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Review

Preparations and applications of synthetic linked azamacrocycle ligands and complexes

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ABSTRACT

Covalently linked azamacrocycles have been known for several decades, but only a modest number of these ligands and their complexes had been described prior to 2000. Since that time, a number of new synthetic methods for their preparation have been discovered, yielding a growing collection of these interesting ligands. Additionally, the number of uses to which these ligands and their metal complexes have been applied has expanded. In this review, the important synthetic methods yielding linked azamacrocycles will be outlined, and their applications will be discussed.

1. Introduction

Inspired by the natural porphyrin and corrin rings (Fig. 1), chemists have produced synthetic azamacrocycles intentionally and in high yields for only about 50 years. Predated only by the phthalocyanines (Fig. 1) [1], an important yet limited early family of synthetic macrocycles with a strong resemblance to the natural sys-

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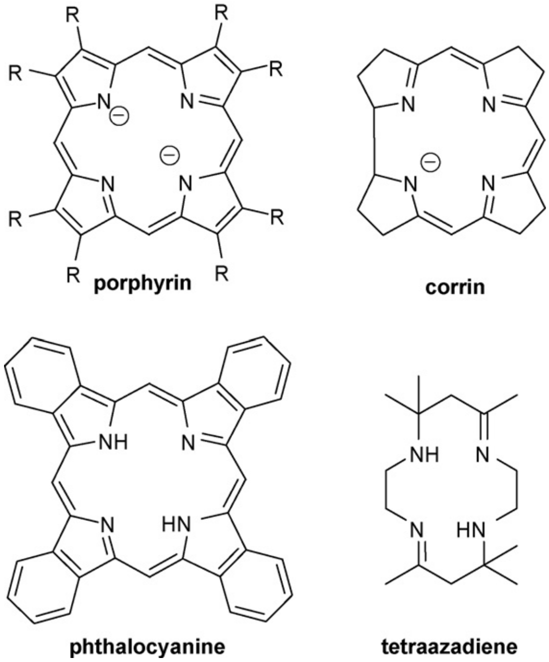

Fig. 1. Naturally occurring (top) and early synthetic (bottom) azamacrocycles.

tems, azamacrocycles in the initial form of tetraazadienes appeared in 1960 (Fig. 1) [2]. This discovery was made several years prior to the crown ethers [3], and synthetic azamacrocycles, crucially aided by the development of metal ion template synthetic routes [2b,4], rapidly developed into a staple for coordination chemistry. In the intervening years, clever synthetic chemists have continued to produce more, and more complex, azamacrocycles with important applications alone and/or in their metal ion complexes [5].

One simple to conceive, yet potentially difficult to carry out, alteration to an azamacrocycle is to join it with another. Architectures produced by joining rings (Fig. 2) include (1) fused ring systems—those in which one or more atom belongs to two or more of the rings; (2) mechanically interlocked multi-ring systems, commonly called catenanes; and (3) linked ring systems—here defined as those not mechanically bonded and having no atoms belonging to more than one macrocyclic ring (**7**).

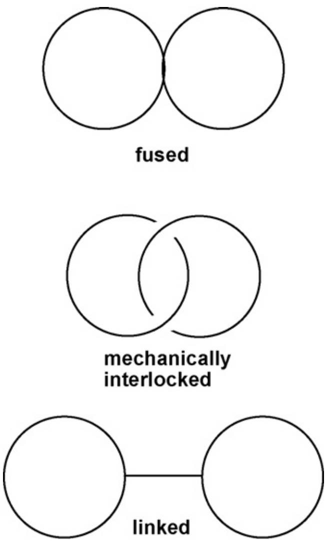

Fig. 2. Types of architectures produced by joining rings. This review will focus on the linked systems.

This review will focus on linked synthetic azamacrocycles (where all donor atoms are nitrogen), concentrating on systems published since the year 2000. Significant progress has been made concerning this subset of linked macrocycles since that time, with no major reviews appearing that we are aware of. Several previous reviews on linked macrocycles were published about that time [6], with two specifically targeting the linked azamacrocycles [7]. Our goal is to update the progress in linked azamacrocycles since then. We will first focus on new synthetic methods (and new examples of old methods) used to produce linked azamacrocycles. We will then turn our attention to the application of linked azamacrocycles to specific problems, beginning with applications of the free ligands and then moving to the major applications of their metal complexes. Due to space constraints, the complexation of metal ions to linked azamacrocycles and the subsequent physical and chemical characterization of those complexes will not be considered a separate "application" for the purposes of this review. The literature since 2000 includes a large number of such studies [8] and would be an excellent topic for review. However, we have chosen to focus this part of the review on instances where these complexes are applied to other chemical problems, as a way to highlight the importance of linked azamacrocycles and their complexes to the broader field of chemistry.

2. Synthetic methods for linking azamacrocycles

2.1. N–N linking

Classically, the nitrogen–nitrogen (N–N) linking of azamacrocycles has proved to be the most common and practical form of linkage due to the reactivity of the nitrogen functionality. However, controlling the mono N–N linkage has often posed a challenge in the presence of the multiple reactive nitrogens. In recent years, several innovative methods for the synthesis of these linked azamacrocycles have been described. These methodologies have most commonly exploited the nucleophilicity of the amine functionality, either as a donor in displacement reactions or as a Schiff base coupling partner.

2.1.1. Bis-aminal strategies

One such broad-scoped methodology was reported by Handel and co-workers in 2001 [9]. The authors described the reactivity of bis-aminals formed by the condensation of tetraazamacrocycles (e.g. cyclen, cyclam, homocyclam) with glyoxal [10]. The alkylation of these bis-aminals to form the corresponding ammonium salts was found to be highly dependent on proper solvent selection. When dihalides were employed as electrophiles, exclusive mono-alkylation was observed in either THF or benzene. The success of this selectivity can be attributed to the low solubility and resulting precipitation of the initially formed ammonium salt in the stated reaction media. However, these mono-ammonium salts were found to be sufficiently soluble in acetonitrile to allow for subsequent reactions. Alkylation with a second equivalent of bis-aminal resulted in the formation of the corresponding N–N linked bis-macrocycle, thus allowing for the formation of either symmetrical or unsymmetrical bis-macrocyclic ligands (Scheme 1). Alternatively, the direct formation of symmetrical bis-macrocycles was achieved in a one-pot process using acetonitrile as the solvent and with proper choice of stoichiometry. The authors found that the bis-ammonium macrocycles could be neutralized by transamination using hydroxylamine.

It was also found that the synthesis of N–N linked macrocycles with pendant arms was possible with the bis-aminal methodology. Exploiting a Gabriel-type synthesis, the authors alkylated cyclen with bromoalkyl phthalimide derivatives (Scheme 2). By control-