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SIZE AND CHARGE DEPENDENCE OF BINDING BY AZACYCLOPHANES

Guy Lepropre and Jacques Fastrez*
Laboratoire de Biochimie Physique et des Biopolymères,
Place L. Pasteur, 1/1B,
1348 Louvain-la-Neuve, Belgium

ABSTRACT. Tetrameric and hexameric azacyclophanes, water soluble in the acidic or in the full pH range, and bearing functional side chains are shown to bind aromatic molecules or transition metal ions. The effect of the macrocycle size and charge on binding is investigated.

For some time, the molecular inclusion of an organic guest molecule into an organic host was mainly confined to the cyclodextrin chemistry [1]. In the last decade, however, quite a number of different systems have been proposed among which cyclophanes appear to form a promising family [2,3,4]. To understand what controls the binding and predict the selectivity, more work needs to be done on the effect of the structure of the host on its properties. It is the purpose of this communication to report on the effect of the size and the charge of the host on the binding.

Several tetrameric or hexameric aza-paracyclophanes bearing functional side chains have been prepared by coupling under high dilution conditions (continuous addition of 150ml of .04 molar solutions of N,N'-dimethoxycarbonylmethyl-p-xylilenediamine and αα'-dibromoxylene to 600 ml of boiling acetonitrile in the presence of potassium carbonate in the course of 5 hours). The isolated yield of Ia (white crystals, mp: 211-2°C) and IIa (oil) is 18% and 13% respectively. The alanine derivative (mp: 204-5°C) is obtained in 12% yield. The valine derivative could not be prepared.

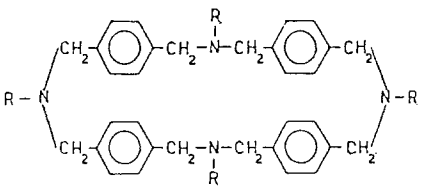
Hydrolysis of Ia by .25 molar sodium hydroxide in methanol/water (80/20% vol), neutralization and desalting on G25 Sephadex yields Ic (80%).

Reduction with borane in THF or lithium aluminium hydride in dioxane yields after the usual work up [5] Id or IId in 65% yield.

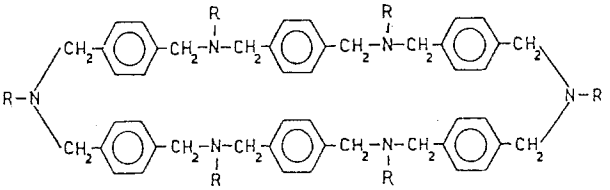
Hydroxylaminolysis of Ia in methanol/THF (75/25% vol), .5 molar in hydroxylamine hydrochloride and 1 molar in sodium methoxide yields after neutralization and desalting 70% of Ie.

All compounds have been characterized by IR, ^{1}H and ^{13}C-NMR spectroscopy and Ia and IIa further by analysis, mass specrometry and/or gel permeation chromatography on a 100Å-5μ-Styragel (500/7.7 mm column in

THF calibrated with cyclic oligoesters of known molecular weight.



I



II

a: R = CH_2COOCH_3, b: R = $CH(CH_3)COOCH_3$, c: R = CH_2COOH, d: R = CH_2CH_2OH, e: R = $CH_2CONHOH$.

Ic is soluble in the entire pH range between pH 1 and 13. The pKas have been determined by potentiometric titration and the protonation scheme checked by proton NMR. It is zwitterionic at pH 5, the carboxylates become protonated below this pH and the amino functions above it. The following pKas corresponding to the equation:

$$H_4A_4 \overset{Ka_1}{\rightleftharpoons} H_3A_4^- \overset{Ka_2}{\rightleftharpoons} H_2A_4^{2-} \overset{Ka_3}{\rightleftharpoons} HA_4^{3-} \overset{Ka_4}{\rightleftharpoons} A_4^{4-}$$

have been obtained in water (0.3M KCl): pKa_1 = 6.34, pKa_2 = 7.43, pKa_3 = 8.28, pKa_4 = 9.30.

The pKas of the carboxylic functions cannot be determined accurately. The first pKa lies around 2.5. The macrocycle is not fully protonated at pH 1.

Ie is water soluble below pH 2.5 and above pH 9.5. It is easily acylated by p-nitrophenylacetate at pH 10. There is no indication of a turnover, a prerequisite for catalysis. This may be related to the fact that, underbasic conditions, O-acyl-hydroxamic acids decompose with Lossen rearrangment [6]. Comparison of the acylation rate (k = 300/M.s) with that of a simple hydroxamic acid, acethydroxamic acid (k = 93/M.s) [7], suggests that the macrocyclic structure does not contribute to facilitate the acylation significantly, either because the ester is very poorly bound to the macrocycle or because the bound substrate is not correctly oriented for reaction. From the observations on the binding ability of the macrocycles reported below, the first hypothesis appears to be more likely.

The binding of several organic molecules has been measured by fluorimetry either by measuring the influence of the macrocycles on the fluorescence of the guest directly (for 1-anilino-8-naphthalene sulfonate (ANS) or 2-toluidino-6-naphthalene sulfonate (TNS) anions) or or by measuring the inhibition of the binding of the formers. The technique has been used previously [2]. The data are collected in Table I.

From the data presented, it is clear that the tetrameric macrocycles bind alpha substituted naphthalene derivatives, simple aromatic compounds or 1-amino-adamantane very poorly, a beta substituted

naphthalenic compound (TNS) is bound more efficiently.

Table I.
Dissociation constants of complexes of organic molecules to azacyclophanes.

Host	Guest	pH	Kd (M)	Note
Ic	1,8-ANS	1.0	$3.4\ 10^{-2}$	a
"	2,6-TNS	2.0	$1.4\ 10^{-2}$	a
"	2,6-TNS	5.5	$1.7\ 10^{-2}$	a
Ie	1,8-ANS	2.0	$2.0\ 10^{-2}$	a
Id	1,8-ANS	1.0	$1.5\ 10^{-2}$	-
"	2,6-TNS	2.0	$1.0\ 10^{-3}$	-
"	1-Naphthalene sulfonate	2.0	$1.4\ 10^{-2}$	b
"	Tosylate	2.0	$2.6\ 10^{-2}$	b
"	1-aminoadamantane	2.0	$4.5\ 10^{-2}$	b
IId	1.8-ANS	1.5	$\leq 3\ 10^{-4}$	-
"	2,6-Naphthalene disulfonate	1.5	$\leq 1\ 10^{-4}$	b

a. Saturation not reached, dissociation constant estimated on the assumption that the effect of the macrocycle on the fluorescence is the same for all cyclophanes.
b. measured by inhibition of the binding of ANS or TNS.

Compared to Id, the hexameric compound IId is more efficient in binding ANS or a beta sustituted naphthalene derivative. It is not clear why the tetrameric macrocycles investigated in this work have a lower affinity for ANS than the corresponding cyclophanes reported by Tabushi et al [2]. (I with R = CH_3. Kd = 1.8 mM). Either the side chains are filling the cavity to some extent, or they are forcing a conformation of the macrocycle where the cavity is essentially closed. This question is being addressed by X-Ray crystallography. The cyclophanes introduced by Koga [3], form more stable complexes, this is likely to be due to the fact that the cavity is larger and that the diphenylmethane unit used to construct them confers some rigidity.

There is some indication that the charge of the macrocycle influences the binding as shown by the fact that the tetraprotonated Id binds TNS better than Ic at pH 2 (where the host is essentially monoprotonated) and at pH 5.5 where it is neutral. Binding by Ic at pH 12 is very weak,if present. The electrostatic effect is nevertheless relatively weak. This observation is consistent with the conclusions to be drawn from the the titration data, where the pKa splitting corrected for the statistical effect (a factor of 16) covers less than two orders of

magnitude.

Ic is also able to form a 1-1 complex with a cupric ion at pH 5.5, with a dissociation constant smaller than 10 μM. Comparison of the spectrum of this complex (λmax = 520 nm) with that of other cupric complexes [8] suggests a structure in which two nitrogens from the skeleton of the macrocycle and two oxygens from its side chains are ligated to the metal ion. In this complex, the macrocycle would be in a "closed form". In agreement with this proposal, the cupric complex is unable to bind ANS.

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