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ARTICLE

Diastereoselective Recognition of α-Mannoside by Hemicryptophane Receptors†

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Four new enantiopure hemicryptophanes were synthesized and their absolute configuration was determined from experimental and calculated ECD spectra. Complexation properties of these receptors were studied toward six carbohydrate stereoisomers derived from glucose, galactose and mannose. All the receptors showed a better affinity for α-mannoside with association constants up to 2.5 10^3 M^{-1}. One of the receptor can complex almost exclusively α-mannoside facing to α-galactoside.

Introduction

Carbohydrates are important molecules omnipresent in living systems. One of their functions is to provide energy, but their chirality is also used for other applications: these compounds, which possess several stereogenic centers, are the most information-rich of biological molecules. For instance, 10^{12} possible oligomers can be built with 6 monomeric D-hexoses whereas only 4096 combinations are possible with nucleotides and $6x10^7$ with amino acids.[1-3] Living systems exploit this variability as a language called glycocode and use carbohydrates as labels.[4] The selective recognition of these labels by natural receptors through non-covalent interactions is the key phenomenon of many processes including protein folding,[5] cell-cell recognition,[6] infection by pathogens[7] or tumor metastases[8]. Thus, a great challenge for the chemist is to mimic these biological receptors and synthesize host molecules also able to recognize selectively carbohydrates thanks to the establishment of intermolecular interactions. This work can be very useful for a better understanding of the recognition processes in living systems. It could also have applications in medicine such as monitoring of carbohydrate concentration or diagnostic of diseases.[9] However, selective recognition of carbohydrates is very challenging for supramolecular chemists because these guest molecules possess complex three-dimensional structures, which often present subtle changes (such as the configuration of a single stereogenic center) so that large selectivity is difficult to achieve.

Among the monosaccharides involved in biological recognition processes, D-mannose plays a role of marker and is specifically recognized by several natural proteins such as concanavalin-A lectin and human mannose receptor.[6,10] This carbohydrate represents a label for N-glycans as it is frequently found at the terminal place of the sugar chain. Interestingly, for several dangerous viral infections like HIV, mannose is overexpressed in the glycan shield of the viral envelope. Consequently, the elaboration of a synthetic receptor selective towards mannose is very attractive for medicinal applications like antiviral therapies, elaboration of vaccines or diagnostic of diseases.[11-14] Nevertheless, despite the relevance of these biological applications, the number of artificial receptors able to recognize selectively mannose and its derivatives versus other carbohydrates is very limited.[11,15-21] Concerning the form of these few host molecules, most of them are open shape receptors and, to the best of our knowledge, only one cage receptor complexing selectively mannosides has been synthesized.[20] Yet, cage host molecules have already proved their remarkable ability to recognize efficiently carbohydrates and especially glucose derivatives.[3,22-26] One advantage of these container-shaped receptors is that they might encapsulate guest compounds, maximizing the contact area and hence the interactions between the two partners. Moreover, their proximity caused by the enfolding might favor the differentiation between structurally close substrates like carbohydrates.

Among the different classes of synthetic cage receptors, hemicryptophanes are chiral heteroditopic molecular cavities composed of a cyclotribenzylene (CTB) moiety connected to another unit by three linkers. These host molecules are able to complex various guest compounds such as zwitterions, ammoniums and ion-pairs.[27-30] By using their inherent chirality, they have also shown applications in the stereoselective recognition of neurotransmitters[31,32] and carbohydrates.[33,34] Indeed, enantiopure isomers of hemicryptophanes **1** and **2** (Figure 1) were previously synthesized and a study of their complexation properties towards α- and β-*n*-octyl-glucopyranosides has revealed good enantio- and diastereoselectivities: for instance host *M-SSS*-**2** binds α-*n*-octyl-glucopyranoside with an association constant of 595 M^{-1}, whereas no recognition is observed with the diastereomer *P-SSS*-**2**.[34] This remarkable ability to distinguish stereoisomers prompted us to pursue this work and to study the complexation properties of hemicryptophanes towards other carbohydrates like mannoside. Here we report the synthesis of four new enantiopure hemicryptophanes and the determination of their absolute configuration by circular dichroism and TD-DFT calculations. Their complexation properties towards mannose, glucose and galactose derivatives have been studied and bring out a good selectivity in favor of the α-D-mannoside: binding constant are up to one hundred times higher for α-D-mannoside than for β-D-galactoside.

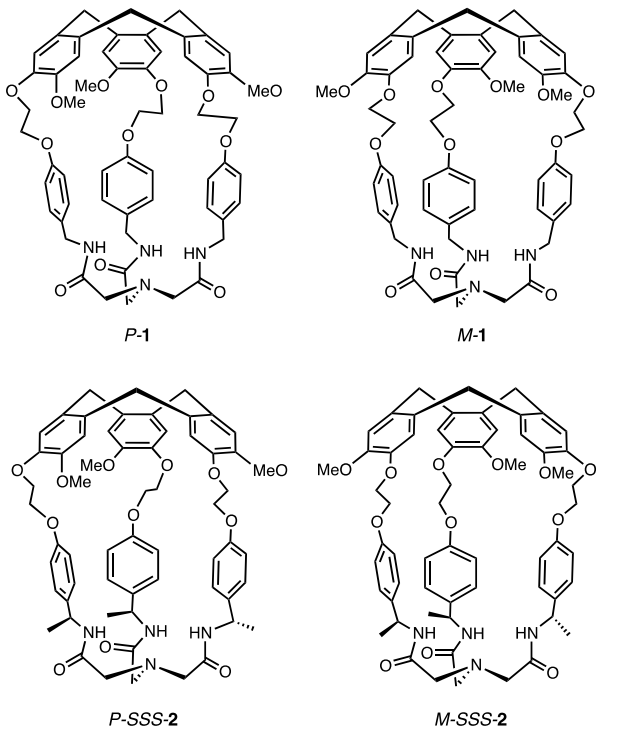
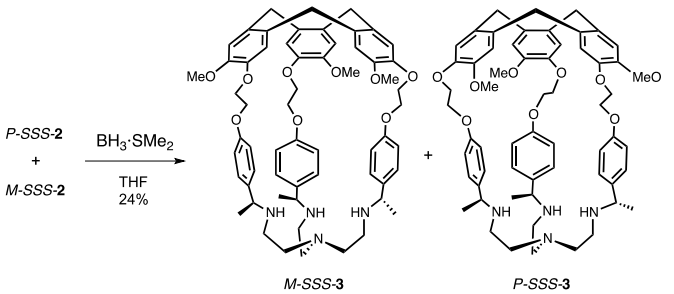


Figure 1. *P* and *M* enantiomers of hemicryptophane **1**; *P-SSS* and *M-SSS* diastereomers of hemicryptphane **2**.

Results and discussion

The synthesis of enantiopure hemicryptophanes is necessary for studying the enantioselective recognition of chiral guest molecules by these receptors. This requires a separation step because during the formation of the CTB unit, both *M* and *P* configurations are obtained (Figure 1). Concerning the diastereomers *M-SSS*-**2** and *P-SSS*-**2**, their separation has proved to be very difficult, since their migration properties on silica were very similar. Finally, the enantiopure receptors were obtained through preparative TLC, but this tedious method was only adapted for the separation of few milligrams of each isomers.[34] Thus, we decided to reduce the amide functions of the two diastereomers of **2** with $BF_3{\cdot}SMe_2$, to obtain two new compounds *M-SSS*-**3** and *P-SSS*-**3** (Scheme 1). This strategy is promising since on one hand, their separation might be easier and on the other hand, these receptors present the characteristics required for efficient sugar complexation; indeed they provide appropriate binding sites for both the polar hydroxyl groups (through hydrogen bonding with the amines) and the apolar surfaces (through C-H···π interactions with the aromatic rings of the hemicryptophane).[3] This strategy turned out to be successful, leading to an easier separation of the two diastereomers by column chromatography on silica gel (ΔR_f = 0.2) and providing at least hundred of milligrams of each isomer. To obtain all the stereoisomers of **3**, the *M-RRR*-**2** and *P-RRR*-**2** compounds synthesized previously[34] were also reduced and separated by column chromatography using the same procedure. The four isomers were obtained in seven steps, starting from the commercially available vanillyl alcohol with an overall yield of 3%.



Scheme 1. Synthesis of the *M-SSS* and *P-SSS* diastereomers of hemicryptophane **3**.

Electronic circular dichroism (ECD) spectra of the four enantiopure receptors were recorded in $CHCl_3$ at 298 K (Figure 2). Each spectrum presents a classical behaviour for hemicryptophanes, which consists of two exciton patterns roughly centred on the isotropic absorption of the ^1L_B (290 nm) and ^1L_A (240 nm) transitions. The absolute configurations of hemicryptophanes are usually determined by comparing the sign of the bands of the experimental ECD spectrum around the ^1L_A transition with those of the calculated ECD spectrum. As these signs are poorly sensitive to the substituent effect in the ^1L_A transition area, they are usually compared to calculated ECD spectra of a reference CTB, previously obtained by Collet and co-workers.[35-37] Based on these previous works, the *P* configuration (respectively the *M* configuration) can be

assigned to the molecules having in their ECD spectra a sequence of signs negative–positive (respectively positive-negative) from high to low energy in the ^1L_A region.[34-39] Thus the first eluted compounds (respectively the second ones) correspond to the *P-RRR* and *M-SSS* enantiomers (respectively the *P-SSS* and *M-RRR*).

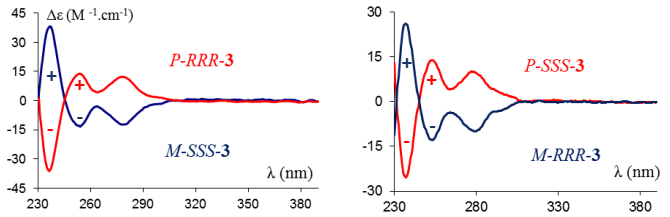


Figure 2. Experimental ECD spectra ($CHCl_3$, 298 K) of the isomers of **3** (left: first eluted compounds; right: second eluted compounds).

To confirm these attributions, calculation of the ECD spectra of *M-SSS*-**3** and *M-RRR*-**3** was performed with the TD-DFT method, using three hybrid functionals (B3LYP, BH&HLYP and CAM-B3LYP) with the SVP basis set (Figure 3). As usually observed, the calculated CD spectra are shifted to some extent when compared to the experimental ones.[40-41] The functionals CAM-B3LYP and BH&HLYP agree well with the experimental spectra, while B3LYP underestimates the rotatory strengths of the transitions and redshifts them by about 20 nm. Nevertheless, the sign sequence is the same for all of them and matches with those of experimental ECD spectra, which confirms the configurational assignment.

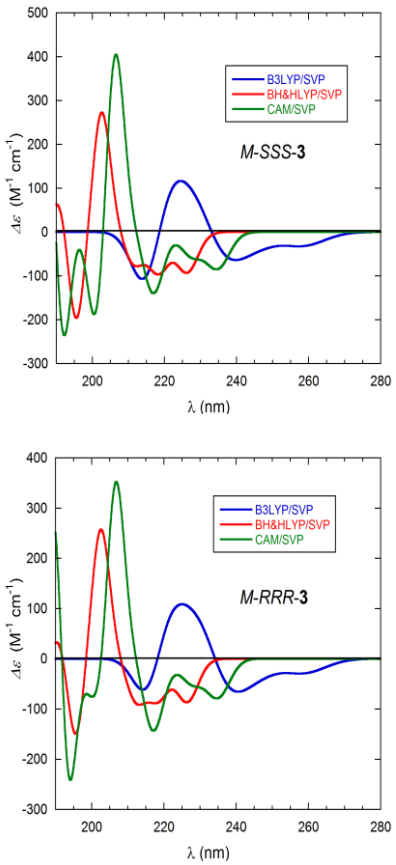


Figure 3. TD-DFT calculated ECD spectra of *M-SSS*-**3** and *M-RRR*-**3** using three functionals.

To study the abilities of these hosts to discriminate closely related carbohydrates, we chose as guest molecules six stereoisomers, which consist of the two n-octylpyranoside anomers of glucose (OctαGlc and OctβGlc), mannose (OctαMan and OctβMan) and galactose (OctαGal and OctβGal) (Figure 4).

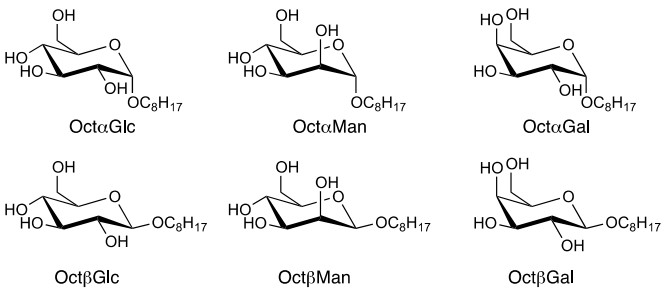


Figure 4. Structure of the carbohydrates used for the complexation studies.

Binding constants between the four receptors and the six carbohydrates were determined by ^{1}H NMR titration experiments in $CDCl_3$ at 298 K. In all cases only one set of signals was observed for the complex and for the receptor, showing that host-guest exchange is fast on the NMR time scale. Complexation induced shifts of either the OMe or the aromatic protons of the linkers were plotted as a function of the

guest/host ratio and these curves were fit with the HypNMR2008 software,[42] using a 1:1 model (Figure S-1). The resulting binding constants K_a are reported in Table 1.

Table 1. Binding constants K_a (M^{-1}) for the 1:1 complexes formed between the different isomers of host **3** and the carbohydrate guests.[a]

Guest	*M-SSS*-**3**	*P-SSS*-**3**	*P-RRR*-**3**	*M-RRR*-**3**
OctαMan	1410	1648	1544	2511
OctβMan	804	387	967	641
OctαGlc	213	141	95	83
OctβGlc	378	400	722	270
OctαGal	29	112	142	22
OctβGal	[b]	13	68	59

[a] K_a determined by fitting ^{1}H NMR titration curves ($CDCl_3$, 500 MHz, 298 K) on aromatic or OMe protons with HypNMR2008; estimated error 10%. [b] No complexation detected.

From these association constants, several conclusions can be drawn. Firstly, the four molecular receptors recognize preferentially mannose derivatives with interesting diastereoselectivities as discussed below. An overall trend of the selectivity towards the different guests can be observed with the following order: OctαMan > OctβMan > OctβGlc > OctαGlc > OctαGal ≥ OctβGal. This hierarchy is in good agreement with the different abilities of the guests to be involved in intermolecular hydrogen bonds. This capacity has been estimated by studying the intramolecular hydrogen bonds occurring in the six carbohydrate structures and ability of these substrates to aggregate.[20,43] The more the saccharide can make H-bonds with other molecules, the higher is the binding constant. This highlights the fact that hydrogen bonding is crucial for the recognition process between hemicryptophanes and carbohydrates.

Secondly, the chirality of the hemicryptophanes also plays a role in the recognition process and influences the discrimination between the different carbohydrates. Indeed, the isomers of hemicryptophane **3** have different levels of selectivity. For example, *M-SSS*-**3** is a much better receptor than *M-RRR*-**3** to differentiate OctαGlc from OctβGal since the selectivity is absolute with the *M-SSS*-**3** isomer, whereas it is not significant with the *M-RRR*-**3** cage. On the other hand, hemicryptophane *M-RRR*-**3** is more appropriate than *P-RRR*-**3** for the differentiation of OctαGal from OctαMan since the ratio $K_{a(Oct\alpha Man)}/K_{a(Oct\alpha Gal)}$ is 10 times higher with the first cage. Thus, according to the desired selectivity, we can choose the more appropriate isomer of hemicryptophane **3** as receptor.

A deeper study of the selectivities can be made, according to the different carbohydrates: i) First we can observe modest diastereoselectivity between the anomers of the different saccharides: the α-mannoside is better recognized by the four cages than its β anomer whereas it is the opposite for the glucoside derivatives. These observations are also in agreement with the different abilities of the anomers to be involved in intra and intermolecular hydrogen bonds.[20,43] The *P-RRR*-**3** (respectively *P-SSS*-**3**) hemicryptophane is the most appropriate receptor for discriminating the two glucose anomers (respectively mannose anomers) with a 1:8 (respectively 1:4) diastereoselectivity. The selectivity between the α and β-galactoside is not discussed here because the binding constants are low for the two anomers, which makes the selectivity issue less relevant. ii) Then, the comparison of two different carbohydrates, which differ only by the configuration of one asymmetric carbon, leads to very interesting diastereoselectivities: for instance, receptor *P-SSS*-**3** binds preferentially OctβGlc from OctβGal with an important 1:31 diastereoselectivity. This discrimination is even exclusive with the *M-SSS*-**3** receptor. Then, the *M-RRR*-**3** hemicryptophane recognizes selectively and efficiently OctαMan from OctαGlc with higher association constant (2511 M^{-1}) and a remarkable 1:30 diastereoselectivity. This selectivity is all the more important given that the structures of the two carbohydrates differ only in the configuration of one stereogenic center. iii) Higher diastereoselectivities can be observed by comparing carbohydrates differing in the configuration of two asymmetric carbons: for instance, OctβMan can be recognized exclusively by receptor *M-SSS*-**3** towards OctβGal with a significant binding constant of 804 M^{-1}. The most interesting result is obtained with the receptor *M-RRR*-**3** which can complex almost exclusively OctαMan facing to OctαGal with the higher association constant K_a= 2511 M^{-1}.

Conclusions

In this work, we have synthesized four new enantiopure hemicryptophane isomers able to discriminate, with high diastereoselectivities, six stereoisomeric derivatives of glucose, galactose and mannose. Selectivity in favor of the α-mannoside was observed for all the receptors, which can complex this carbohydrate in chloroform with good association constants (> 10^3 M^{-1}). Moreover, it was noticed that the level of selectivity between two substrates varied according to the receptor used. As a consequence, depending on the selectivity desired, it is possible to choose the most appropriate hemicryptophane isomer for further applications.

Experimental

Synthetic procedures

The reduction was carried out under argon atmosphere and THF was dried and degassed on a solvent station by passage through an activated alumina column followed by an argon flush. Compound **2** was prepared according to the published procedure.[34]

Synthesis of hemicryptophane 3

The previously obtained *M-SSS*-**2**/*P-SSS*-**2** mixture[34] (307 mg, 0.296 mmol) was dissolved in a solution of BH_3•SMe_2 in THF (2 M, 15 mL, 30 mmol). The solution was stirred for four days at 65 °C, then additional 8 mL of the borane solution were added and the solution was stirred for 2 more days. After cooling to room temperature, methanol (8 mL) and aqueous 1M HCl (1 mL) were successively added dropwise. The solution

was then heated at 40 °C for one day. The solvents were removed under vacuum, the residue was dissolved in chloroform (10 mL), methanol (7 mL) and aqueous 1M HCl (1 mL) and the mixture was stirred for two days at 60 °C. The solvents were removed and the crude products of four parallel reactions were dissolved in chloroform (50 mL) and 1M aqueous NaOH (50 mL). The organic layer was separated and the aqueous phase was extracted with chloroform (3 x 40 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel (chloroform/methanol/triethylamine 90/10/2) to give *M-SSS*-**3** and *P-SSS*-**3** as white solids (142 mg, 12% for *M-SSS*-**3** and 140 mg, 12% for *P-SSS*-**3**).

M-SSS-**3** hemicryptophane (1st eluted): ESI-MS m/z: 993.5349 ($[M + H]^+$, calculated : 993.5372 for $C_{60}H_{73}N_4O_9$). ^{1}H NMR ($CDCl_3$, 298 K, 500.10 MHz) δ 6.97 (s, 3H, ArH), 6.93 (d, 6H, J = 8.0 Hz, ArH), 6.80 (s, 3H, ArH), 6.57 (d, 6H, J = 8.0 Hz, ArH), 4.74 (d, 3H, J = 13.7 Hz, $ArCH_2Ar$), 4.37-4.41 (m, 3H, $O(CH_2)_2O$), 4.30-4.34 (m, 3H, $O(CH_2)_2O$), 4.15-4.21 (m, 6H, $O(CH_2)_2O$), 3.64 (s, 9H, OMe), 3.52 (m, 6H, $ArCH_2Ar$ and NCH), 2.36 (m, 6H, NCH_2), 2.24 (m, 6H, NCH_2), 1.19 (d, 9H, J = 6.5 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 298 K, 125.76 MHz) δ 157.5 ($C_{Ar}O$), 148.9 ($C_{Ar}O$), 146.5 ($C_{Ar}O$), 138.2 (C_{Ar}), 133.4 (C_{Ar}), 132.0 (C_{Ar}), 127.5 (C_{Ar}), 117.5 (C_{Ar}), 115.2 (C_{Ar}), 114.0 (C_{Ar}), 68.2 (OCH_2), 67.4 (OCH_2), 57.7 (NCH), 56.1 (OMe), 54.9 (NCH_2), 45.6 (NCH_2), 36.6 ($ArCH_2Ar$), 23.6 (CH_3). IR ν = 2930, 2863, 2832, 1608, 1509, 1457, 1261, 1218 cm^{-1}. $[\alpha]^{25}_D$ = –94 (*c* 0.01, CH_2Cl_2).

P-SSS-**3** hemicryptophane (2nd eluted): ESI-MS m/z: 993.5370 ($[M + H]^+$, calculated : 993.5372 for $C_{60}H_{73}N_4O_9$). ^{1}H NMR ($CDCl_3$, 298 K, 500.10 MHz) δ 7.05 (s, 3H, ArH), 6.85 (s, 3H, ArH), 6.77 (d, 6H, J = 8.0 Hz, ArH), 6.44 (d, 6H, J = 8.0 Hz, ArH), 4.78 (d, 3H, J = 13.6 Hz, $ArCH_2Ar$), 4.51-4.55 (m, 3H, $O(CH_2)_2O$), 4.36-4.40 (m, 3H, $O(CH_2)_2O$), 4.20-4.24 (m, 3H, $O(CH_2)_2O$), 4.11-4.16 (m, 3H, $O(CH_2)_2O$), 3.65 (s, 9H, OMe), 3.57 (d, 3H , J = 13.6 Hz, $ArCH_2Ar$), 3.26 (m, 3H, NCH), 2.27-2.40 (m, 8H, NCH_2), 2.11 (b, 4H, NCH_2), 1.16 (d, 9H, J = 6.5 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 298 K, 125.76 MHz) δ 157.5 ($C_{Ar}O$), 148.6 ($C_{Ar}O$), 146.4 ($C_{Ar}O$), 138.4 (C_{Ar}), 133.0 (C_{Ar}), 131.9 (C_{Ar}), 127.5 (C_{Ar}), 116.9 (C_{Ar}), 115.2 (C_{Ar}), 113.9 (C_{Ar}), 67.9 (OCH_2), 67.6 (OCH_2), 57.5 (NCH), 56.0 (NCH_2), 54.3 (OMe), 45.8 (NCH_2), 36.7 ($ArCH_2Ar$), 23.3 (CH_3). IR ν = 2956, 2854, 1608, 1509, 1457, 1261, 1216 cm^{-1}. $[\alpha]^{25}_D$ = +57 (*c* 0.01, CH_2Cl_2).

Enantiomers *M-RRR*-**3** and *P-RRR*-**3**, have been synthesized using the same procedure, starting from the previously obtained *M-RRR*-**2**/*P-RRR*-**2** mixture.[34] As these compounds are the enantiomers of the products presented above, ^{1}H NMR, ^{13}C NMR, IR spectroscopy and ESI-MS spectrometry gave the same results. $[\alpha]^{25}_D$(*P-RRR*-**3**) = +88 (*c* 0.01, CH_2Cl_2). $[\alpha]^{25}_D$(*M-RRR*-**3**) = –52 (*c* 0.01, CH_2Cl_2).

Complexation of octyl-D-gluco-, galacto- and manno-pyranosides by hemicryptophane 3.

Solutions of hosts (1.0 mM in $CDCl_3$, 500 μL) were titrated in NMR tubes with small aliquots of solutions of guests (10 mM in $CDCl_3$). Complexation induced shifts $\Delta\delta$ of the aromatic protons or the OCH_3 protons of the host were measured after each addition and plotted as a function of the guest/host ratio.

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Notes and references

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† Electronic Supplementary Information (ESI) available: ^{1}H and ^{13}C NMR spectra; titration curves; HypNMR2008 reports for the determination of K_a values. See DOI: 10.1039/b000000x/

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