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Review

Barbituric acids as a useful tool for the construction of coordination and supramolecular compounds

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ABSTRACT

In spite of its impressive record in medicinal chemistry, the role of barbituric acid H_3BA (pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione) in coordination, organometallic and supramolecular chemistries has not yet been analyzed and reviewed. However, H_3BA can be readily functionalized and provides rich opportunities to create coordination bonds and non-covalent interactions. Thus, derivatives of H_3BA (barbituric acids, BAs) are widely used for the preparation of a wide range of complexes with various metals of almost all groups of the periodic table. The review systematizes information on the synthesis, tautomerism, acid–base properties of BAs and their use for the construction of organometallic and coordination compounds, as well as coordination polymers and supramolecular assemblies. The role of different metal ions and the structure of BAs in directing the preparative pathways and tuning particular structural properties of the resulting compounds are discussed. Some valuable applications of BAs, in particular in the construction of molecular receptors, magnetic and nonlinear optic materials, bioactive compounds, drug cocrystal design, catalysis and photochemistry are also envisaged.

Abbreviations: AHBA, arylhydrazones of barbituric acids; BAs, barbituric acids, barbiturates; DMF, dimethylformamide; DMSO, dimethylsulfoxide; en, ethylendiamine; H_3BA, barbituric acid; H_2DMBA, dimethylbarbituric acid; H_2DEBA, diethylbarbituric acid (veronal); H_3NBA, 5-nitrobarbituric acid; HNNDMBA, N,N′-dimethylbarbituric acid; HNNDVA, N,N′-dimethylvioluric acid; H_5PURP, purpuric acid; H_3TBA, thiobarbituric acid; H_3VA, violuric acid; NH_4H_4PURP, ammonium purpurate; NLO, nonlinear optics; phen, 1,10-phenanthroline; py, pyridine; RAHB, resonance-assisted hydrogen bond; THF, tetrahydrofuran; 2,2′-bpy, 2,2′-bipyridine; 4,4′-bpy, 4,4′-bipyridine.

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1. Introduction

The chemistry of derivatives of barbituric acid (pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione, H_3BA) (Scheme 1), commonly known as barbiturates (BAs), has been a subject of permanent attention due to their significance in biology and medicine [1,2]. Thus, barbiturates are used as depressants for the central nervous system, sedative hypnotics, anticonvulsants and anesthetics; most of them exert a sedative effect in small doses and a hypnotic effect in larger doses. H_3BA itself is not biologically active, and the pharmacological properties of BAs mainly depend on the side groups attached to the C5 atom of the pyrimidine ring [1,2]. In spite of their impressive record in medicinal chemistry, the application of BAs in coordination and supramolecular chemistries is relatively recent and still has not been reviewed.

H_3BA contains five (three O and two N, Scheme 1) potential metal binding (donor–acceptor) sites, what makes them versatile polyfunctional ligands. Due to the ability of the activated CH_2 group to lose one of the protons, the pyrimidine ring is additionally stabilized by resonance delocalization (Scheme 1), while the donor–acceptor properties of the heteroatoms vary along the molecule [3]. Thus, the most acidic proton in H_3BA is one of the methylene hydrogen atoms with pK_a of 4.03 [4]; deprotonation at this site allows the formation of a planar carboanion. Moreover, the pyrimidine ring of H_3BA can be easily functionalized at position 5. For instance, introduction of a diazo moiety at this position gives rise to arylhydrazones of BAs (AHBAs), which provide interesting solvatochromic and coordination properties [5–11]. AHBAs also can be used as disperse fluorescent dyes, as charge generation agents for electrophotography and photoreception, or as non-linear optical materials [12].

In addition to their metal binding properties, BAs also possess multiple sites for the creation of non-covalent bonds, namely hydrogen bonding. Hence, BAs can be used as building blocks to construct supramolecular assemblies with distinctive properties. Indeed, diverse complex salts and organic cocrystals of different packing topologies and with interesting supramolecular hydrogen networks have been obtained with the use of barbituric acids [13–19]. The combination of coordination properties and possibilities to create non-covalent interactions ensure a rich metallosupramolecular chemistry of BA compounds. On the other hand, the donor–acceptor features of BAs are important for crystal design of pharmaceuticals, molecular recognition and catalytic activity [20–22].

Historically, the coordination chemistry of BAs can be traced back to the synthesis of a copper(II) complex of 5,5-diethylbarbituric acid (H_2DEBA, Veronal) with pyridine (py), $[Cu(HDEBA)_2(py)_2]$ [23]; complexes of this type are important agents in the detection and identification of barbituric drugs. The current version of the Cambridge Structural Database reveals more than 900 hits, concerning crystal structures of BAs, and among them ca. 200 relate to complexes comprising H_3BA and its derivatives [24]. In metal complexes, BAs generally exist in the deprotonated form with hydroxyl O or pyrimidine N donors coordinated to metal ions, what leads to discrete mono-, bi- or polynuclear structures [25–30]. In this review we will mainly deal with the fully structurally characterized complexes and supramolecular assemblies, unless mentioned otherwise. The transition metal complexes are normally treated according to the increasing atomic number of their central metals.

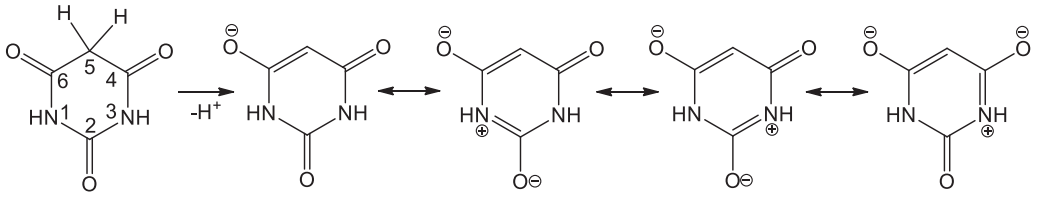
2. Barbituric acids: synthesis and properties

2.1. Synthesis

Barbituric acid was synthesized for the first time in 1864 by Adolf von Baeyer; the synthesis involved the condensation of urea with diethyl malonate [31,32]. The barbiturates were introduced for medical use as early as 1900s; since then more than 2500 BAs have been synthesized, and about 50 were marketed, mainly for pharmacological use, indicating their high popularity. A number of syntheses of BAs have been described in the literature [33–36] and the most important of them are depicted in Scheme 2. For example, malonic acids, malonyl dichlorides or malonic esters condense with urea to give H_3BA (Scheme 2a and b). By far the most common procedure toward barbituric acids is the Michael method [34], which consists of condensation of urea with the appropriate diethyl malonate in the presence of sodium ethoxide in anhydrous alcohol (Scheme 2b). This method has been generally adopted for the industrial production of barbituric acids and also represents the most common laboratory preparative procedure. Similarly H_2DEBA can be prepared by condensation of urea with diethyl-2,2-diethylmalonate in the presence of sodium ethoxide followed by the elimination of two molecules of ethanol (Scheme 2c) [35]. The reaction of 1,3-disubstituted urea with 2,2-disubstituted malonic acids in many instances also leads to barbiturates. Thus, when 2,2-disubstituted malonic acid and two moles of 1,3-disubstituted urea are brought together in THF solution, an exothermic reaction leads to the formation of a crystalline 1,3,5,5-tetrasubstitutedpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (Scheme 2d) [33].

A modification of the BA synthesis which involves an alkali hydroxide as condensing agent and liquid ammonia as solvent results in dialkylbarbituric acids [34]. According to this procedure, a mixture of diethyl dialkylmalonate, urea and an alkali hydroxide in liquid ammonia leads to the desired product. However, when diethyl malonate or monoalkylated diethyl malonates were tried, none of the desired barbituric acids were isolated. Similarly, malonamide or its C-alkyl derivatives and ethyl carbonate in liquid ammonia in the presence of alkali condense to the corresponding derivatives of barbituric acid (Scheme 2e). This reaction appears to be quite general, giving good yields of barbituric acids from malonamide, C-alkylmalonamides or C,C-dialkylmalonamides [34].

Another feature with synthetic relevance comprises the ability of BA to be easily modified further, e.g. at the active methylene in position 5. Thus, treatment of aromatic diazonium salts with barbituric acid in ethanolic solution containing base (Japp-Klingemann reaction, Scheme 3) gives AHBAs [6,7,9–11,37,38], which can be used further as intermediates in organic synthesis [38] or as ligands in coordination chemistry [6,7,9–11,37]. Similarly, nitrite reacts with barbituric acid in acidic solution to give the nitroso derivative, 5-(hydroxyimino)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (H_3VA,



Scheme 1. Molecular structure of barbituric acid (H_3BA) and resonance forms of its deprotonated form.