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Molecular Tweezers for Dicarboxylic Acids Based on a Saddle-Shaped Metallomacrocyclic Platform

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Abstract

A new metal containing molecular receptor was prepared from a 15-membered nickel(II) macrocyclic cyclidene platform and two cyclic tetramine (cyclen) recognition cites. In the saddle shaped conformation of the platform, the cyclen receptors are positioned for ditopic binding of difunctional substrates. NMR titration experiments demostrate that the molecule binds dicarboxylic acids in DMSO with apparent equilibrium constants ranging from 10 to 10^4 M^{-1}. Incusion of dicarboxylates into the protonated macrocyclic host is shape-selective, with *cis*-1,2-dicarboxylates (succinate, maleate, and o-phthalate) being the best guests.

Introduction

Molecular recognition of anions is a rapidly growing area of supramolecular chemistry [1–4]. Unlike metal cations, anions ordinarily do not form strong coordination bonds with their "ligands" (receptors), thus multiple interactions between the anion and the receptor are needed for efficient anion recognition. Di- and polycarboxylates remain among the most attractive targets for molecular recognition [5–30], since the presence of several carboxylate functional groups is typical for a variety of biomolecules, ranging from simple aliphatic di- and tricarboxylic acids involved in the citric acid cycle, to amino acids and proteins. Indeed, ditopic receptors bearing two guanidinium groups selectively recognize aspartate pairs in α-helical oligopeptides, indicating the potential utility of dicarboxylate receptors in protein surface recognition [31, 32].

One of the challenges in designing ditopic receptors for dicarboxylic acids is to accomplish shape complementarity between the functional groups in the guest and the binding sites in the host. The first examples of dicarboxylate binding systems, which were reported by the research groups of Lehn [33–35], Kimura [36], Breslow [37], and Schmidchen [38–40] in the early 1980's, clearly demostrate three approaches to properly positioning two carboxylate binding sites: incorporating polyammonium receptors into the macrocycles [34–36, 38], attaching two receptor groups to a linear spacer [33, 37, 39], or placing the binding groups on the walls of a cleft [40]. Encapsulation of the guests into the macrocycles, further extended to their three-dimensional recognition by cryptands and cages [15, 20, 23, 24, 41–45], offers excellent binding affinities and selectivities due to a high degree of preorganization of the hosts. This route, however, is synthetically challenging. In contrast, ditopic receptors connected by a linear spacer are relatively easy to synthesize, but they allow for only limited preorganization of the host. Even though the flexibility of the hosts does not necessarily compromise their affinity for the guests ("induced fit" binding) [12, 46], and substantial size selectivity can also be accomplished in bimolecular 1:1 complexation of dicarboxylates with rigidly linked hosts [47, 48], the composition and structure of the host-guest adducts is not easily predictable in these cases. A variety of crystalline oligomers were isolated in the solid state (see [49–51] for some examples), thus making these systems perfectly suitable for crystal engineering, but not always appropriate for shape selective substrate recognition in solutions. Rigid cleft-like scaffolds, poetically advocated by Schmidtchen ("Though encapsulation of ions in cages was first to rely on, the better perspective for being selective have locular hosts for anions" [40]), can be considered as a reasonable, synthetically accessible compromise between the first two approaches. Functionalized clefts successfully recognize dicarboxylate guests [5, 40, 52–56], and the search for new spacers continues to yield ditopic receptors with desirable properties [6, 8, 11, 13, 16, 17, 22, 27–30, 57].

We present the preparation of a ditopic receptor for dicarboxylic acids based on a metal-containing macrocyclic cleft. Metal ions were shown to play several advantageous roles in designing dicarboxylate receptors: (1) self-assembly of polyfunctional receptors was accomplished via coordination of several receptor fragments to the metal ions [9, 25, 26, 58, 59]; (2) direct coordination to the metal centers was used for carboxylate binding [23, 45, 60-63]; (3) binding affinities were increased due to favorable electro-

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static interactions between positively charged metal centers in metallocenes and the anionic guests [8, 64, 65]; and (4) metals served as redox- [8, 64, 65], fluorescent [9], or colorimetric [59] reporters of carboxylate binding events. In our design, the metal ion is incorporated into the macrocyclic platform with high affinity, so that no loss of the metal is expected during the recognition process. Saddle shaped cyclidene macrocycles (Figure 1) [66] were selected as scaffolds for the clefts. Two tetraaza macrocyclic fragments (cyclens) were used as receptor sites (Figure 1, compound **2**), because protonated polyamine macrocycles are known to strongly bind dicarboxylates due to the combination of electrostatic interactions and hydrogen bonding [10, 14, 23, 34–36, 67–70]. The distinctive features of our scaffold include the relative flexibility of the cleft, which in principle allows for the regulation of the substrate affinity and selectivity via conformational changes in the cyclidene platform, and the positioning of the guest right above the metal center, thus suggesting potential involvement of the metal in the catalytic regioselective transformations of the substrate. Indeed, the 15-membered cyclidene platforms can adopt both "open" (planar) and "closed" (saddle shaped) conformations [66]. This non-rigidity is needed in order to eventually obtain switchable receptors. The question arises whether these relatively flexible functionalized clefts can act as ditopic receptors. The results of dicarboxylic acid binding studies with a difunctional receptor **2** as a host are reported in this manuscript.

Experimental

Chemicals (reagent grade) and anhydrous solvents were purchased from Aldrich or Acros and used as received. 1,4,8,12-Tetraazacyclododecane (cyclen) was purified by vacuum sublimation and stored under an inert atmosphere. Starting dimethoxy cyclidene **1** and a bis-dimethylamino cyclidene **3** were synthesized according to the published procedures [71].

NMR spectra were recorded on a Bruker AM-300 spectrometer, IR spectra on a Mattison 1000 FTIR spectrometer, and UV-Vis spectra on a Hitachi U-2000 spectrophotometer. Mass-spectra (electrospray ionization) were measured at Mass Consortium (San Diego, CA). Elemental analyses were performed by Desert Analytics, Tucson, AZ.

Synthesis of [7,13-dimethyl-6,14-bis[1-(1,4,7,10-tetraazacyclododec-1-yl)-ethylidene]-1, 5, 8, 12-tetraazacyclopentadeca-4,7,12,15-tetraenato] nikel(II) hexafluorophosphate, **2**$(PF_6)_2 \cdot 4H_2O$.

Under an inert atmosphere, sublimed cyclen (0.572 g, 3.32 mmol) was dissolved in dry CH_3CN (10 mL) and added dropwise to the solution of dimethoxy cyclidene **1**$(PF_6)_2$ (0.330 g, 0.475 mmol) in 10 mL of dry CH_3OH. The reaction mixture immediately turned dark red. The reaction mixture was stirred for 0.5 hr at room temperature, and then the solvents were removed under vacuum. The residue was redissolved in dry CH_3OH (2 mL) and gradually added to a large excess of dry ether (400 mL). The orange precipitate was formed, which was immediately filtered and carefully washed with ether. Yield 0.33 g (71.6%). Anal: Calcd. for $C_{33}H_{70}N_{12}NiO_4P_2F_{12}$ (**2**$\cdot 4H_2O$), %: C, 37.83; H, 6.73; N, 16.04. Found: C, 37.26; H, 6.29; N, 15.94. Mass spectrum (electrospray): 685 (M^+), 829 (M + PF_6), 975 (M + 2PF_6). The compound is moisture sensitive and decomposes in the air over a period of several hours. The complex is stable in the dry box over a period of several weeks.

NMR titration experiments. 1 mM solution of host **2** in deuterated DMSO was prepared, and a 0.5 mL aliquot was transferred to a 5mm NMR tube. After the spectrum was recorded, aliquots of 50 mM DMSO solution of a guest were added, in 2.5 μL portions at the initial part of the titration curve (during addition of the first equivalent of the guest), and in 5 μL portions at the remaining part of the curve, until the saturation behavior was observed. Spectra were recorded after each addition. Association constants were obtained by nonlinear least-squares fit of the titration curve plot for reversible 1:1 complexation [72, 73].

Results and discussion

Synthesis

Preparation of the receptor **2** is based on a general reaction of the O-alkylated Jäger macrocycle **1** with primary or secondary amines developed by Busch and co-workers [66, 71]. We carried out the reaction of ([Ni[$(MeOEthi)_2Me_2$[15]tetraeneN_4]]$(PF_6)_2$) (**1**) with cyclen in a 1:1 acetonitrile-methanol mixture (Scheme 1). In order to avoid the substitution at several amino groups of cyclen, the solution of the activated Jäger complex **1** was mixed with a concentrated solution of a large (at least 5-fold) excess of cyclen. A competitive side reaction, base-promoted deacylation of **1** [74, 75], became a predominant process in the presence of moisture; a similar process is likely to cause air- and moisture-sensitivity of **2**. If the reaction was carried out in dry solvents under inert atmosphere, no deacylation was observed, and pure complex **2** was isolated, as evidenced by elemental analysis and mass spectroscopy. Proton NMR, although somewhat broadened (thus rendering the integration useless) and fairly complex, clearly shows the presence of both the nickel(II) cyclidene platform and the cyclen substituents in compound **2** (Figure 2a). The absence of a characteristic doublet at 4.8 ppm, indicative of a bridgehead proton in the deacylated product [75], confirms that no loss of acyl substituents from the cyclidene platforms has occurred. The complexity of the NMR spectrum of **2** can be attributed to the tautomeric equilibria in a DMSO solution of this complex, as discussed below. The UV-Vis spectrum of complex **2** is similar to the UV-Vis spectrum of its analog **3** missing additional potential complexation sites. Consequently, the nickel(II) ion remains trapped within the cyclidene platform in **2**, rather than being scrambled between cyclidene and cyclen sites.

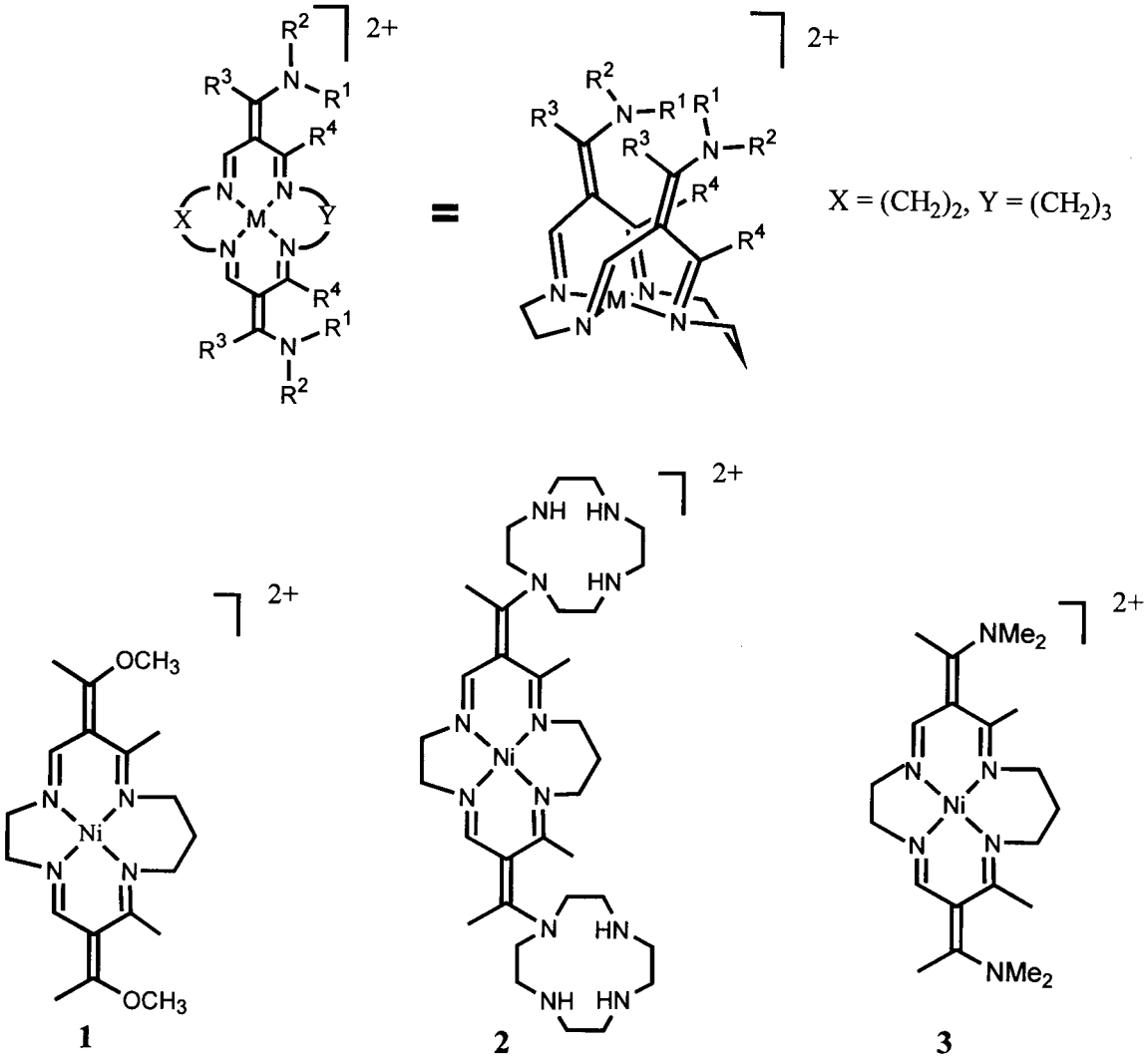
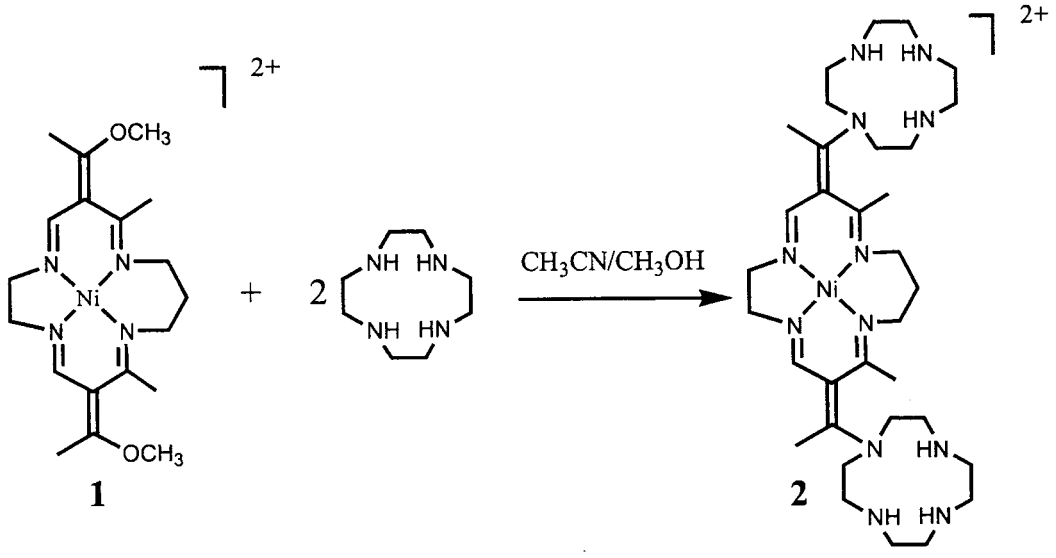


Figure 1. Cyclidene macrocyclic complexes.



Scheme 1.

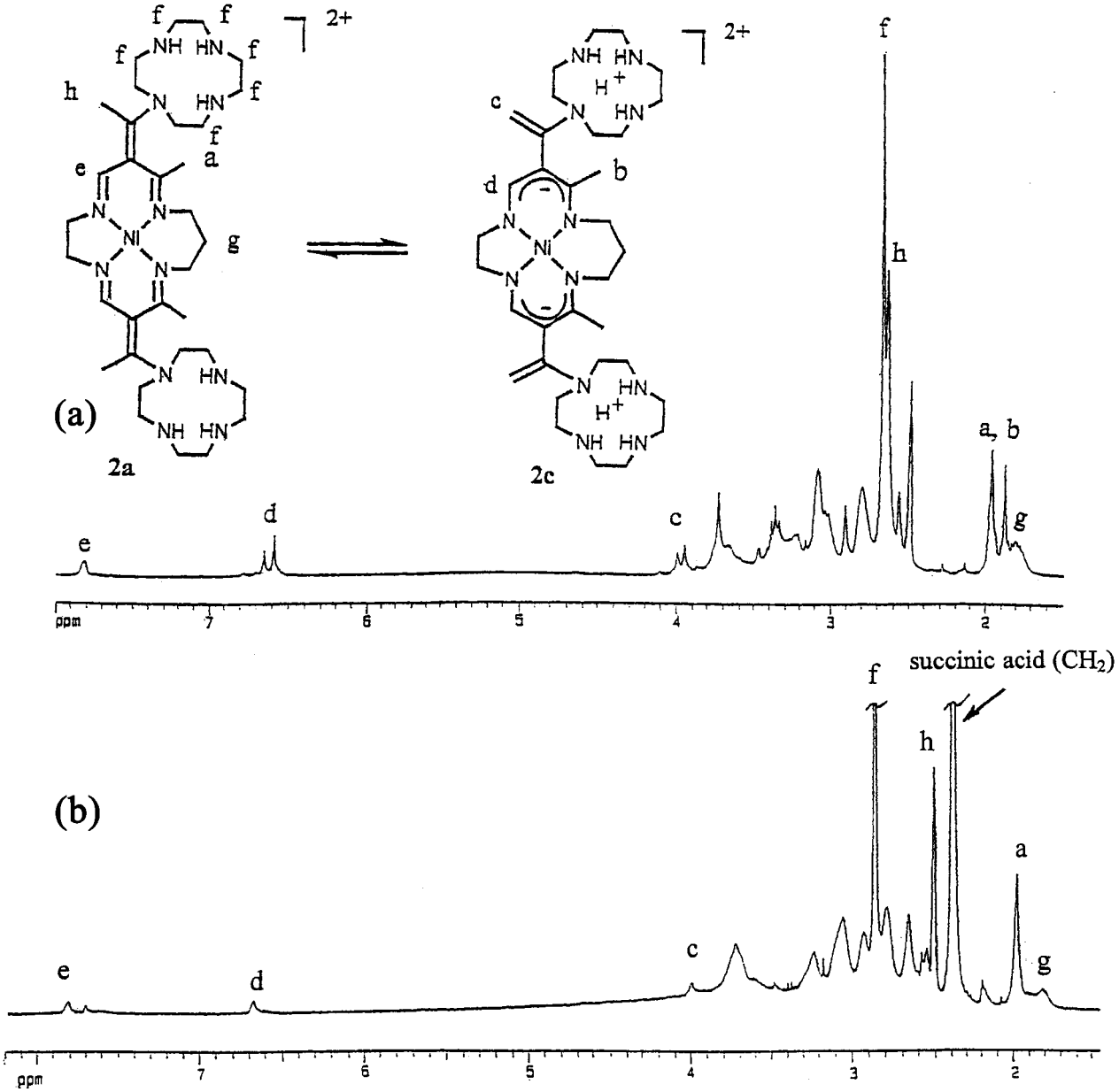
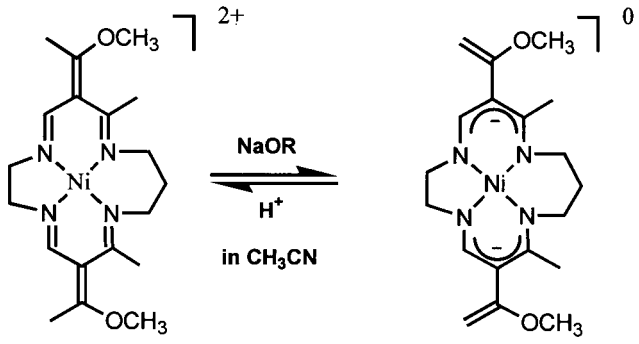


Figure 2. ^{1}H NMR spectra of **2** in DMSO: (a) 0.01 M solution of pure **2**; (b) 4.2 mM solution of **2** containing a 6-fold excess of succinic acid.

Protonation-deprotonation equilibria

Complex **2** has both acidic and basic sites within the molecule. The methyl groups in the R^3 positions of the cyclidene platforms can be deprotonated, as was shown by previous work from Busch's research group. O-Alkylated Jäger complexes (cyclidene precursors) were quantitatively and reversibly deprotonated with a strong base NaOR [76, 77] (Scheme 2), and one of the deprotonated complexes was structurally characterized [77]. Deprotonation of *N*-alkylated cobalt(II) cyclidene complexes was proven to be the first step in the autoxidation of their dioxygen adducts [78]. Cyclen is a strong base (pK_1 = 10.5, pK_2 = 9.6) [79]; thus the receptor arms in **2** are potentially capable of deprotonating the CH_3 groups of the cyclidene platform. The ^{1}H NMR spectrum of **2** (Figure 2a) is in agreement with with this hypothesis: the presence of three kinds of vinyl protons (one signal, e, at 7.81 ppm, is typical of a neutral 6-membered unsaturated chelate ring in cyclidenes, and two signals, d, at 6.65 and 6.59 ppm, appear in the positions characteristic of the deprotonated chelate ring) and at least two kinds of R^4 methyl protons (a, b), as well as the presence of two signals at 3.95 and 4.00 ppm typical of $=CH_2$ groups (R^3) in the deprotonated cyclidenes, suggested that complex **2** exists as a tautomeric mixture of three complexes: **2a**, **2b**, and **2c** (Scheme 3). The fraction of the forms with deprotonated cyclidene platform depends on the excess of cyclen used for the synthesis of **2**. At least 50% of the product was present in tautomeric forms **2b** and **2c** (resulted from partial or complete intramolecular deprotonation of the R^3 substituents in the cyclidene platform). Addition of acids to the solution of **2** resulted in a substantial decrease in intensities of the signals assigned to the species with the deprotonated $=CH_2$ groups in R^3 positions (tautomers **2b** and **2c**), and in



Scheme 2.

substantial shifts of many signals in the spectrum (Figure 2b). When two equivalents of a strong acid (triflic) were added to the solution of **2**, signals a and b merged, and signals c and d completely disappeared. These spectral changes were reversible. Similarly, reversible changes in the UV-Vis spectra of **2** were observed upon addition of two equivalents of trichloroacetic acid to the DMSO solution (Figure 3).

The possibility of an intramolecular proton transfer from a methyl group to the cyclen residue in compound **2** was confirmed by the experiments on intermolecular proton transfer from a dimethylcyclidene $[Ni[(N(CH_3)_2Ethi)_2Me_2[15]tetraeneN_4]](PF_6)_2$ (**3**) to free cyclen in solutions. The UV-Vis spectrum of **3** in DMSO (Figure 4) changes upon addition of cyclen. Reversibility of this process was shown by the addition of an excess of CCl_3COOH to the mixture of **3** and cyclen. The spectral changes are similar to those observed for complex **2** (Figure 3), which is in agreement with structural similarities of chromophores in **2** and **3** (both in their deprotonated and protonated forms). It appears that free cyclen is capable of deprotonating complex **3** in a DMSO solution (Scheme 4). This suggestion was further confirmed by ^1H NMR experiments in d_6-DMSO (Figure 5). Addition of cyclen to the solution of complex **3** causes the appearance of the second peak of vinyl protons at 6.5 ppm (2H), which belongs to the deprotonated form of this complex (**4**). A signal of the methylene group of $CH_2{=}CN(CH_3)_2$ resulting from the deprotonation of a methyl group at the R^3 position appears at 3.76ppm and partially overlaps with cyclen NH protons. The signal of a CH_3 group (R^4) of CH_3-$CN(CH_2)_2$ at 2.45 ppm drops in intensity. Addition of an excess of CCl_3COOH to this solution restores the original spectrum, showing that the deprotonation is reversible. Similar ^1H NMR spectral changes due to reversible deprotonation of the cyclidene precursor **1** were reported by Busch and co-workers [76].

The free tetraaza macrocycle cyclen has four secondary amino groups which can be protonated, with the first two protonation constants close to each other and typical of a strong base [79]. Attachment of cyclen residues to the cyclidene platform modifies their acid-base properties. Indeed, the tertiary amino group in complex **2** is involved in extensive conjugation with the cyclidene and essentially has an amide character. The basicity of this group is further reduced by the dipositively charged nickel(II) center in the cyclidene. As a result, NMR titration of complex **2** in d_6-DMSO with

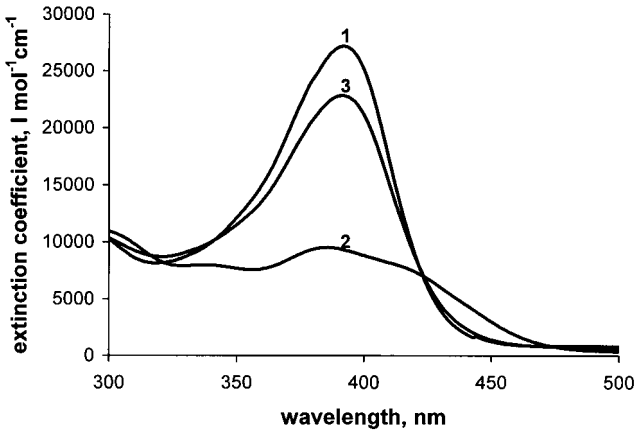
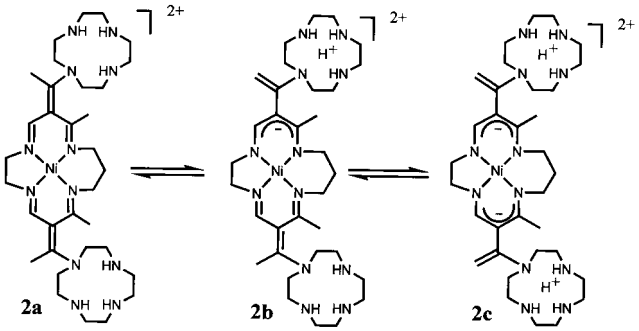


Figure 3. UV-Vis spectra of **2** (1.8×10^{-5} M) in DMSO: 1 – solution of the pure complex; 2 – solution of complex **2** in the presence of an 8-fold molar excess of cyclen; 3 – solution (2) neutralized with 8 equivalents of trichloroacetic acid.



Scheme 3.

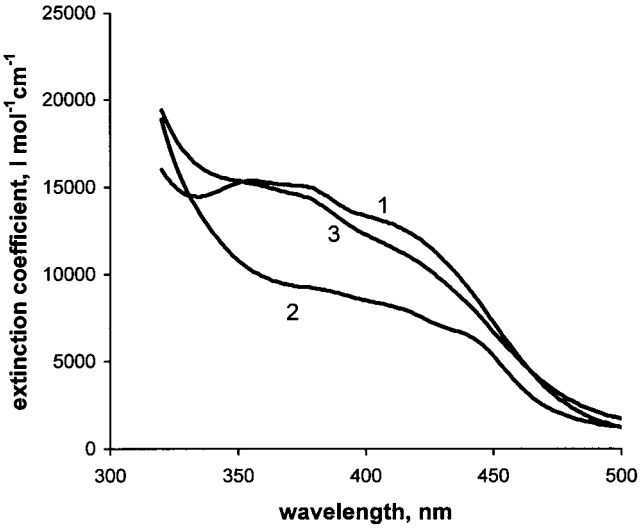


Figure 4. UV-Vis spectra of **3** (4.7×10^{-5} M) in DMSO: 1 – solution of the pure complex **3**; 2 – solution of complex **3** in the presence of an 8-fold molar excess of cyclen; 3 – solution (2) neutralized with 8 equivalents of trichloroacetic acid.

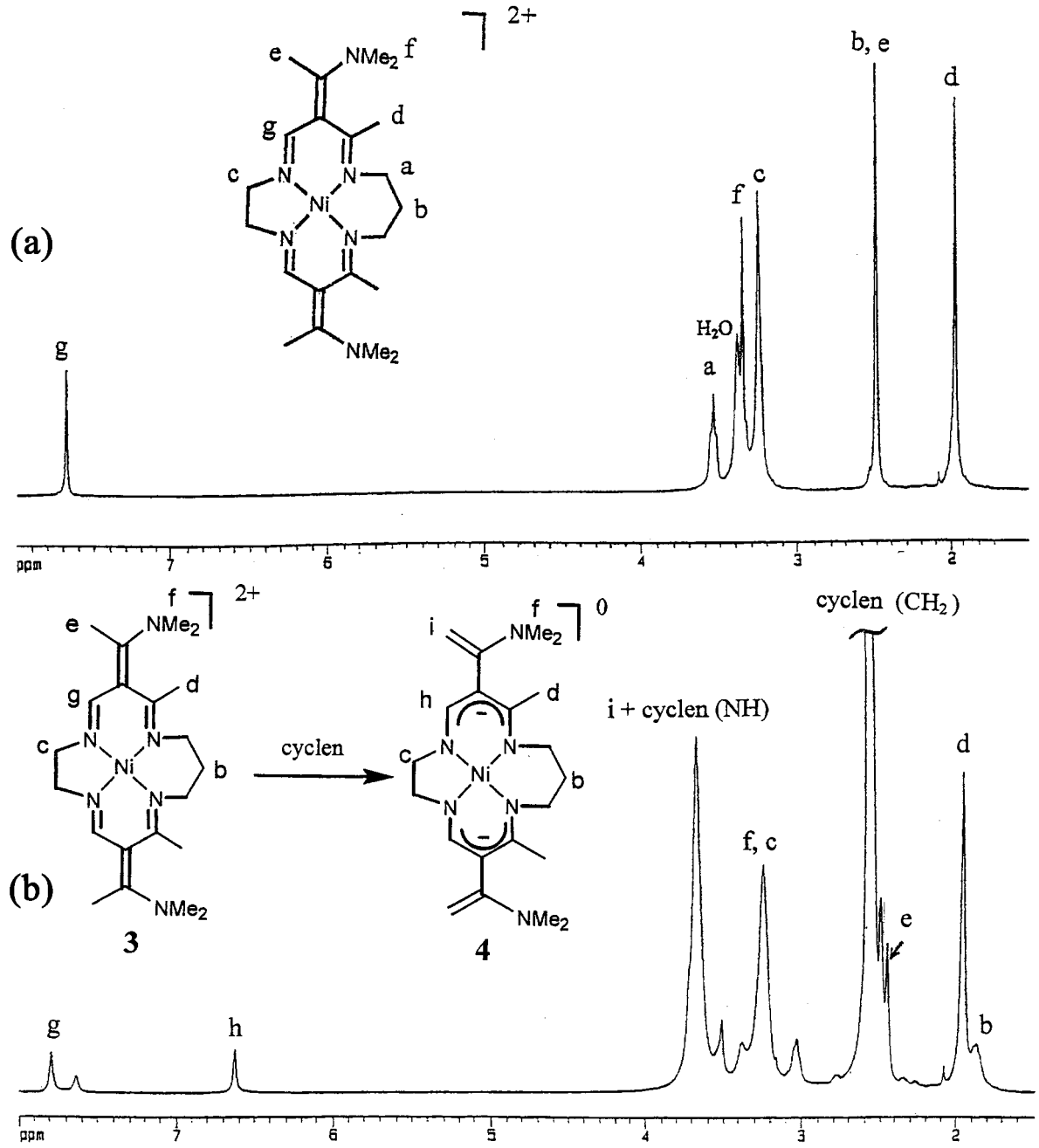
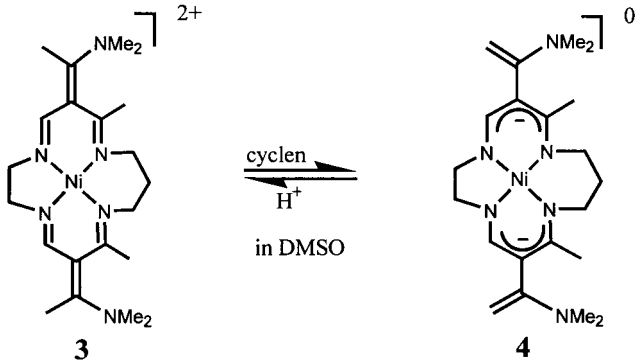


Figure 5. ^{1}H NMR spectrum of **3** in DMSO: (a) 0.05 M solution of pure complex **3**; (b) 0.05 M solution of **3** in the presence of an 8-fold excess of cyclen.



Scheme 4.

triflic acid shows two distinct steps, involving two and four protons, respectively. Thus, one secondary amino group in each cyclen residue in **2** retains its strong basic properties, while two other secondary amino groups in each cyclen behave as weak basic centers.

Interaction with dicarboxylic acids

Complex **2** reacts with a number of dicarboxylic acids (Table 1), as observed by ^{1}H NMR spectroscopy. The gradual addition of a dicarboxylic acid to a d_6-DMSO solution of **2** causes significant changes in the ^{1}H NMR spectrum similar to those shown in Figure 2. The signal of the methyl group (a) at 1.88 ppm grows in intensity, which is accompanied

by the decrease in intensity of the signal (b) at 1.96 ppm. A multiplet at 4.00 ppm (c) and a multiplet at 6.68 ppm (d) disappear, and the intensity of the singlet (e) increases. These changes indicate that the CH_2 groups at the R^3 positions of the cyclidene platform, which were originally present in the tautomeric forms **2b** and **2c**, become protonated.

The most significant change in the spectrum was observed for the methylene protons of the cyclen residue (f), which moved downfield ($\Delta\delta \sim 0.2$ ppm) from its original position at 2.66 ppm. This indicates that the cyclen arms are also protonated. This signal was used as a probe for the investigation of complex formation.

The final chemical shifts of cyclen protons for all adducts are nearly the same (2.87 ± 0.04 ppm), meaning that the protonation state of the cyclen arms in all adducts is similar. The analogous, although somewhat larger chemical shift of the cyclen protons (up to 2.93 ppm), was observed upon titration of **2** with two equivalents of triflic acid. It is thus reasonable to assume that each cyclen substituent is monoprotonated in the adducts of **2** with dicarboxylic acids, and that the protonated cyclen arms are involved in hydrogen bonding with dicarboxylates (the latter interaction lowers the shifts of the cyclen protons, as compared to diprotonated **2**). Notably, aliphatic monocarboxylic acids (e.g., acetic acid) do not display saturation behavior upon interaction with complex **2**: addition of up to 10 equivalents of CH_3COOH to **2** results in small monotonic changes in the chemical shifts of the cyclen protons, with the largest value of 2.74 ppm being significantly lower than the chemical shift of doubly protonated **2**. Another control experiment showed that titration of the cyclen-free analog of **2**, complex **3**, with dicarboxylic acids did not give rise to any significant changes in the ^1H NMR spectrum.

The stoichiometry of the host-guest complexes was established by the method of continuous variations (Job's method) [72, 73, 80, 81]. For all dicarboxylic acids listed in Table 1, Job's plot analysis unambiguously showed the 1:1 stoichiomertry of the complexes (Figure 6).

Association constants were determined from the binding curves (Figure 7) by nonlinear regression methods that gave excellent fits to a 1:1 model for the association between a host and a guest. The results of NMR titrations are summarized in Table 1. Since the measured equilibrium constants K_{meas} fall in the range from 10 to 10^4 M^{-1}, the NMR method is indeed adequate for accurate equilibrium measurements in the systems under investigation [73].

Relatively strong 1:1 complexation between complex **2** and dicarboxylic acids, and the lack thereof in case of monocarboxylic acids, suggests that both cyclen receptor arms in **2** participate, in a cooperative manner, in the encapsulation of dicarboxylate guests (Scheme 5). This proposed binding mode implies that shape complementarity between the host (receptor **2**) and the guest (dicarboxylic acid) is beneficial for high affinity binding. Comparison of the measured dicarboxylic acid binding constants (Table 1) does not immediately reveal this trend, because of the composite nature of the K_{meas} values. It is reasonable to assume that the following equilibria exist in the reaction solution:

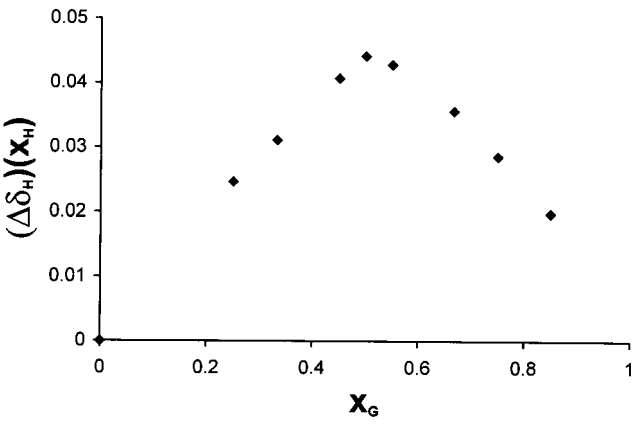


Figure 6. Job's plot for the system containing **2** and succinic acid in DMSO. The total concentration of the host **2** (H) and the guest (G) was kept constant at 2×10^{-2} M. The change in chemical shift of the CH_2 group of the cyclen residue of the host **2** ($\Delta\delta_H$) was followed. The value $(\Delta\delta_H)(x_H)$, where x_H denotes molar fraction of the host, was plotted vs. molar fraction of the guest (x_G).

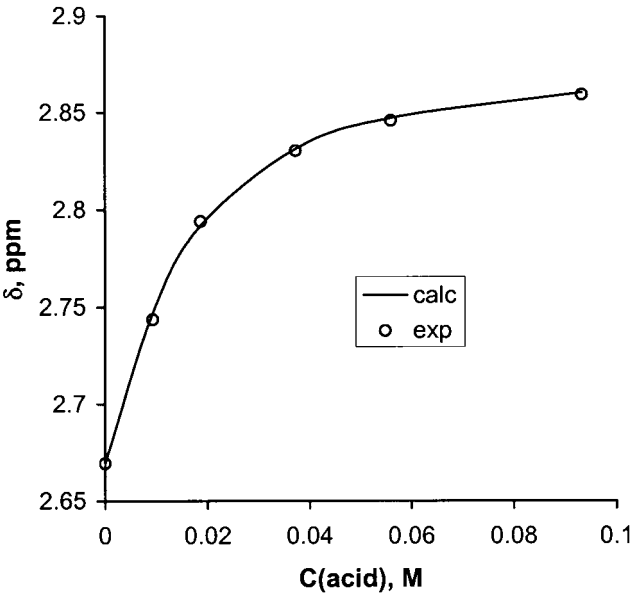
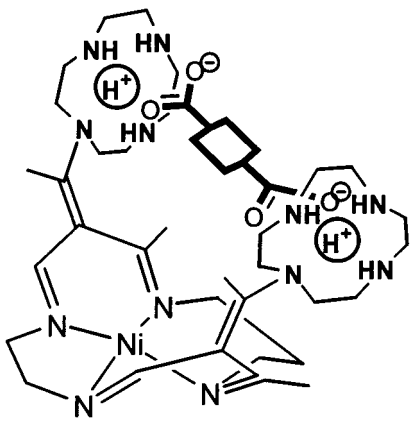


Figure 7. ^1H NMR-titration curve of **2** with succinic acid: the chemical shift of the CH_2 group of the cyclen residue of **2** ($C = 1.18 \times 10^{-2}$ M) vs. the concentration of added succinic acid. $K_{meas} = 118$ M^{-1}.



Scheme 5.

Table 1. Equilibrium constants of dicarboxylic acid binding to complex **2** (DMSO, 25 °C). Equilibria in the system are described by eq. 1-6

Acid	K_{meas}	$Log(K_{meas})$	pK_{a1} *	pK_{a2} *	$Log(K_{assoc})$ + Const
Malonic	7000	3.85	1.38	5.68	10.901
Maleic	4000	3.60	1.92	6.22	11.74
Phthalic	3500	3.54	2.93	5.41	11.88
Fumaric	1100	3.04	3.03	4.38	10.45
Terephthalic	890	2.95	3.54	4.46	10.95
Isophthalic	680	2.83	3.7	4.6	11.13
Succinic	118	2.07	4.21	5.63	11.91
Glutaric	41	1.61	4.34	5.27	11.22
Sebacic	13	1.11	4.4	5.22	10.73

* Acidity constants (in aqueous solutions) are quoted from Y.Y. Lur'e, Spravochnik po analiticheskoi khimii; Khimia: Moscow, 1979.

$$R(COOH)_2 \rightarrow R(COOH)COO^- + H^+ \quad K_{a1} \qquad (1)$$

$$R(COOH)COO^- \rightarrow R(COO)_2^{2-} + H^+ \quad K_{a2} \qquad (2)$$

$$Receptor + 2H^+ \rightarrow (Receptor)H_2^{2+} \quad K_{b(2)} \qquad (3)$$

$$(Receptor)H_2^{2+} + R(COO)_2^{2-} \rightarrow Adduct \quad K_{assoc} \qquad (4)$$

The measured binding constant K_{meas} can be expressed as the product of two sequential dissociation constants of an acid (K_{a1}, K_{a2}), the protonation constant of the complex **2** ($K_{b(2)}$), and an association constant for host-guest adduct formation (K_{assoc}).

$$K_{meas} = K_{a1}K_{a2}K_{b(2)}K_{assoc} \qquad (5)$$

It is not surprising that the measured binding constants appear to depend on the strengths of the acids (Table 1), since both K_{a1} and K_{a2} contribute to the overall binding affinity of complex **2** with respect to a particular guest. There is no linear correlation, however, between the log K_{meas} and pK_a of the guests. A comparison between three relatively weak aliphatic dicarboxylic acids (succinic, glutaric, and sebacic) is particularly revealing: both pK_{a1} and pK_{a2} of these acids are nearly identical, while their binding constants with complex **2** differ by an order of magnitude. Clearly, factors other than the acidity of the guests play a role in their binding to host **2**. Another variable in equation (5) is the association constant K_{assoc} (the measure of the association between the doubly protonated host **2** and the dianion of the guest), while the remaining term, the protonation constant of complex **2** ($K_{b(2)}$), does not change throughout the series. It is the K_{assoc} value that is expected to depend on the shape complementarity between the host and the guest. This value can be estimated from a rearranged Equation (5):

$$Log\ K_{meas} + pK_{a1} + pK_{a2} = Log\ K_{assoc} + Const. \qquad (6)$$

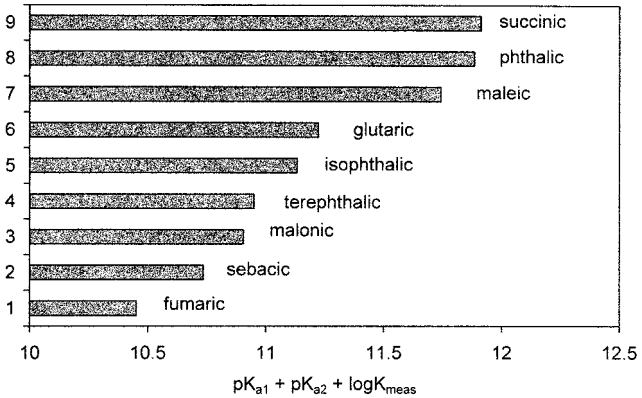


Figure 8. The diagram of the relative values of association constants (log K_{assoc} + Const., see Eq. (6)) of the host–guest complexes formed between complex **2** and dicarboxylic acids.

The calculated values of (log K_{assoc} + Const) are summarized in Table 1 and Figure 8. Unfortunately, only a limited number of acid dissociation constants in DMSO are available [82, 83], so aqueous dissociation constants were used in our calculations. The acidity constants in DMSO-water mixtures are almost identical to those measured in pure water [84], and the trends in acidity do not change significantly in pure DMSO [82, 83]. According to the diagram plotted in Figure 8, complex **2** shows substantial selectivity for succinic, phthalic and maleic acids. In all three of these acids, two carboxylate groups are attached to the neighboring carbon atoms and can be positioned *cis* to each other. The importance of the appropriate distance between the two carboxylate groups is evident from the comparison of aliphatic diacids: the binding affinity, optimal for succinic acid, decreases for both shorter (malonic acid) and longer (glutaric and sebacic acids) homologs. While flexible aliphatic linkers allow for a variety of spatial arrangements of the two carboxylate groups, rigid unsaturated aliphatic or aromatic diacids fix the functional groups in a well-defined geometry. Since maleic acid (*cis*-isomer) is bound stronger than fumaric acid (*trans*-isomer), it is clear that the *cis* orientation of the two carboxylates is beneficial for their interaction with receptor **2**. A very similar orientation of the carboxylates is provided by o-disubstituted aromatic compounds, and indeed *o*-phthalic acid is bound

stronger than the isomeric *m*- and *p*-derivatives (isophthalic and terephthalic acids). It thus appears that vicinal *cis*-1,2-dicarboxylates show the strongest interactions with the difunctional receptor **2**. Presumably, this geometry of the guests corresponds to an optimal binding geometry of the host **2**. This assumption is in agreement with structural data for cyclidene complexes [66]. The only crystallographically characterized saddle-shaped 15-membered cyclidene precursor has a cavity width of 7.23 Å, which is not substantially different from the cavity width in unbridged 16-membered cyclidenes (6.39 − 6.85 Å) [85]. Extensive X-Ray studies of covalently bridged 16-membered cyclidenes (X = Y = $(CH_2)_3$, Figure 1) [86] and molecular modeling studies on these systems [87–89] demonstrated that the hexamethylene linker (R^1) has an optimal length in order to span the cyclidene cavity with the least steric strain. Notably, the best dicarboxylate guests of host **2** also have six atoms in the chain (two carboxylate oxygens, two carboxylate carbons, and two carbons in the linker) that spans the receptor cavity in a supramolecular fashion. Analysis of the data in Figure 8 shows that significant shape selectivity in dicarboxylate binding can be accomplished with the relatively flexible ditopic receptor **2** which acts as a pair of tweezers for the shape-complementary substrates.

Conclusions

A metal containing saddle shaped macrocyclic complex **1** was successfully used as a scaffold in the synthesis of a bifunctional receptor **2** for dicarboxylic acids. Tetraaza macrocyclic receptor arms were attached to the edges of a 15-membered nickel(II) cyclidene platform. The resulting molecular tweezers interact with dicarboxylic acids in DMSO, as evidenced by NMR titration studies. The supramolecular 1:1 host-guest complexes are formed due to electrostatic attraction and hydrogen bonding between the protonated host and the dicarboxylate guests. The ditopic receptor exhibits moderate shape selectivity with respect to vicinal *cis* dicarboxylates.

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