35°$ (c 2.13, MeOH); (m/z) HRMS (ESI^+): calculated 321.1314 for $C_{15}H_{22}NaO_6$ $(M + Na)^+$, found 321.1309.

1-(benzyloxycarbonyl)-4,7,10-*tris*(*2S*)-2-hydroxy-3-[4-(2-(2-hydroxyethoxy)ethoxy)phenoxypropyl]-1,4,7,10-tetraazacyclododecane, **22**

Synthesis of this compound was by a method analogous to that used for the preparation of the HTPE free variant, [5] using 1-benzyloxycarbonyl)-1,4,7,10-tetraazacyclododecane, **19** (415 mg, 1.35 mmol) and **20** (1.04 g, 4.08 mmol), to give **22** as a thick brown oil (1.44 g, quantitative). ^{13}C NMR ($CDCl_3$): δ 156.26 (1C, *C*=O); 152.95 (3C, Ph); 152.77 (3C, Ph); 136.54 (1C, Bn, *ipso*); 128.29 (1C, Bn); 127.80 (1C, Bn); 127.77 (1C, Bn); 127.70 (2C, Bn); 115.40 (6C, Ph); 115.33 (6C, Ph); 72.46 (3C); 71.23 (1C); 70.42 (1C); 70.30 (1C); 69.47 (3C); 67.86 (3C); 66.93 (2C); 66.72 (1C); 65.98 (1C); 61.28 (3C); 59.15 (3C); 52.76 (2C, cyclen); 50.05(2C, cyclen); 47.50 (2C, cyclen); 44.43 (2C, cyclen); (m/z) HRMS (ESI^+): calculated 1069.5591 for $C_{55}H_{81}N_4O_{17}$ $(M + H)^+$, found 1069.5568.

1-(benzyloxycarbonyl)-4,7,10-*tris*(*2S*)-2-hydroxy-3-[4-(2-(2-(2-hydroxyethoxy)-ethoxy)ethoxy) phenoxypropyl]-1,4,7,10-tetraazacyclododecane, **23**

Synthesis of this compound was by a method analogous to that used for the preparation of **22** using **19** (503 mg, 1.64 mmol), and **21** (1.50 g, 4.94 mmol), to give **23** as a thick brown oil (1.93 g, quantitative). ^{13}C NMR ($CDCl_3$): δ 156.18 (1C, *C*=O); 152.89 (3C, Ph); 152.74 (3C, Ph); 136.49 (1C, Bn, *ipso*); 128.26 (1C, Bn); 127.75 (4C, Bn); 115.37 (6C, Ph); 115.27 (6C, Ph); 72.34 (3C); 70.47 (3C); 70.31 (1C); 70.03 (3C); 69.53 (3C); 67.76 (3C); 66.91 (2C); 66.80 (1C) 66.02 (3C); 61.33 (3C); 59.08 (2C); 58.00 (1C); 53.61 (2C, cyclen); 52.68 (2C, cyclen); 50.61 (2C, cyclen); 47.47 (2C, cyclen); (m/z) HRMS (ESI^+): calculated 1201.6378 for $C_{61}H_{93}N_4O_{20}$ $(M + H)^+$, found 1201.6383.

1,4,7-*tris*(2*S*)-2-hydroxy-3-[4-(2-(2-hydroxyethoxy)ethoxy)phenoxypropyl]-1,4,7,10-tetraazacyclododecane, **3**

Synthesis of this compound was by a method analogous to that used for the preparation of **2** [5], using **22** (396 mg, 0.37 mmol), and, cyclohexene (158 mg, 1.92 mmol), to give **3** as a thick brown oil (345 mg, quantitative). ^{13}C NMR (CD_3CN): δ 153.35 (3C, Ph); 153.19 (3C, Ph); 115.85 (12C); 72.93 (3C); 71.67 (1C); 71.13 (2C); 69.92 (3C); 68.30 (3C); 67.11 (3C); 61.66 (3C); 59.10 (3C); 52.50 (2C, cyclen); 51.80 (2C, cyclen); 50.20 (2C, cyclen); 44.20 (2C, cyclen); (m/z) HRMS (ESI^+): calculated 935.5223 for $C_{47}H_{75}N_4O_{15}$ $(M + H)^+$, found 935.5187.

1,4,7-*tris*(2*S*)-2-hydroxy-3-[4-(2-(2-(2-hydroxyethoxy)ethoxy)-ethoxy)phenoxypropyl]-1,4,7,10-tetraazacyclododecane, **4**

Synthesis of this compound was by a method analogous to that used for the preparation of **3** using **23** (457 mg, 0.39 mmol), and, cyclohexene (183 mg, 2.22 mmol), to give **4** as a thick brown oil (415 mg, quantitative). ^{13}C NMR (CD_3CN): δ 153.15 (1C, Ph); 153.09 (1C, Ph); 153.05 (1C, Ph); 152.98 (1C, Ph); 152.91 (1C, Ph); 152.85 (1C, Ph); 115.63 (2C, Ph); 115.59 (4C, Ph); 115.48 (6C, Ph); 72.54 (2C); 72.51 (1C); 70.72 (2C); 70.70 (1C); 69.78 (3C); 67.96 (3C) 61.56 (2C); 61.50 (3C); 71.27 (2C); 70.27 (1C); 69.66 (2C); 69.42 (1C); 59.00 (2C); 58.45 (1C); 50.10 (4C, cyclen); 44.05 (4C, cyclen).

Synthesis of receptor complex materials

Racemic 3-(glycidoxy)propyl-functionalised silica gel (70–230 mesh) was prepared by a literature procedure [19], as was 1,4,7-tris((2*S*)-2-hydroxy-3-phenoxypropyl)-1,4,7,10-tetraazacyclododecane, **2** [5].

Receptor complex **5**

To a stirred suspension of racemic 3-(glycidoxy)propyl-functionalised silica gel (70–230 mesh) (1.5 g, 1.1 mmol GPS g^{-1} material) in dry toluene (40 cm^3) a solution of **2** (2.57 g, 4.13 mmol) dissolved in dry toluene (10 cm^3) was added and the mixture was stirred at 60 °C for 2 days. The suspension was filtered, washed with dry toluene and subjected to soxhlet extraction with MeOH for 4 h to obtain **5** as a light brown powder. Residual **2** was recovered by evaporating the washing and soxhlet solvents. Found: C, 18.09; H, 2.67; N, 1.75% corresponding to a loading of 0.31 mmol g^{-1}. ^{13}C NMR (CPMAS): δ 159.7 (3C), 129.4 (6C), 120.0 (3C), 114.8 (6C), 72.5–51.1, br (21C), 23.2 (1C), 8.8 (1C). IR (KBr, DRIFT): $\nu_{(C-H)}$ 2942 cm^{-1}, 2875 cm^{-1}; $\nu_{(C=C)}$ 1602 cm^{-1}, 1497 cm^{-1}; $\delta_{(Ar-H)}$ 752 cm^{-1}, 690 cm^{-1}.

Receptor complex **6**

To a stirred suspension of racemic 3-(glycidoxy)propyl-functionalised silica gel (70–230 mesh) (2.0 g, 1.1 mmol g^{-1}) in dry acetonitrile (30 cm^3) a solution of **3** (6.2 g, 6.6 mmol) dissolved in dry acetonitrile (5 cm^3) was added and the mixture was stirred at 60 °C for 3 days. The suspension was filtered, washed with dry acetonitrile and subjected to soxhlet extraction with MeOH for 4 h to obtain **6** as a light brown powder. Found: C, 14.89; H, 2.47; N, 0.93% corresponding to a loading of 0.17 mmol g^{-1}. ^{13}C NMR (CPMAS): δ 157.5 (3C), 128.0–107.5 br (15C), 77.5–55.0, br (33C), 26.9 (1C), 12.5 (1C). IR (KBr, DRIFT): $\nu_{(C-H)}$ 2981 cm^{-1}, 2888 cm^{-1}; $\nu_{(C=C)}$ 1509 cm^{-1}, 1458 cm^{-1}; $\nu_{(Si-O-Si)}$ 955 cm^{-1}, $\delta_{(Ar-H)}$ 794 cm^{-1}.

Receptor complex **7**

This was prepared by the same method as used for, **6**, but using racemic 3-(glycidoxy)propyl-functionalised silica gel (70–230 mesh) (2.0 g, 1.1 mmol g^{-1}) and **4** (7.04 g, 6.6 mmol). Found: C, 11.85; H, 2.25; 0.54% N corresponding to a loading of 0.10 mmol g^{-1}. ^{13}C NMR (CPMAS): δ 157.5 (3C), 128.0–108 0.5 br (15C), 76.0–54.5, br (39C), 27.5 (1C), 12.5 (1C). IR (KBr, DRIFT): $\nu_{(C-H)}$ 2981 cm^{-1}, 2888 cm^{-1}; $\nu_{(C=C)}$ 1508 cm^{-1}, 1457 cm^{-1}; $\nu_{(Si-O-Si)}$ 953 cm^{-1}, $\delta_{(Ar-H)}$ 796 cm^{-1}.

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