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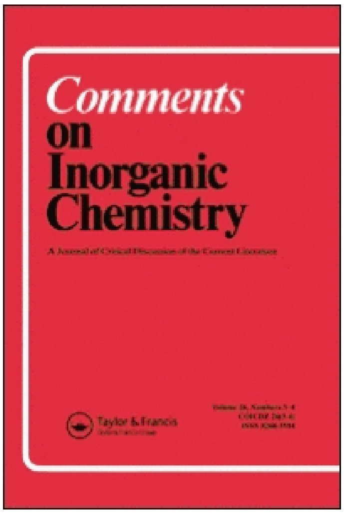

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Large Polyazacycloalkanes and Small Macrocyclic Cages

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To cite this Article Micheloni, Mauro(1988) 'Large Polyazacycloalkanes and Small Macrocyclic Cages', Comments on Inorganic Chemistry, 8: 3, 79 — 100
To link to this Article: DOI: 10.1080/02603598808035787
URL: http://dx.doi.org/10.1080/02603598808035787

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Large Polyazacycloalkanes and Small Macrocyclic Cages

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Key Words: *macrocycles, synthesis, structures, thermodynamic*

INTRODUCTION

Synthetic macrocyclic compounds have attracted much interest among chemists. Many hundreds of publications, including numerous books,[1] have been published in this active field during the last few years. The current interest stems from different points of view, including selective ion recognition, transport processes, reaction catalysis, industrial applications, model systems and others.[1-5]The driving force which moves all of these interests is the challenge of the design and synthesis of new macrocyclic compounds with new chemical properties.

LARGE POLYAZACYCLOALKANES

The adjective "large" has been used[6] to describe azamacrocycles having more than six nitrogen donor atoms. These compounds are

Comments Inorg. Chem.
1988, Vol. 8, No. 3, pp. 79–100
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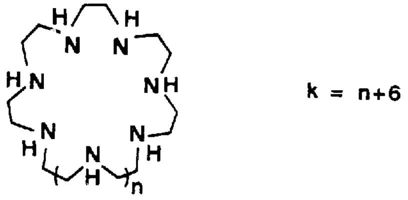
represented by the general formula [3·k]aneN$_k$, with k = 7, 8, 9, 10, 11, 12. In Fig. 1 are given the names and abbreviations hereafter used for these compounds. The possibility of binding more than one metal ion within the macrocyclic framework, as well as the employment of these compounds in the development of the anion coordination chemistry, has made these compounds interesting to us and worthy of study. In Fig. 2 the general synthetic route followed to synthesize large polyazacycloalkanes is shown schematically. Such a procedure is modeled on that described by Atkins *et al.*,[7] and consists of cyclizing the appropriate polyamminic segments. Important steps in the reaction sequence of Fig. 2 are the elongation of the linear polyammines and the cyclization reaction. The final macrocyclic compounds are purified as the hydrochlorides and characterized by standard techniques. As expected, the overall yield is strongly reduced as the size of the macrocycle increases.

EQUILIBRIUM STUDIES AND STRUCTURAL ASPECTS

All the stepwise equilibrium constants, protonation and metal complex formation, have been determined at 25°C by potentiometry.



[3k]aneN$_k$	name	abbreviation
[21]aneN$_7$	1,4,7,10,13,16,19-heptaazacycloheneicosane	L7
[24]aneN$_8$	1,4,7,10,13,16,19,22-octaazacyclotetracosane	L8
[27]aneN$_9$	1,4,7,10,13,16,19,22,25-nonaazacycloheptacosane	L9
[30]aneN$_{10}$	1,4,7,10,13,16,19,22,25,28-decaazacyclotriacontane	L10
[33]aneN$_{11}$	1,4,7,10,13,16,19,22,25,28,31-undecaazacyclotritriacontane	L11
[36]aneN$_{12}$	1,4,7,10,13,16,19,22,25,28,31,34-dodecaazacyclohexatriacontane	L12

FIGURE 1 Drawing of the large polyazacycloalkanes investigated with names and abbreviations.

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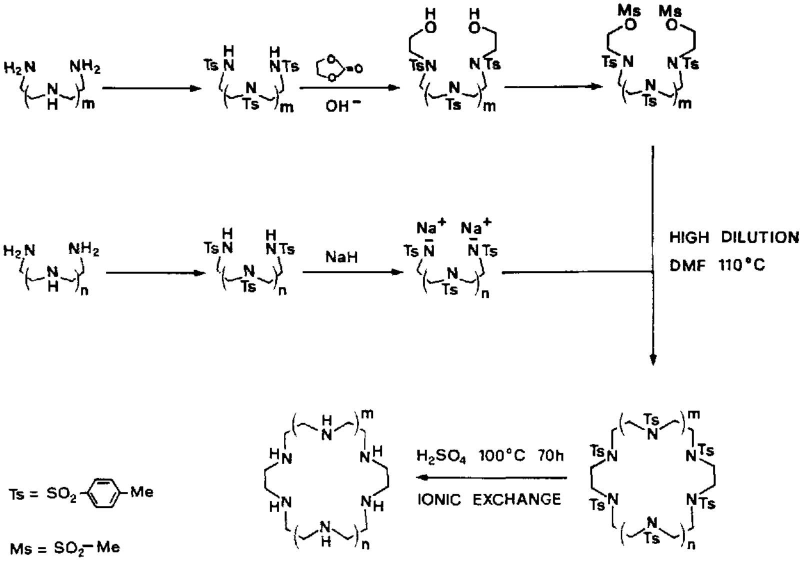

FIGURE 2 Reaction sequence for the synthesis of large polyazacycloalkanes.

The basicity constants for the [3·k]aneN$_k$ series are reported in Table I. A few general conclusions can be drawn on the basicity behavior of large polyazacycloalkanes: (i) the overall basicity (logβ_k) steadily increases with the size of the macrocycle (see Fig. 3) and the average contribution to the overall basicity can be estimated as 5.9 log units for each $-CH_2-CH_2-NH-$ unit added to the macrocyclic ring; (ii) each macrocycle behaves as a relatively strong base in the first half of its protonation steps and as a weaker base in the second half. This sort of grouping of the basicity constants is typical of azamacrocycles and can be rationalized in term of electrostatic repulsions among the positively charged $>NH_2^+$ groups arranged in the cyclic framework and of hydrogen-bonding formation.[6,8–11] The grouping of the basicity constants is much more evident for smaller macrocycles,[12,13] where the charges that accumulate in the macrocyclic framework as the degree of protonation increases experience stronger repulsions than in the case of the larger macrocycles. The values of the basicity constants and the cyclic topology make large polyazamacrocycles able to form many highly protonated, positively charged, species in the neutral

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TABLE I

Protonation constants (logarithms) of large polyazacycloalkanes in aqueous solution at 25°C, $I = 0.15$ mol dm^{-3}

Reaction	log*k*					
	L = L7[a]	L = L8[b]	L = L9[c]	L = L10[d]	L = L11[e]	L = L12[e]
H[f] + L = HL	9.7	9.7	9.6	9.9	9.8	9.8
H + HL = H_2L	9.3	9.3	9.4	9.4	9.5	9.6
H + H_2L = H_3L	8.6	8.8	8.8	9.0	9.0	8.9
H + H_3L = H_4L	6.4	7.9	8.3	8.6	8.6	8.9
H + H_4L = H_5L	3.8	4.6	6.4	7.8	8.1	8.1
H + H_5L = H_6L	2.4	3.4	4.2	5.2	6.5	7.8
H + H_6L = H_7L	2.2	2.7	3.2	3.8	4.5	5.7
H + H_7L = H_8L	–	1.9	2.3	3.0	3.6	4.3
H + H_8L = H_9L	–	–	1.8	2.0	2.8	3.6
H + H_9L = $H_{10}L$	–	–	–	1.8	2.2	2.7
H + $H_{10}L$ = $H_{11}L$		–	–	–	1.7	2.3
H + $H_{11}L$ = $H_{12}L$	–	–	–	–	–	1.0

[a] Values determined first at $I = 0.5$ mol dm^{-3} in Ref. 8.
[b] Values determined first at $I = 0.5$ mol dm^{-3} in Ref. 6.
[c] From Ref. 9.
[d] From Ref. 10.
[e] From Ref. 11.
[f] Charges omitted for clarity.

pH region. These species have such a spatial distribution of binding sites that they are able to strongly interact with anions and thus can be employed in anion coordination studies. The possibility of easy formation of polynuclear metal complexes is another interesting property of large polyazamacrocycles. In Table II are reported the logarithms of the formation constants of copper(II) complexes. One can see that, with only the exception of the smallest macrocycle of the series L7, which also forms a mononuclear complex, all of the other macrocycles form polynuclear copper(II) complexes. For the largest macrocycles of the series L11 and L12, the trinuclear species are also formed. All of the species formed are very stable as indicated by the high stability constants. In few cases, the strong interaction between the copper(II) ion and the donor atoms has been confirmed by the high exothermicity of the formation reaction of the binuclear species: $\Delta H^\circ = -39.0$ kcal mol^{-1} for $[Cu_2L8]^{4+}$, from Ref. 6; $\Delta H^\circ = -42.8$ kcal mol^{-1} for $[Cu_2L9]^{4+}$, from Ref. 9; $\Delta H^\circ = -45.5$ kcal mol^{-1} for $[Cu_2L10]^{4+}$, from Ref. 10. These calorimetric results show a trend for the for-

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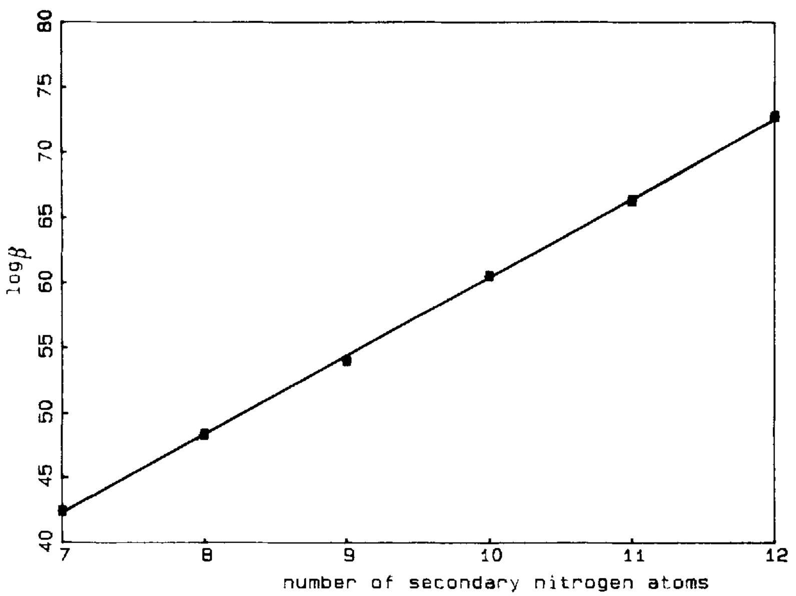

FIGURE 3 Logarithms of the overall basicity constants of large polyazacycloalkanes belonging to the [3·k]aneN$_k$ series.

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mation enthalpies of the binuclear species, which become more negative as the overall size of the macrocycle increases. A similar trend is also found for the overall stabilities of the binuclear species (see Table II). We believe that these trends can be explained, considering that as the size of the macrocycle increases, the number of donor atoms involved in the coordination to the metal ions as well as the ligand flexibility increase. Furthermore another contribution to the above trends may arise from the decrease in the electrostatic repulsions between the coordinated metal ions as the size of the macrocycle increases. Cyclic voltammetric studies, in aqueous solution on some binuclear copper(II) complexes,[6,8] indicate that the complexes undergo reversible reductions into the binuclear copper(I) species by two independent monoelectronic steps. The reduced species are unstable with respect to demetalation and reduction to metal. The abundance of donor atoms in the macrocycles of this series allows the formation of many protonated species at each equilibrium as shown in Table II. In the case of L10 the solid, monoprotonated, binuclear complex

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TABLE II

Stability constants (logarithms) of copper(II) complexes of large polyazacycloalkanes

Reaction	log*k*					
	L = L7[a]	L = L8[b]	L = L9[c]	L = L10[d]	L = L11[e]	L = L12[e]
Cu[f] + L = CuL	24.4	–	–	–	–	–
2Cu + L = Cu_2L	30.7	36.6	36.0	37.8	38.8	39.2
2Cu + L + H = Cu_2LH	–	–	40.7	43.4	45.3	47.1
2Cu + L + 2H = Cu_2LH_2	–	42.0	43.8	47.2	51.2	53.9
2Cu + L + 3H = Cu_3LH_3	–	–	47.1	50.5	53.9	58.1
2Cu + L + 4H = Cu_2LH_4	–	–	–	–	–	61.4
2Cu + L + H_2O = Cu_2LOH + H	17.0	26.1	26.2	26.4	27.3	–
3Cu + L = Cu_3L	–	–	–	–	48.0	51.4
3Cu + L + H = Cu_3LH	–	–	–	–	–	55.4
3Cu + L + H_2O = Cu_3LOH + H	–	–	–	–	40.6	42.5

[a] Values taken from Ref. 8.
[b] From Ref. 6.
[c] From Ref. 9.
[d] From Ref. 10.
[e] From Ref. 11.
[f] Charges omitted for clarity.

$[Cu_2(L10)HCl_2]\ (ClO_4)_3 \cdot 4H_2O$ has been isolated and characterized by X-ray analysis.[10] The formation of stable polynuclear hydroxo species is another binding characteristic of large polyazacycloalkanes. For the $[Cu_2(L8)OH]^{3+}$ species, the magnetic susceptibility, measured in solution, decreases significantly on increasing the pH and the hydroxo species concentration, supporting the hypothesis that the hydroxide group is bridging the two copper(II) ions and increases the metal–metal interactions.[6] Recent equilibrium studies[14] have demonstrated that, with many other metal ions such as cobalt(II), nickel(II), zinc(II) and cadmium(II), large polyazacycloalkanes from very stable polynuclear complexes. Although in the $[3 \cdot k]aneN_k$ series many solid polynuclear complexes have been isolated and characterized, only in a few cases was the isolation of good crystals for X-ray analysis possible. In Fig. 4 a few examples are reported of crystal structures of complexes of large macrocycles. Figure 4(a) shows the structure of the cation $[Cu_2(L8)Cl_2]^{2+}$ in which each copper atom is coordinated in a distorted square-pyramidal fashion by four nitrogen atoms and one chloride ion,[6] the nitrogen atoms forming the basal plane, with the copper atom 0.36 Å out of the plane. The intramolecular Cu–Cu distance is 6.138 Å. The crystal structure of $[Cu_2(L8)Cl_2]ClO_4)_2$ consists of centrosymmetric binuclear $Cu_2(L8)$ units held together by chlorine bridges forming pairs of polymeric ···Cu–Cl–Cu···Cl···Cu chains. The structure of the binuclear cation $[Cu_2(L10)HCl_2]^{3+}$ is shown in Fig. 4(b).[10] As already found for the macrocycle L8, each copper atom is coordinated by four nitrogen atoms and one chlorine atom forming a slightly distorted square pyramid. Since the binuclear species is protonated, the site of protonation must be on the two uncoordinated nitrogens N(1) and N(1′) (see Fig. 4(b)). Owing to the presence of the twofold axis, the two nitrogen atoms are crystallographically equivalent and therefore the proton is statistically distributed between them. The distance of 3.90 Å between N(1) and N(1′) rules out any possibility of bridging by the hydrogen atom. The intramolecular Cu–Cu distance is 7.26 Å. The structure of $[Cu_2(L10)HCl_2]\ (ClO_4)_3 \cdot 4H_2O$ consists of binuclear $[Cu_2(L10)HCl_2]^{3+}$ cations, disordered perchlorate anions and water molecules bridging the complex cations in the crystal lattice by hydrogen bonds. In Fig. 4(c) is shown the crystal structure of the $[Zn_2(L10)NCS]^{3+}$ cation.[15] In this cation the two zinc atoms show

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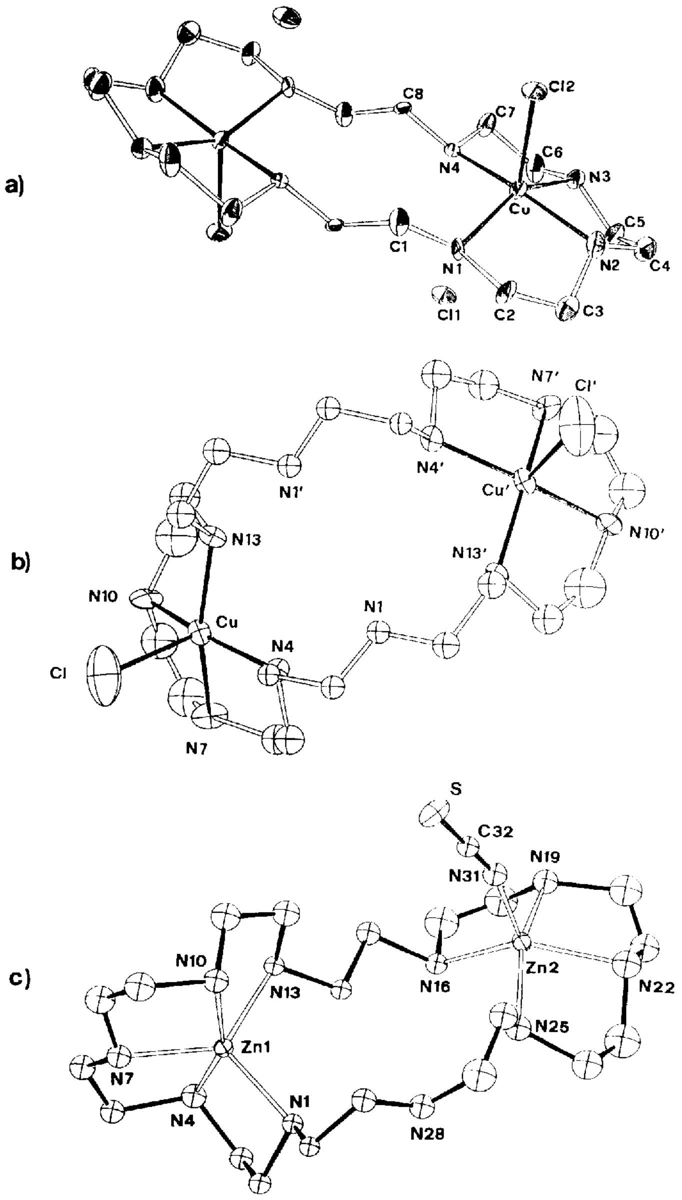

FIGURE 4 (a) ORTEP drawing of the $[Cu_2(L8)Cl_2]^{2+}$ cation. (b) ORTEP drawing of the $[Cu_2(L10)HCl_2]^{3-}$ cation. (c) ORTEP drawing of the $[Zn_2(L8)NCS]^{3+}$ cation.

essentially the same five-coordinate stereochemistry. However, one zinc atom is coordinated by five nitrogen atoms of the macrocycle, whereas the other zinc atom is coordinated by four nitrogen atoms of the macrocycle and by the nitrogen atom of the thiocyanate. The different modes of coordination shown by the two zinc ions is surprising, especially if one considers that before crystallization the Zn^{2+}/NCS^- ratio in solution was equimolar. It is difficult to explain this result in terms of a balance between the stronger donor character of the macrocyclic nitrogens compared with that of the thiocyanate group and the decrease of electrostatic repulsion between the two metal ions, achieved through the binding of an anion. In this structure, where the Zn–Zn distance is 6.40 Å, the macrocycle wraps around the two zinc atoms in a rather strained configuration. The structure of $[Zn_2(L10)NCS]\ (ClO_4)_3$ is completed by perchlorate anions. The crystal structure of the binuclear complexes $[Zn_2(L8)Cl_3]\ (ClO_4)\cdot H_2O$ and $Na[Cd_2(L10)Cl_2]\ (ClO_4)_3$ have been already solved and will be published.[16] I want to conclude this short section, dedicated to structural aspects, by drawing the reader's attention to the fact that, in spite of a large effort to obtain crystals of binuclear complexes, we have been able so far to grow good crystals, suitable for X-ray analysis, only with the more "symmetric" macrocycles L8 and L10.

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ANION COORDINATION

Anion coordination is a relatively new and not extensively explored field in spite of the important role played by anions in many important biological and non-biological processes.[17–22] All large polyazacycloalkanes form highly charged protonated species in the neutral pH range. The cyclic topology of these polycharged cations increases the electric field and makes these species strongly interacting with anions. In Fig. 5 the crystal structure of a "supercomplex" $[H_8(L10)]\ [Co(CN)_6]_2Cl_2\cdot 10H_2O$ containing the octaprotonated macrocycle $[H_8(L10)]^{8+}$ and the hexacyanocobaltate(III) $[Co(CN)_6]^{3-}$ is reported.[21,22] The structure is completed by chloride anions and water molecules. The structure shows that the macrocycle adopts a very stiff configuration, elliptical in shape, imposed by the Coulombic repulsions between the protonated nitrogen atoms, which form two parallel stiff chains and prevent the

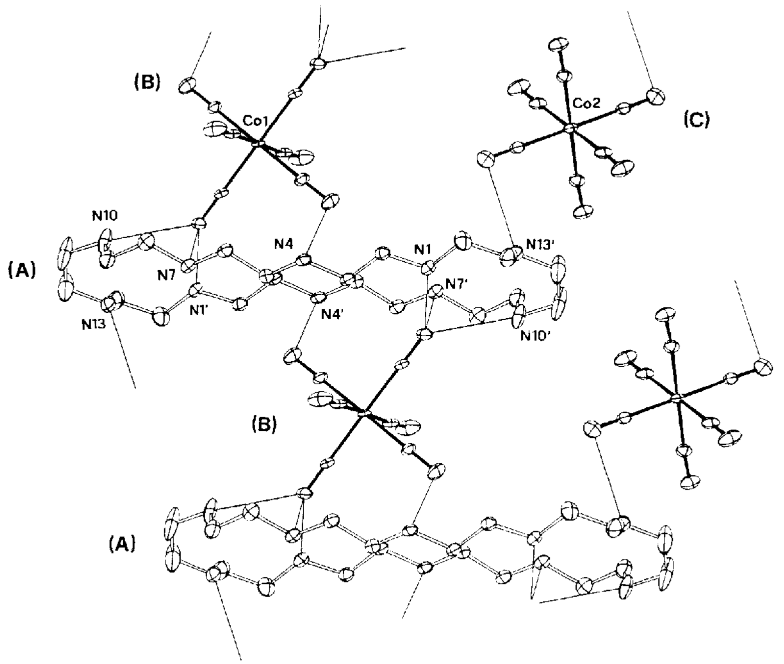

FIGURE 5 Part of packing of the "supercomplex" [H_8L10] [$Co(CN)_6$]$Cl_2 \cdot 10H_2O$ showing the macrocyclic ring (A), [$Co(CN)_6$]$^{3-}$ anions (B) and (C) together with the hydrogen bonds. (Adapted from Ref. 21.)

anionic species [$Co(CN)_6$]$^{3-}$ from going inside the macrocyclic cavity. It should be noted that this spatial separation of charge has a great influence on the receptor cavity shape. The overall strong interaction between the protonated macrocycle and the [$Co(CN)_6$]$^{3-}$ anion, responsible for the supercomplex formation, is due to electrostatic interactions and to the presence of several hydrogen bonds formed between the cyanide groups of one of the hexacyanocobaltate(III) anions and the macrocyclic nitrogen atoms. Because the conformation of the macrocyclic ring is essentially determined by electrostatic repulsions, it is very likely maintained in solution. Recent equilibrium and electrochemical studies[22] in aqueous solution on the binding of the complex anions [$Fe(CN)_6$]$^{4-}$ and [$Co(CN)_6$]$^{3-}$ to polyammonium macrocycles of different sizes, in-

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cluding L7, L9, L10, and L11, show the absence of any selectivity and are consistent with strong interactions, mainly Coulombic in nature, between the anion and the protonated second-sphere ligand.

SMALL CAGES

This section will deal with the chemistry of a series of small synthetic cages with the general formula reported in Fig. 6. These cages are made up of a basal twelve-membered tetraazamacrocycle in which two *trans* nitrogen atoms are connected through two propylenic chains disposed around the X group (see Fig. 6). The chemical properties of these compounds, in which a "tridimensional" cavity is present, are essentially influenced by three factors[23]: (i) size of the cavity; (ii) rigidity; (iii) nature of the donor atoms present. The size of the cavity receptor is in any case very small so that only very small ions can be encapsulated. Rigidity is the second important characteristic, due to the presence of short ethylenic chains on the twelve-membered macrocycle, which makes this part of the molecule rather rigid. The unit bridging the two unmethylated nitrogen atoms is relatively more flexible as it contains two propylenic chains, but the two methyl groups further contribute to the overall molecular crowding and rigidity. The synthetic strategy followed for the preparation of these macrocycles is schematically reported in Fig. 7. The first important step, which is common to all cages, is the preparation of a *trans*-dimethylated twelve-membered tetraazamacrocycle.[24] The creation of the tridimensional cavity by bridging with the appropriate unit the two secondary nitrogen atoms is the second step of the synthesis. It is worthwhile to note that all syntheses so far used to

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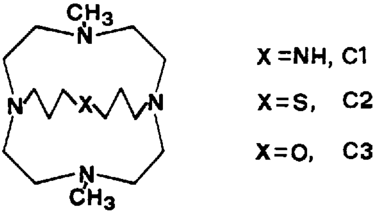

FIGURE 6 General formula and abbreviations of the macrobyciclic cages studied.

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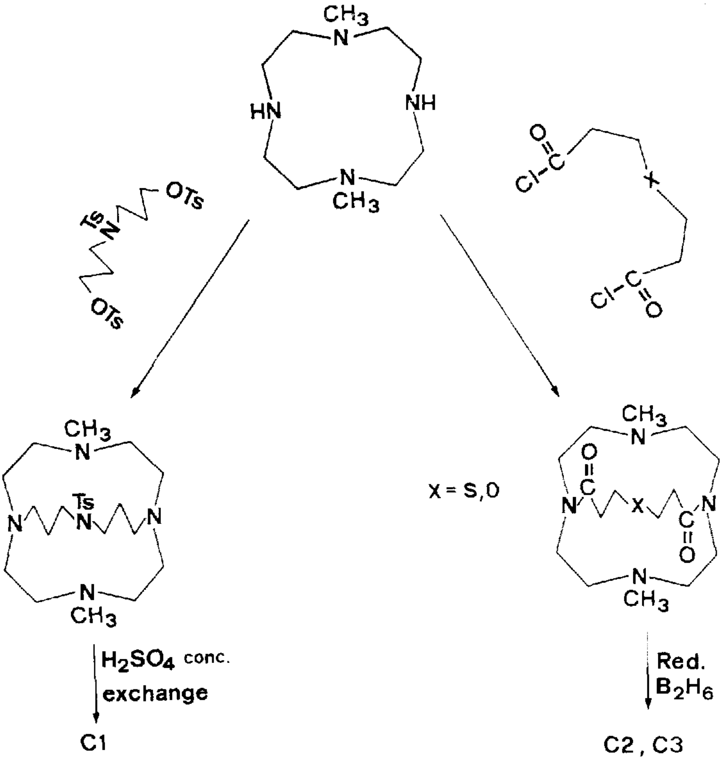

FIGURE 7 Reaction sequence for the synthesis of macrobicyclic cages.

obtain the macrocyclic cages of the series are non-template syntheses. This means that at the end of the synthetic route the free or, at most, the monoprotonated cage is obtained, which can be used for studying both protonation and metal complex formation reactions.

PROTONATION EQUILIBRIA

The first compound of the series C1 (see Fig. 6) can take up three protons at most, even if five potential protonation sites are available. In the solid state mono- and tri-protonated salts of C1 have been obtained.[25] In aqueous solution this macrocyclic cage behaves as a very weak base in the third protonation step ($\log k_3 < 2$ for the stepwise equilibria (1))

$$[H_{(i-1)}\mathrm{C1}]^{(i-1)+} + \mathrm{H}^+ = [\mathrm{H}_i\mathrm{C1}]^{i+} \tag{1}$$

and as a moderate base in the second protonation step ($\log k_2 = 8.41$). In the first protonation step C1 behaves as an extremely strong base: the proton cannot be removed even in strong alkaline solution. The ^{13}C n.m.r. spectra of $[\mathrm{HC1}]^+$ in water and in 3 mol dm^{-3} KOH solution are identical. The spectrum of the $[\mathrm{HC1}]^+$ species (see Fig. 8) shows six sharp signals accounting for overall C_{2v} symmetry, possibly time averaged among lower symmetry conformers and/or tautomers. No changes in both the pure water and 3 mol dm^{-3} KOH spectra were detected after one week. The assignments were made by using the APT technique and two dimensional ^{1}H–^{13}C n.m.r. The ^{1}H n.m.r. spectrum of $[\mathrm{HC1}](\mathrm{ClO_4})$ in dry CD_3CN or $CDCl_3$ shows a complex multiplet pattern (see Fig. 9) between 1.5 and 3.0 p.p.m., where the signal of the methyl group is recognizable at 2.28 p.p.m. and a broad signal is present

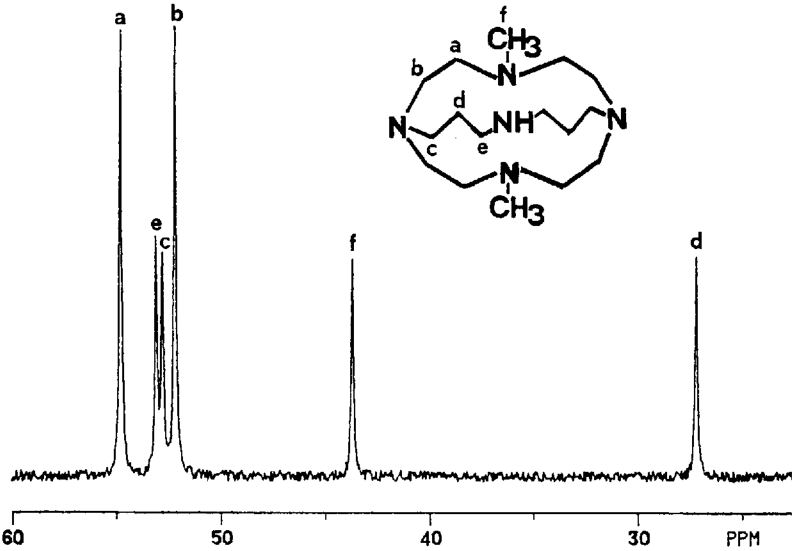

FIGURE 8 ^{13}C n.m.r. spectrum of the $[\mathrm{HC1}]^+$ species and relative assignments.

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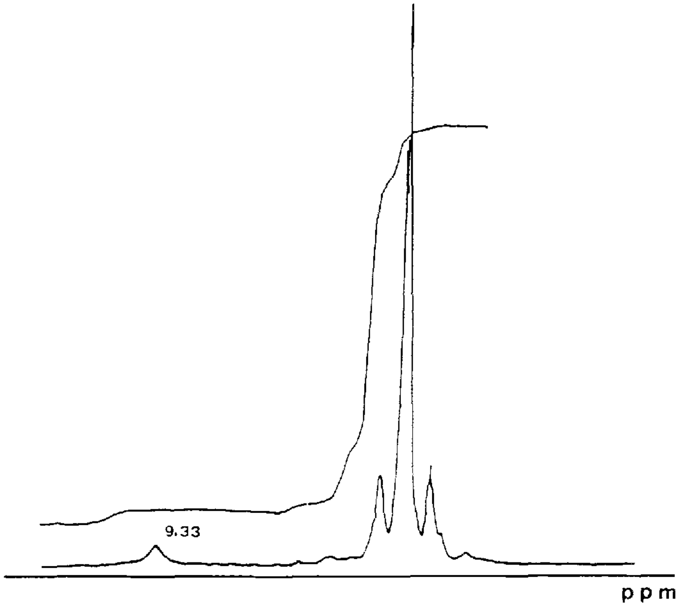

FIGURE 9 ^1H n.m.r. spectrum of [HC1] (ClO_4) in deuterated acetonitrile.

at 9.3 p.p.m. The last signal, which integrates for two protons, is attributable to the "trapped" deshielded $>NH_2^+$ protons. This signal disappears by addng two equivalents of CH_3OH or water, due to excessive linewidth, indicating intermediate or fast proton exchange on the n.m.r. experiment time scale with "external" active hydrogens. These results, i.e., the extremely high basicity (unmeasurable in aqueous solution) and the fast proton exchange, allow us to classify C1 as a "fast proton sponge." In order to better investigate the origin of both the high thermodynamic stability and the high kinetic liability of the monoprotonated species $[HC1]^+$, the X-ray crystal structure of the [HC1]Br salt was carried out.[26]In Fig. 10 the structure of the $[HC1]^+$ cation is shown. The five nitrogen atoms are located at the apices of a slightly distorted square pyramid, with the four tertiary nitrogens forming the basal plane and the secondary nitrogen atoms at the vertex. The nitrogen atoms are in the endo conformation, the ethylenic chains being all below the basal plane. The structural data confirm that protonation

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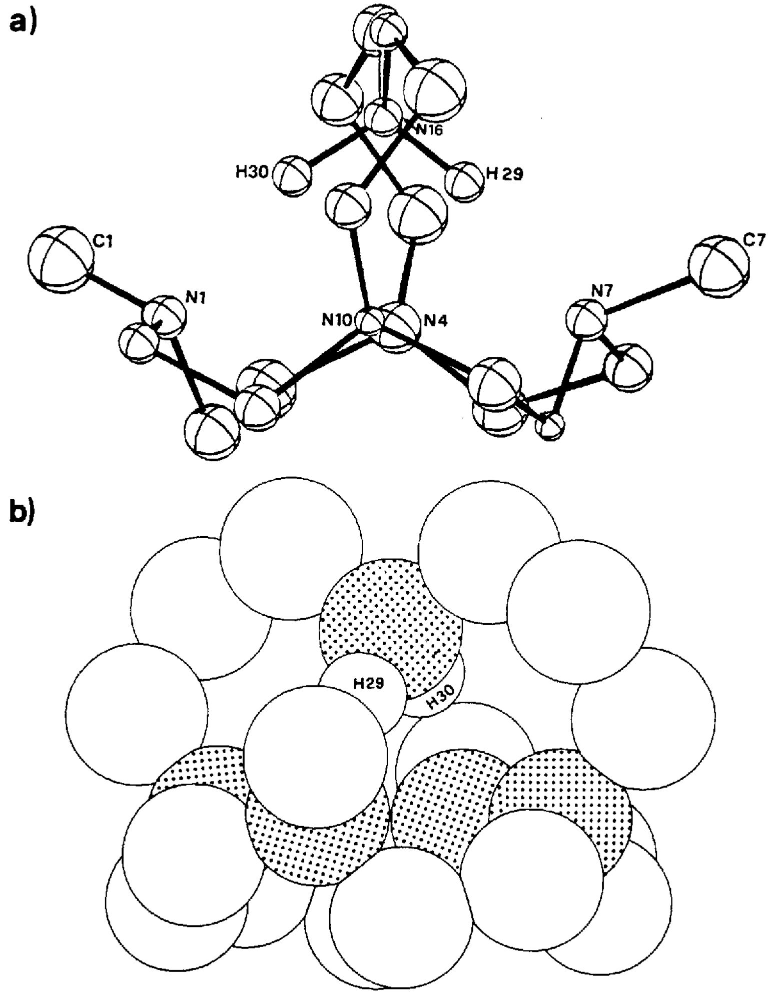

FIGURE 10 (a) View of the $[HC1]^+$ cation showing only part of the labelling. (b) Space-filling representation of the $[HC1]^+$ cation (dotted atoms are nitrogens).

occurs on the secondary amino group. The two hydrogen atoms H29 and H30, bonded to the secondary nitrogen N16, form hydrogen bonds with N7 and N1, respectively. The H···N distances, 2.28 and 2.04 Å, show that these hydrogen bonds are rather weak, probably due to the steric repulsions between the secondary nitrogen and the methyl groups and/or to internal constraints of the macrocyclic backbone. However, each hydrogen of the $>NH_2^+$ group further interacts with both bridgehead nitrogen atoms. In conclusion the array of six hydrogen bonds between the hydrogen atoms of the $>NH_2^+$ group with the four tertiary nitrogen atoms makes the structure particularly stable from the thermodynamic point of view, albeit no single hydrogen bond is exceedingly strong. These structural features of the $[HC1]^+$ species allow us to also explain the fast protonation/deprotonation kinetic. Indeed, the hydrogen atoms of the $>NH_2^+$ group, lying on the "surface" of the molecule, can easily interact with the solvent and rapidly exchanged with the active hydrogen atoms of the solvent molecules. These results are in sharp contrast to the behavior observed for the monoprotonated forms of the small cryptands and diazabicycloalkanes,[27] where the proton, located inside the intramolecular cavity, exhibits a slow transfer reaction. The addition of the second proton to form the $[H_2C1]^{2+}$ species produces marked changes in the ^{13}C n.m.r. spectra, indicating consistent conformational changes in the second protonation step. The value of the second protonation constant ($\log k_2 = 8.41$) is slightly smaller than those usually found for the second protonation step of secondary amino groups of monocyclic polyazacycloalkanes. The addition of the third proton to the cage C1 to form $[H_3C1]^{3+}$ is difficult because of the electrostatic repulsions among the positive charges close to each other, so that the relative equilibrium constant cannot be accurately measured in the usual pH-range. For the species $[H_3C1]^{3+}$ only one set of six peaks is found in the ^{13}C n.m.r. spectrum. The interesting protonation behavior of C1 (proton sponge) is due to the presence of the secondary nitrogen atom and to a suitable molecular topology which allows the formation of a hydrogen-bond framework. In order to better understand the role played by the group present in the di-propylenic bridging unit we have synthesized the sulphur cage (C2) by replacing the NH group with sulphur. In this way we expect that the overall molecular topology should not change. Both in the solid state and in aqueous solution the cage C2 can take up at most two protons.[28] C2 behaves as a rather strong base in both protonation steps ($\log k_1 = 11.91$; $\log k_2 = 8.78$). As expected C2 does not show protonic sponge behavior even though the stepwise protonation constants are un-

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expectedly high for tertiary nitrogen atoms. The stepwise protonation enthalpies, determined by direct calorimetry, show that both protonation steps are very exothermic reactions ($\Delta H_1^0 = -13.3$ and $\Delta H_2^0 = -11.5$ kcal mol^{-1}). The high basicity of C2 in the first protonation step is entirely due to a very favorable enthalpic term ($\Delta H_1^0 = -13.3$ kcal mol^{-1}). This means that the added proton should interact very strongly with the tertiary nitrogen atoms to form the monoprotonated species [HC2]$^+$. In other words, the hydrogen atom of the $\geqslant$NH$^+$ group should be well embedded within the electron density of all the nitrogen atoms. In conclusion the sulphur cage C2, in which one sulphur atom has replaced the secondary nitrogen >NH in C1 without substantial modification of the overall molecular topology, is less basic than C1 and its basicity is measurable. Nevertheless the basicity of C2 is very high for a compound having only tertiary nitrogens, thus indicating the very important role played by the molecular topology in the proton transfer reactions of these macrocyclic cages. The oxygen derivative C3 has been the third cage of the series so far synthesized.[29] The cage C3 behaves as a diprotic base, both in solid state and in solution. The first proton cannot be removed even in strong alkaline solution, showing a protonic sponge behavior. In conclusion all the macrocyclic cages belonging to the series are powerful proton receptors and two of them, the aza cage C1 and the oxygen derivative C3, are fast proton sponges: they compete successfully with OH$^-$ in binding protons in aqueous solution. It is interesting to note that if the solvent pure water is replaced with a water/DMSO mixture (50% by mole, $pK_w = 17.6$), all protonation constants are then measurable,[30] even those which are not in pure water.

METAL COMPLEXES

Many metal ions, Li$^+$, Na$^+$, K$^+$, Be^{2+}, Mg^{2+}, Al^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+} and Zn^{2+}, were tested for complex formation with the cage C1. By using ^{13}C n.m.r. spectroscopy no evidence for metal coordination was found for Na$^+$, K$^+$, Be^{2+}, and Al^{3+}, whereas only weak interaction is revealed for the Mg^{2+} ion. With all the other metal ions, except lithium, solid complexes were isolated and characterized. For the diamagnetic ions the formation of the complex was followed by ^{13}C n.m.r., considerable variations in the spectra being found when the metal ion is encapsulated. In the case of the copper complex the ability of C1 to encapsulate metal ions was confirmed by the X-ray crystal structure analysis on $[CuC1](ClO_4)_2\cdot H_2O$. The structure consists of $[CuC1]^{2+}$ cations, $(ClO_4)^-$ anions and water molecules. The copper ion is wholly enclosed by the cage (see Fig. 11), adopting a five-coordinate geometry, which can be described as a distorted square pyramid with the secondary nitrogen in the apical position. Other important experimental evidence supporting the encapsulation is the great inertness of the complex towards strong acid solutions: samples of $[CuC1]\ (ClO_4)_2$ can stay in perchloric acid solutions of different concentration (0.1 up to 7 mol dm^{-3}) at 50°C for many days without any detectable decomposition. Cobalt(II) and nickel(II) ions are

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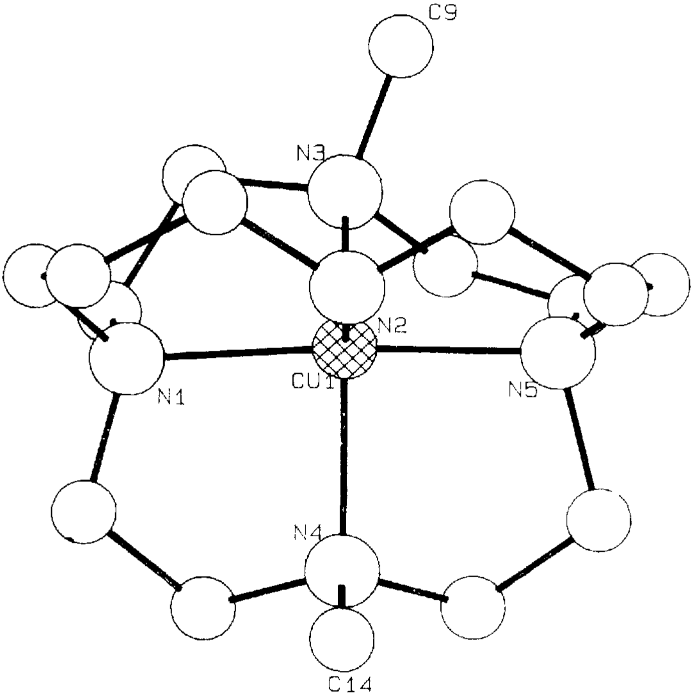

FIGURE 11 Drawing of the $[CuC1]^{2+}$ cation showing only part of the labelling.

also encapsulated into the cage cavity and show great inertness towards acidic decomposition. The ^{13}C n.m.r. spectrum of the zinc complex with C1 indicates encapsulation of the zinc ion. The spectrum consists of nine sharp signals (see Fig. 12) at room temperature in water or DMSO solution. The methyl groups give rise to two signals. The spectrum is indicative of C_s symmetry with the zinc atom and the nitrogen atoms of the $>N-CH_3$ and $>NH$ groups lying in the symmetry plane. The zinc complex is also very inert towards strong acid media. The lithium reacts with $[HC1]^+$ only at high pH. In 1 mol dm^{-3} KOH the formation of the lithium complex is complete as demonstrated by the occurrence of a nine-line ^{13}C n.m.r. spectrum, similar to that of the zinc complex and indicating C_s symmetry. With a 1:2 lithium to $[HC1]^+$ ratio the nine-line pattern occurs along with the six-line pattern due to $[HC1]^+$, signals integration indicating 1:1 metal-to-ligand ratio for the lithium species. Upon addition of 1 mol dm^{-3} HCl the ^{13}C n.m.r. spectrum showed only signals due to $[H_3C1]^{3+}$, indicating the destruction of the lithium complex within the recording time. The selective encapsulation of the lithium ion by the cage C1 is a remarkable ligational property of this cage. Even more interesting

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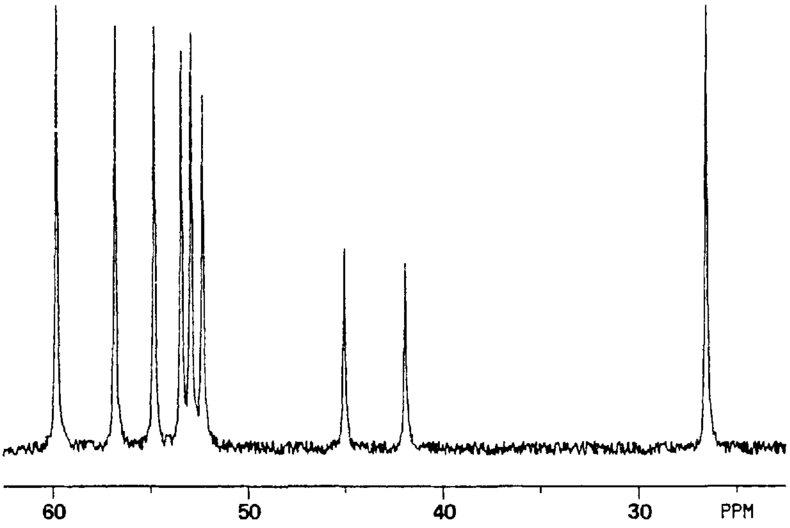

FIGURE 12 ^{13}C n.m.r. spectrum of $[ZnC1]^{2+}$ complex.

is the fact that lithium can be encapsulated but the sodium ion is not, showing 100% discrimination between these two alkaline ions.

The sulphur cage C2 shows much less tendency to bind metal ions than the other cages. A solid compound of composition CuC2 $(ClO_4)_2$ was isolated and characterized. Electronic spectra inertness toward acid solution indicates the encapsulation of the copper(II) ion into the cage cavity. The thermodynamic parameters for the formation reaction of $[CuC2]^{2+}$ are: $\log k = 18.2$, $\Delta H^0 = -14.0$ kcal mol^{-1} and $T \Delta S^0 = 10.8$ kcal mol^{-1}. The stability of the $[CuC2]^{2+}$ complex is not very high, but what is more relevant is that such stability is almost entirely due to an extremely favorable entropic contribution. These results are consistent with the encapsulation of the Cu(II) ion into the cage cavity. Although the ligational properties of the oxygen cage C3 towards metal ions are still under study, some preliminary results indicate that the coordination behavior of C3 is somehow similar to that of the cage C1.

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CONCLUSIONS AND OUTLOOK

The remarkable proton transfer properties of small macrocyclic cages, as well as their ability to discriminate between alkaline ions, make these compounds interesting from both the theoretical and practical point of view.

To synthesize new compounds is an amazing game which has attracted chemists for centuries. Surely this is one important reason to justify the ever growing interest toward the field of macrocyclic chemistry, where theory and experiment merge together to design chemical structures with expected chosen properties. Besides this general consideration there are also more practical reasons which make the near future of macrocyclic chemistry very promising; indeed the already numerous applications of macrocyclic compounds (see Ref. 1) will sharply increase.

Acknowledgments

I am indebted to my colleagues A. Bianchi, M. Ciampolini, E. Garcia-España and P. Paoletti for their contributions, well documented in this article.

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