1

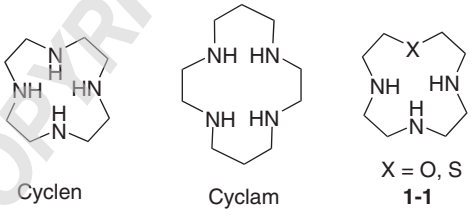
Introduction

1.1 Classification of Macrocyclic Polyamines

Macrocyclic polyamines (MPAs) are important complexing agents for cations, anions, and neutral molecules. In this book, MPAs are defined as having at least three nitrogen atoms and nine atoms in the ring. Although polyazamacrocycles containing amide and imine functional groups cannot be named amines strictly, these macrocycles are also included here. According to the functional groups in the ring, MPAs can be divided into aliphatic MPAs, aromatic-containing MPAs, macrocyclic polyimines, macrocyclic polyamides, and cryptands.

1.1.1 Aliphatic Macrocyclic Polyamines

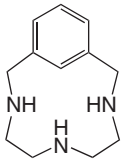
In an aliphatic macrocycle, all carbon and hetero atoms are sp^3-hybridized. Cylen and cyclam are the most used aliphatic MPAs. One or more nitrogen atoms can be substituted with other heteroatoms, such as oxygen or sulfur, to afford heteroatom-substituted MPAs (compound **1-1**).



1.1.2 Aromatic-Containing Macrocyclic Polyamines

To adjust the rigidity of MPAs, aromatic motifs such as benzene and pyridine are introduced. Most aromatic-containing MPAs have a linker between the aromatic motif and the nitrogen atom (compounds **1-2** and **1-3**). Modern transition metal catalysis enables the direct combination of the aromatic motif with the nitrogen atom through the formation of C_{Ar}—N bonds (compound **1-4**).

Macrocyclic Polyamines: Synthesis and Applications, First Edition. Xiaoqi Yu and Ji Zhang.



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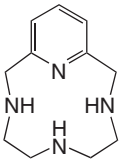

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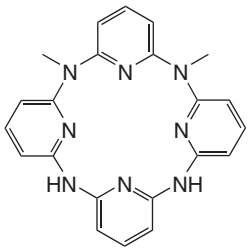

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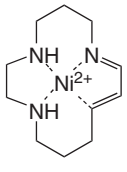
1.1.3 Macrocyclic Polyimines

Macrocyclic polyimines have at least one imine bond in the ring. Because aliphatic macrocyclic Schiff bases have rather low hydrolytic stability, they often complex with a suitable metal template (compound **1-5**). Aromatic-containing macrocyclic polyimines are hydrolytically stable to a certain extent in the absence of a template (compound **1-6**).



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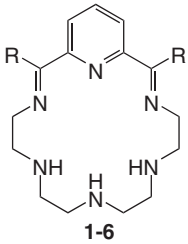

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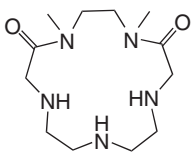
1.1.4 Macrocyclic Polyamides

Macrocyclic polyamides have at least one amide bond in the ring (compounds **1-7** and **1-8**). Macrocyclic polyamides possess the dual features of cyclic peptides and MPAs. Amide-containing macrocycles are usually prepared by cyclocondensation of acids with amines or coupling of the amide-containing precursors.



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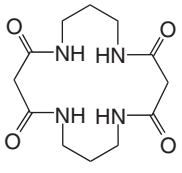

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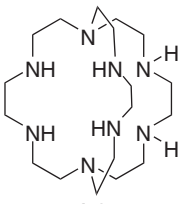
1.1.5 Cryptands

Cryptands (compound **1-9**) are three-dimensional analogs of crown ethers but offer much better selectivity and strength of binding. Spherical cryptands (compound **1-10**) can be described as twice-bridged azamacrocycles.



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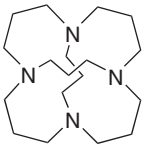

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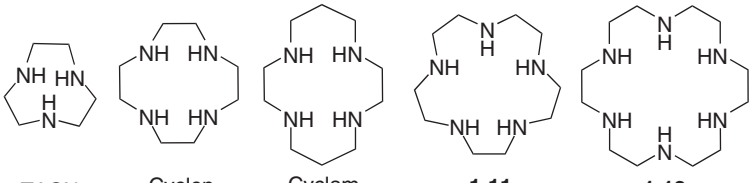
1.2 Properties of Macrocyclic Polyamines

1.2.1 Acid–Base Properties

Except for the nitrogens on the aromatic ring, the amino groups on MPAs are mainly aliphatic secondary amines, which always have relatively strong basicity, and the pK_a values of their protonated species are in the range of 9–11. However, the secondary amines on MPAs have a much wider pK_a range. Generally, the first protonation steps of MPAs are much easier (pK_a 9–11, similar to common secondary amines) than the last protonation steps (pK_a 1–3, low basicity). This behavior might be attributable to charge-repulsion effects [1] due to the higher positive charge density on the cycle compared with open-chain polyamines. Some typical aliphatic MPAs with their pK_a values for each amine are listed below; for detailed data, the reader may refer to the review by Izatt and coworkers [2]. The positive charge of MPAs under neutral conditions facilitates their interaction with negatively charged biomolecules such as nucleic acids and some proteins. MPA derivatives may bind to nucleic acids through electrostatic interaction, protect the nucleic acid cargo from degradation, and deliver the cargo to target cells or tissues (Chapter 4). Moreover, the wider pK_a range of amines may afford the vector materials special pH buffering capability in the intracellular environment, leading to enhanced endosomal escape.



pK_a of protonated amines:	TACN	Cyclen	Cyclam	**1-11**	**1-12**
	10.42	10.51	11.54	10.85	10.46
	6.82	9.49	10.53	9.65	9.51
	0.7[58]	1.6	2.43	6.00	9.01
		0.8[155]	1.97[220, 221]	1.74	4.30
				1.16[432]	~2
					~1[722]

1.2.2 Coordination Property

Macrocyclic structures are extremely favorable for metal complexation. Similar to crown ethers, the nitrogens on MPAs may coordinate to metal ions of

appropriate size. They show a pronounced ability to bind a wide variety of metals and, in many cases, undergo marked conformational changes during binding [3]. The increased stability of a metal coordination complex of a tetra-amine macrocyclic ligand over that of similar noncyclic tetra-amine ligands has been called the macrocyclic effect. 1,4,7-Triazacyclononane (TACN) has a smaller cavity, and the binding ability is weaker than that of cyclen or compound **1-11**. Cyclen may coordinate well to first-row transition elements such as Cu^{2+} and Zn^{2+}, and the resultant metal complexes are widely used as artificial nucleases (Chapter 3), chemical sensors (Chapter 6), ionophores (Chapter 7), or chemical catalysts. MPA **1-11** has a larger cycle, which facilitates its binding with larger metal ions such as Cd^{2+} and Hg^{2+}. In addition, MPAs with a cavity larger than that of **1-11** may also coordinate with more than one first-row transition metal ion [2]. The analogs of **1-12** with 7–9 nitrogens can form dinuclear complexes, whereas those with 11 or 12 nitrogens can form even trinuclear complexes. In addition, pendant coordinating groups can also be attached to the nitrogens on the macrocycle, resulting in more extensive metal coordination properties and applications [4]. For example, some MPA derivatives with carboxylic groups on the arms may act as chelating agents to coordinate with lanthanide metal ions. For example, the Gd-complexes of cyclen derivatives are used intensively in the field of bio-imaging, as described in detail in Chapter 5.

Although most applications involving MPAs employ their metal complexes, the polyamine itself may also serve as a bioactive species. Certain MPAs might act as promising cytotoxic agents by depleting the ATP level of tumor cells [5]. Combinatorial chemistry studies have also found that polyazapyridinophanes possess potent antimicrobial activities [6]. These findings are not included in this book.

1.3 Applications of Macrocyclic Polyamines

As mentioned earlier, most MPA applications employ their metal complexes, which have been used (i) as enzyme mimics, especially artificial nucleases for the cleavage of nucleic acids, (ii) as magnetic resonance imaging (MRI) contrast agents for advanced diagnosis, (iii) as carrier molecules in studies of the selective uptake and transport of metal ions in biological systems, (iv) as gene carriers, (v) as chemical sensors or receptors for metal ions or bioactive molecules, and (vi) in metal recovery that depends on selective extraction. In addition, non-metal chelating MPAs have been used as nucleic acid carriers due to their positive charge in aqueous solution.

The main application areas are reviewed in detail in this book. Chapter 3 presents recent progress on metal or metal-free chemical nucleases based on MPAs, which cleave nucleic acids through a hydrolytic or oxidative mechanism; Chapter 4 introduces non-viral nucleic acid vectors, including cationic lipids and polymers, based on the MPA structure; Chapter 5 presents the use of MPA derivatives as contrast agents in bio-imaging studies; Chapter 6 focuses on the design and synthesis of fluorescent chemosensors for metal ions and bioactive molecules; and Chapter 7 introduces other applications, such as the use of MPA derivatives as ionophores or electrophoretic separation agents.

References

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