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A Tetrakis(tetrazolyl) Analogue of EDTA

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The tetrazole moiety is usually established in situ with the corresponding inconveniences, such as reactant incompatibility, yield. In most of these cases, the tetrazole is formed in its nonprotected form. Subsequent protection is unattractive because of the promiscuous formation of two regioisomers. No particular protecting group has seen widespread use. The growing field of site-selective oxidation of unactivated hydrocarbons makes use of metal complexes based on multidentate ligands displaying nitrogen coordination sites. We have characterized an easily accessible, benzyl-protected synthon that allows the convergent introduction of the tetrazolylmethyl moiety and its smooth deprotection by catalytic hydrogenation. With the straightforward synthesis of the new hexadentate ligand EDTT, we have demonstrated the utility of this synthon for the fields of coordination, medicinal, and organocatalytic chemistry.

Introduction

The selection of available organic multidentate ligands for coordination chemistry is constantly growing. Metal complexes with refined or novel properties are in great need for fields as diverse as spin transition materials[1,2] or site-selective oxidation of unactivated hydrocarbons.[3–7] Particularly, the latter often favors the use of redox-active iron complexes with open coordination shells to accommodate the substrate and in which the metal ion is in the oxidation state +2. Such complexes are characterized by the preferred or even exclusive presence of nitrogen donor sites, sites that favor the ferrous state according to the HSAB theory. Pendant arms offering imine-type nitrogen coordination sites derived from pyridine, imidazole, or Schiff bases are particularly popular. These arms are frequently grafted onto aliphatic nitrogen atoms because this atom offers the very welcome possibility of creating branched multidentate ligands, which leads to five-membered chelate rings (for example, see ref.[8]). Neither of these two types of N-coordinating sites presents a negative charge as is often observed for O-coordinating moieties (carboxylate, phenolate, catecholate). The corresponding complexes are thus mostly cationic or strongly cationic, which limits (a) their thermodynamic stability, (b) the range of catalytic properties attainable, (c) the media where they can be employed, and (d) the span of accessible redox potentials.

By expanding the armamentarium of pendant arms available to the coordination chemist with new anionic N ligands, a vast number of new binary metal complexes are within our reach, some of which have potentially unique properties. Of course, the deprotonated carboxamide bond has been known as an N ligand since the discovery of the Biuret reaction. But the acidity of the carboxamide moiety is negligible ($pK_a \approx 26$ in DMSO),[9] and only the thermodynamic driving force of the formation of a particularly strong binary complex with Cu^I in conjunction with the aid of 1% KOH shifts the deprotonation equilibrium to the anionic form. The intuitive presumption that incorporation of the N–H "acidic" nitrogen atom into an extended π system would appreciably lower the pK_a does not hold. For example, "monoacidic" dipyrrins[10] have received growing attention as anionic N ligands, particularly for BODIPY-derived dye development,[11,12] but they still show rather high pK_as (pK_a = 18–21 in DMSO/H_2O/Me_4NOH).[13] Further, their utility in the generation of a multidentate ligand is severely limited by their complete rigidity. In fact, they can be regarded as a coplanar fragment of the porphyrin system. Even lower N–H acidity has been determined for the porphyrins.[14] More recently, Limbach and Schwesinger et al. estimated a pK_a of approximately 37 in acetonitrile.[15] In any case, this tetradentate system already dictates the identity of four of the six coordinating units because of its unique planar structure, and the grafting of a pendant arm on it for occupation of a fifth coordination site leads to thermodynamically very weak macrocyclic chelate rings.

Results and Discussion

In view of the above considerations, we have therefore opted for the use of the tetrazole unit to provide the *N*-anionic coordination site. Tetrazole exhibits a very attrac-

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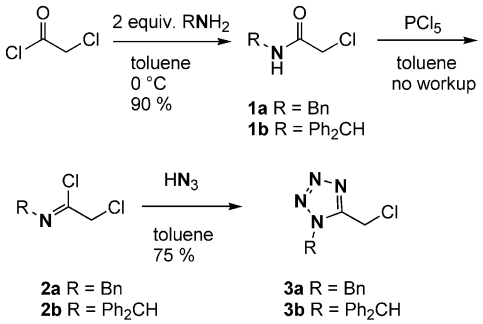
tive aqueous pK_a of 4.90,[16] which is comparable to that of acetic acid. Even 5-methyltetrazole still shows a pK_a of 5.56, and further substitution on the 5-methyl group can significantly lower this value.[17,18] The tetrazole moiety thus offers a full negative charge at neutral pH for effective coulombic compensation of metal-associated positive charges, and thus contributes to maximum complex strength at this pH, provided that all other requirements for structural and orbital complementarity are satisfied. The exploitation of tetrazole as a monodentate ligand dates far back.[19,20] But its incorporation into multidentate ligands that leads to five-membered chelate rings upon complexation has not yet been attempted. In the domains of medicinal chemistry and drug design,[21,22] and lately also more frequently in organocatalysis,[23–26] the tetrazole moiety is of particular interest as a carboxylic acid "isoster".[27] Here, it is usually established in situ with the corresponding inconveniences (reactant incompatibility, yield). In most of these cases, the tetrazole is formed in the nonprotected form.[28] Subsequent introduction of a protecting group is rarely attempted in view of the mixture of two regioisomers obtained and the low yields encountered. A recent approach establishes the in situ formation of tetrazole as well, but this time in the protected form.[29] However, this method requires the prior establishment of an activated (acylated) nitrile and its reaction with an activated azide, measures that encourage consideration of alternative strategies. Specifically, introduction of a preformed, preprotected tetrazole in the form of a readily accessible synthon would be attractive. Our thorough study of the literature also revealed that no protecting group for tetrazoles has yet found widespread acceptance and application. In fact, of the two principal monographs on protecting group chemistry,[30,31] only that by Wuts and Greene[30] offers any solution for azoles, but it basically limits coverage to imidazoles and pyrroles. Pyrazoles or tetrazoles, in particular, are not covered at all.

Unprotected 5-aminomethyltetrazoles (bidentate ligand character) were synthesized by a direct synthesis.[32] However, no methyl groups bearing a suitable leaving group for introduction into various systems by nucleophilic substitution were presented in that study. The only research on the preparation of a suitably substituted tetrazole was performed by Harvill et al. in 1952,[33] who applied the classic tetrazole synthesis introduced by von Braun.[34] However, while including the *N*-benzyl group in their study, they did not consider it as a potential protecting group. We applied their protocol by fusing easily accessible hydrazoic acid with the corresponding chloromethylchloroimine (Scheme 1). The presence of a protecting group that can be removed by catalytic hydrogenation was obviously at the heart of the attractiveness of this synthetic target.

Chloroacetyl chloride was thus reacted with exactly 2 equiv. of the benzylamine or diphenylmethylamine to furnish the corresponding amides **1a** and **1b**, respectively, in almost quantitative yield (Harvill et al. reported a yield of 39% for a different protocol[20]). The second equivalent of amine can of course be recycled from the mixture by simple



Scheme 1. Introduction of the flexible N substituent in a previously reported[33] access to a tetrazolyl-bearing synthon.

extraction. We were cautious because of the known difficulty of removing the benzyl group from nitrogen sites. We thus included the diphenylmethyl group in our study for its demonstrated superiority in its removal from regular aliphatic amines.[35] Subsequent transformation into the chloroimines **2a**,**b** by use of phosphorus pentachloride is straightforward, but care has to be taken in driving out all traces of hydrogen chloride before proceeding to the next step (see Supporting Information).

A concentrated solution of hydrazoic acid in toluene is easily prepared by extraction of a sodium azide solution treated with sulfuric acid, whilst working under a properly operating fume hood. This solution is then merged with the toluene solution of the crude chloroimine and stirred at room temperature overnight to give tetrazoles **3a**,**b** in 75% yield over two steps (Harvill et al. reported a yield of 52%). Only 2 equiv. NaN_3 should be used in order to prevent losses in yield as a result of secondary attack on the chlorine-bearing methylene group. The 1,5-substitution pattern of the thus obtained tetrazoles, intrinsically tied to the constitution of the starting material, was demonstrated through X-ray structure analysis of a crystalline sample of **3b** (Figure 1). We first explored hydrogenation of these compounds in order to learn the precise conditions for efficient removal of the protecting group. During the experiments, we eventually realized that the chlorine atom is reliably replaced by a hydrogen atom, no matter how smooth the conditions ap-

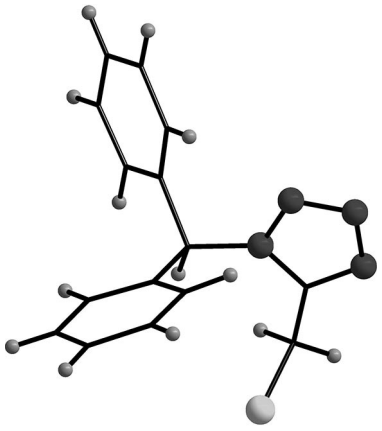
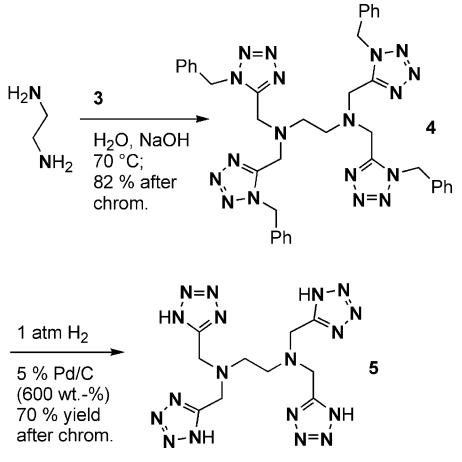


Figure 1. 1,5-substitution pattern in **3b** (X-ray structure analysis).

plied. We also learned that the benzyl group leaves so easily that use of the more labile diphenylmethyl group would not be necessary. We thus decided to continue to demonstrate the introduction of the tetrazolylmethyl moiety into nucleophile-displaying entities using only the benzylated version **3a**.

In our desire to generate bidentate N-coordinating moieties offering a negative charge at physiological pH and that lead to five-membered chelate rings, we identified the classic EDTA ligand as the appropriate target to transform into a tetrakis(tetrazolyl) analogue, *N*,*N*,*N*′,*N*′-tetrakis(tetrazolylmethyl)-1,2-ethanediamine EDTT (**5**, Scheme 2). EDTT should a priori display the same zwitterionic character as EDTA. The use of acetonitrile as solvent and K_2CO_3 as base (commonly used conditions for alkylation) did not advance the reaction of ethylenediamine with a quantity of **3a** that slightly exceeds four equivalents. After one week, virtually all possible species were detected in the reaction mixture by LCMS analysis. However, four decades ago, the formation of the all-picolyl analogue of EDTA (TPEN: an altogether basic hexadentate ligand that has found widespread application as a membrane-permeable Zn chelator to induce apoptosis by Zn deprivation)[36] was accomplished in a heterogeneous reaction by treating an aqueous solution of ethylenediamine and NaOH with the insoluble liquid picolyl chloride (48% yield).[37] When we applied similar conditions, we were forced to heat the mixture to 70 °C in order to melt solid **3a** and achieve some degree of homogeneity by vigorous stirring. To our delight, we thus obtained the crude target compound **4** in an overnight reaction in quantitative yield. Column chromatography on silica gel preconditioned with TEA somewhat limited the yield of pure basic **4** to 82%. A supplementary attempt at reacting the diphenylmethyl analogue **3b** in this fashion was not successful because **3b** did not melt even at 100 °C.



Scheme 2. Grafting of four tetrazolyl units onto ethylenediamine.

In contrast to our observations with **3a**, we were surprised to discover that hydrogenation of pure **4** with catalytic amounts of 5% Pd/C in a mixture of dichloromethane and ethanol (**4** is scarcely soluble in ethanol) at 1 atm hydrogen hardly advanced at all. We then embarked on a thorough optimization of the conditions monitored by LCMS analysis. Eventually, it was established that complete removal of all four protecting groups was possible in 48 h with 600 wt.-% of catalyst powder, at 20 °C and 1 atm hydrogen. Importantly, any additional amount of catalyst added at a later time to jumpstart a potentially slowing hydrogenation was ineffective even when applying great care in purging the flask with hydrogen; it is thus imperative that the necessary amount of catalyst for complete conversion is added at the beginning. On the positive side, no side products were formed at this "catalyst" loading as demonstrated by monitoring with mass spectrometry. However, we observed that a picolyl group, if linked to an aliphatic nitrogen atom present in a compound bearing multiple benzyltetrazolylmethyl groups, is effectively removed under these conditions. Purification of the resulting zwitterionic target compound **5** was accomplished by chromatography on a reversed-phase column (C18) by using a mobile-phase gradient composed of acetonitrile and water. Of course, ion exchange chromatography would be an alternative means. In our hands, the final yield of pure **5** was thus 70%.

Conclusions

We have demonstrated that introduction of a tetrazolylmethyl group into a nucleophile-bearing compound is straightforward when a preformed tetrazolyl synthon is used rather than when this heterocycle is established in situ as reported widely in the literature. The synthon already contains the benzyl moiety, a protecting group particularly popular for its smooth removal conditions, which are compatible with most chemistries found in the target compounds. No complications stemming from a lack of 1,2-regioselectivity have to be feared. The presented protocol of synthon preparation as originally developed by Harvill et al.[33] is likely transferable to tetrazoles bearing other 5-substituents, provided that they are compatible with PCl_5 treatment of the corresponding amide. Benzyl removal is catalytic and requires only a hydrogen-filled balloon. However, in the case of multiple units grafted onto one molecule and particularly in the presence of tertiary amine sites, the quantity of Pd/C has to be significantly increased. We wish to stress here that compounds **4** and **5** appear to be much more stable thermodynamically relative to picolyl-bearing species such as TPEN[37] or TPTACN.[38] The latter tend to lead to rapid darkening in the course of the reactions whether they are starting material *or* the product.[37,38] It is thus often difficult to obtain light-colored samples by purification, and the yields are accordingly limited. By contrast, the chemistry of compounds/ligands decorated with the tetrazolylmethyl group, whether benzyl-protected or not, is characterized by high yields and colorless material.

Supporting Information (see footnote on the first page of this article): Experimental procedures and full spectroscopic data for all new compounds are presented.

CCDC-696050 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The

Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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