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Synthesis of a Water-Soluble, Soft N-Donor BTzBP Ligand Containing Only CHON

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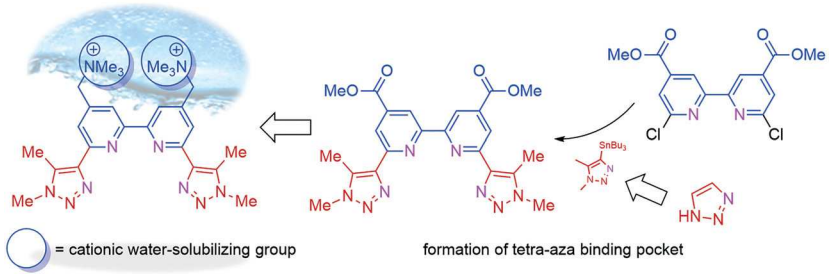

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Abstract A hydrophilic ligand that contains only C, H, O, and N substituents and uses a 6,6′-bis(1*H*-1,2,3-triazol-4-yl)-2,2′-bipyridine (BTzBP) structural core has been synthesized. The effect of adding water-soluble groups onto extractant ligands has been extensively studied to facilitate the efficient partitioning of 4f and transuranic 5f elements for the treatment of spent nuclear fuel. Soft, N-donor ligands exhibit greater binding affinities for the trivalent actinides over the trivalent lanthanides, making BTzBP ligands an ideal candidate in the search for extractants to be used on an industrial scale. To date, hydrophobic BTzBPs have been shown to exhibit physical and chemical properties that might be conducive to nuclear waste processing conditions. However, hydrophilic BTzBPs have yet to be reported. Herein, we show the synthesis of a hydrophilic BTzBP ligand featuring cationic water solubilizing groups attached to the bipyridal rings.

Key words BTzBP, separations, actinide, lanthanide, solvent extraction, CHON, triazolyl

To meet the increasing demand for clean and reliable energy, the production of electricity through nuclear energy is an integral element to meet the baseload needs for the future. As a side effect, there will be an increase in the nuclear waste inventory and, with no long-term storage options, waste management solutions need to be developed. Partitioning and Transmutation (P&T) of spent nuclear fuel is a rational approach to the challenge of reducing the volume and radiotoxicity of high-level waste.[1] A major technological challenge for this option is the ability to efficiently separate the transuranic elements (Am, Cm, Np) from the ever-present fission product lanthanides (La–Ho and Y).[2] Prior to Am/Cm transmutations, the neutron scavenging lanthanides must first be eliminated.[1,2]

Due to the nearly identical chemical behavior of the An(III) and Ln(III), development of efficient separation methods is challenging. Both the An and Ln have predominate trivalent oxidation states, similar ionic radii that decrease with increasing atomic number across groups, and similar ionic bonding in complexes.[3] However, it has been demonstrated that complexing ligands containing donor atoms softer than oxygen (e.g., nitrogen, sulfur) exhibit greater binding affinities for An(III) than Ln(III) as a result of covalent interactions between Am^{3+} and soft N-donor heterocycles.[4] Thus, the number of syntheses of ligands containing N-donor atoms have increased due to the interest in developing better An(III)/Ln(III) separation methods.

An interesting array of new molecules have been reported during the past 25 years, and processes for their use have arisen but, to date, none have reached the stage of full-scale application.[5] One could conclude from the present status that there may well be room for new approaches based on advanced reagents. For implementation on an industrial scale, reagents must satisfy numerous criteria, making ligand design challenging. These reagents must selectively extract An(III) over Ln(III), be sufficiently soluble in the desired solvent, and be resistant to acid hydrolysis and radiolysis. Ideally, the reagent should also consist exclusively of C, H, O, and N (the 'CHON' principle) so that wastes may be incinerated when they can no longer be used, without generating corrosive by-products.[6]

Of the nitrogen-containing ligands studied for the purpose of conducting liquid-liquid separations, a large number of bis-triazinyl bipyridines (BTBPs) and bis-triazinyl

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phenanthrolines (BTPhens; Figure 1A) have been intensively investigated due to their selectivity for An(III) over Ln(III) in acidic media and to evaluate how structural features affect separations and to overcome slow rates of extraction, poor solubility in nonpolar diluents, and acidic or radiolytic/hydrolytic instability observed for this ligand class.[7–9]

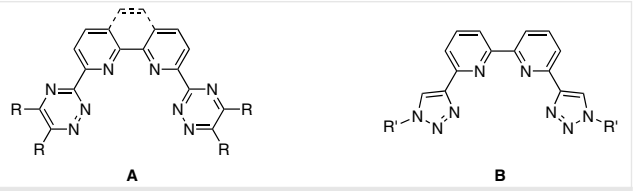


Figure 1 General structure of BTBP, BTPhen, and BTzBP N-donor ligands

To address the challenge of stability, previous investigations focused on the synthesis of novel hydrophobic tetradentate nitrogen-based complexants by combining 1,2,3-triazolyl rings with the favorable binding configuration of a bipyridine core. These BTzBP ligands (Figure 1B) have been shown to extract An(III) over Ln(III) selectively ($SF_{Am/Eu}$ ca. 70) with the use of a cation exchanging co-extractant (2-bromohexanoic acid), have good metal-binding kinetics, and be resistant to degradation in highly acidic and oxidative media.[10] These results establish the essential viability of this class of complexants and suggest avenues for additional improvements.

Recently, the innovative Selective ActiNide EXtraction (i-SANEX) process has shown promise for the extraction of both An(III) and Ln(III) into the organic layer using *N*,*N*,*N*′,*N*′-tetraoctyldiglycolamide (TODGA), followed by the back-extraction of the An(III) into the aqueous layer with an appropriate hydrophilic ligand.[11] A diverse array of triazinyl BTP, BTBP, and BTPhen ligands using sulfonates as the solubilizing groups have been made and have demonstrated marked selectivity for An(III) over Ln(III).[12] However, the use of sulfonates is not ideal for incineration and would generate additional waste streams post processing.[6] In contrast, only a limited number of hydrophilic ligands have been made that combine the beneficial features of the triazolyl unit of the BTzBP ligands with water-solubilizing groups.

The PyTri series of ligands have shown good solubility in water and dilute HNO_3 solutions (ca. 150–200 mM) while exhibiting good $SF_{(Eu/Am)}$ = 100 (Figure 2A).[13] On the other hand, the BTrzPhen ligands (Figure 2B) gave a $SF_{(Eu/Am)}$ about half that of the PyTri ligands, but with a ligand concentration eight times less (solubility is ca. 10 mM in 0.3–3.0 M HNO_3 solutions). In addition, the BTrzPhen ligands also exhibited $SF_{(Cm/Am)}$ of 2.5.[14]

With the BTzBP ligands having ideal physical and chemical characteristics in organic solvents and the BTrzPhen ligands exhibiting preferential binding of Cm over Am, making a hydrophilic BTzBP ligand is an important advancement for these ligand classes. Herein, we report the

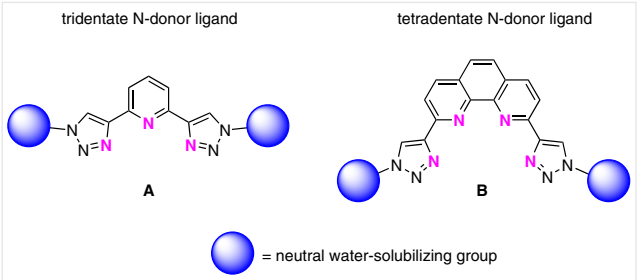
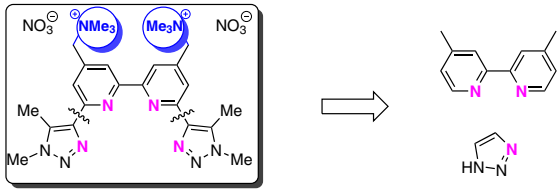


Figure 2 Core structures of hydrophilic triazolyl based tri- and tetradentate ligands

synthesis of a new hydrophilic BTzBP ligand introducing a new water-solubilizing group to these ligand classes by incorporating cationic trimethyl ammonium groups on the backbone of the bipyridyl group, while remaining CHON compliant (Scheme 1).



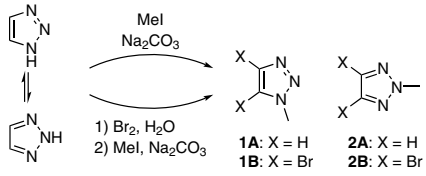
Scheme 1 Hydrophilic BTzBP ligand with a cationic water-solubilizing group

Installation of the triazolyl unit onto the bipyridyl backbone involves two general synthetic pathways. The use of 'click' chemistry utilizing azides has provided many convenient syntheses for a variety of triazolyl scaffolds.[15] In this synthesis, a small R group (Me) was used at the N1 position. However, azides with a low carbon-to-nitrogen ratio are highly reactive and can be explosive.[16] While methyl azide reagents have been synthesized *in situ* to be used in click chemistry,[17] modifying and adding a triazolyl unit directly provided a high yielding and safer method to scale the reaction up to a multigram scale.

The key synthetic step is a Stille coupling between the triazolyl and bipyridyl units. Using 1,2,3-triazole as the starting point, modification of the N1 and C5 positions of compound **1** is necessary in order to add the required $SnBu_3$ group at the C4 position, allowing for the correct arrangement of the nitrogen atoms to form the binding pocket.

Making the desired compound **1** is complicated by the fact that the 1,2,3-triazole exists as two interconverting isomers. As a result, substitution of any desired group on the nitrogen atom makes two different isomers at the N1 and N2 positions in different ratios depending on the conditions used. Wang et al. have shown how substituents and solvents affect the alkylation and acylation of 1,2,3-triazoles and 4,5-dibromo-1,2,3-triazoles.[18] As the size of the substituent increased, so did the yield of isomer **2**. Similarly,

the larger Br on the 4,5-dibromo-1,2,3-triazole led to an increase in the yield of isomer **2**. Interestingly, when Wang et al. decreased the temperature from room temperature to 0 °C, the reaction further favored the formation of isomer **2** (Scheme 2).



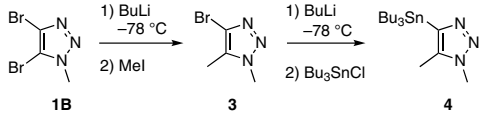
Scheme 2 Methylation of the 1,2,3-triazolyl unit and the dibromination of C4 and C5

Therefore, to increase the amount of the desired isomer **1B**, the reaction was heated in a screwcap vial at 25, 100, and 110 °C for 1 h. Isolated yields of the desired isomer **1B** increased from 49, 57, to 60%, respectively. In fact, ^{1}H NMR analysis of the crude reaction mixture after heating at 110 °C showed a 2.0:1 ratio of isomer **1B**/**2B**, effectively showing an equal statistical probability of substituting at the N1 vs. N2 positions.

For both compounds **1A** and **1B**, the C5 position is the more reactive position. Ohta et al. have shown that subsequent deprotonation and reactions of **1A** can take place first at the C5 and then at the C4 position.[19] However, these yields were typically less than 60%, and, in the case of substituting a methyl group, it was less than 50%. As an alternative approach, bromination of the 1,2,3-triazole was explored.

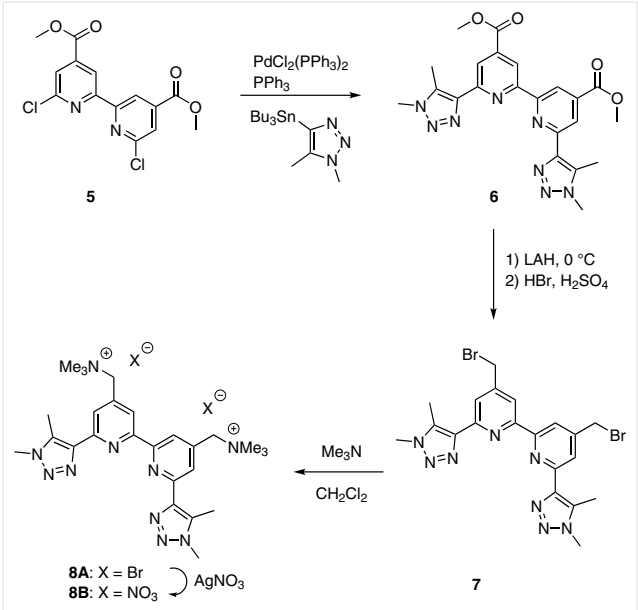
Bromination of the 1,2,3-triazole was carried out in a water/bromine mixture, resulting in the precipitation of 4,5-dibromo-1,2,3-triazole as a white solid.[20] Bromine was added twice to the filtrate to ensure complete bromination, which gave an overall yield of 98%. Attempts were first made to carry out the modification of **1B** by adding a hydrogen at the C5 position. However, when the subsequent halide exchange reaction was attempted at the C4 position, deprotonation of the hydrogen at the C5 position was kinetically competitive to the halide exchange at C4, resulting in the substitution of the Bu_3Sn group at both the C4 and C5 positions.

To eliminate the mixture of products being formed, a methyl group was added first in place of hydrogen by carrying out the halide exchange reaction on **1B** with *n*-BuLi at –78 °C and then quenching the reaction with MeI to make **3** (92% yield) (Scheme 3). Overall, use of the brominated **1B** proved to be more efficient (91% over two steps) than the direct substitution from **1A** (<50%).[19] Then, in a similar fashion, the Bu_3Sn group was added by the halide exchange with *n*-BuLi at –78 °C followed by quenching the reaction with Bu_3SnCl, giving the desired Stille reagent **4** that could be used without further purification. Therefore, the desired Stille reagent **4** can be made from 1,2,3-triazole in four steps with good to high yields.



Scheme 3 Modification of the 4- and 5-position of the triazolyl unit

To install the triazolyl rings onto the bipyridyl backbone forming the tetra-aza framework, a Stille coupling reaction between compounds **4** and **5** was carried out in toluene at 110 °C for 18 h (Scheme 4). During this time, the product **6** precipitated out of the solution and was collected via filtration to give an isolated yield of 70%.



Scheme 4 Four-step synthesis to make the hydrophilic BTzBP N-donor ligand

The final sequence in the synthesis was to covert the ester into the ammonium salt to enhance its hydrophilicity. The ester was reduced with lithium aluminum hydride to yield the diol (66% yield). Conversion of the hydroxyl groups into an appropriate leaving group, Br, with HBr in H_2SO_4 allowed for the formation of **7** in 85% yield.

The last step was to substitute the leaving group with a trimethylamine group to form the bis-trimethyl ammonium salt. This was accomplished by adding trimethylamine to a dichloromethane suspension of **7**. After stirring for 24 h, removal of the solvent left **8a** in 99% yield. Conversion into the nitrate salt **8b** was carried out by dissolving **8a** in water and adding $AgNO_3$.[21] Filtration and removal of the

solvent gave the final CHON-compliant water-soluble, N-donor BTzBP ligand.

A survey of the solubility of **8a** in different concentrations of nitric acid (the desired solvent for the An/Ln target ions) showed that, even in de-ionized water, the ligand has a molar solubility of ca. 35 mM (ca. 3× greater than that observed for the BTrzPhen ligands). This increases slightly to ca. 5 mM in 1 M HNO_3. However when the concentration of HNO_3 was increased to 2 and 4 M, an even more substantial increase in solubility to ca. 175 and >780 mM, respectively, was observed. A preliminary analysis of these solutions showed no degraded or hydrolyzed products by ^1H NMR spectroscopy after four weeks at room temperature.

In conclusion, this new, water-soluble, CHON-compliant, N-donor BTzBP ligand can be made in a high yielding and readily purified route. The change in nature and placement of the solubilizing group on these classes of ligands increases its solubility by ca. threefold compared to the BTrzPhen ligands, making this ligand an excellent candidate for future extraction and solution studies.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707163.

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(21) **Characterization Data for 8b:** ^{1}H NMR (D_2O 400 MHz): δ = 2.63 (s, 6 H), 3.20 (s, 18 H), 4.00 (s, 6 H), 4.69 (s, 4 H), 8.01 (s, 2 H), 8.18 (s, 2 H). ^{13}C NMR (100 MHz, D_2O): δ = 9.2, 34.5, 52.9, 67.6, 122.8, 124.6, 134.8, 138.1, 141.8, 151.4, 155.2. IR (ATR): 669.1, 750.1, 872.9, 902.2, 934.0, 977.3, 1067.3, 1113.4, 1162.8, 1277.9, 1326.0, 1480.8, 1560.3, 1606.1, 2910, 2955, 3035, 3373 cm^{-1}. HRMS (ESI): *m*/*z* $[M]^{+2}$ calcd for $C_{26}H_{38}N_{10}$: 245.1635; found: 245.1630.