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Encaging the Verkade's Superbases: Thermodynamic and Kinetic Consequences

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Supporting Information

ABSTRACT: Proazaphosphatranes, also known as Verkade's superbases, are nonionic species, which exhibit catalytic properties for a wide range of reactions. The properly designed host molecule **3** and its protonated counterpart $[\mathbf{3}\cdot\mathrm{H}]^+\mathrm{Cl}^-$ were synthesized to study how confinement can modify the stability and the reactivity of a Verkade's superbase. The results show that the encapsulation does not alter the strong basicity of the proazaphosphatrane, but dramatically decreases the rate of proton transfer.

The use of molecular containers for the design of receptors containing a reactive site is very attractive, as they can act as supramolecular catalysts and can mimic biological entities such as enzymes.[1] Changes in reactivity in the confines of an enzyme active site have driven chemists to explain and duplicate these through the formation of supramolecular structures.[2] Synthetic host molecules have thus been developed to display specifically tailored functional groups inside their cavity.[3] In particular, endohedral location of highly reactive species in such artificially protected and confined spaces has demonstrated the great potential of this approach.[4] Here we report on the synthesis of a proazaphosphatrane included in the cavity of a hemicryptophane structure,[5] leading to the first encaged Verkade's superbase. Themodynamic and kinetic consequences on the proton transfer are also discussed.

Recently, we have described the synthesis of hemicryptophane **1** containing the tris-(2-aminoethyl)amine (tren) moiety.[6] The tren ligand is known to form atrane structures through metal complexation, an interesting class of compounds well represented across the periodic table and widely studied.[7] In particular, the proazaphosphatranes **2**, first synthesized by Verkade et al., along with the related azaphosphatranes $[\mathbf{2}\cdot\mathrm{H}]^+\mathrm{Cl}^-$ (Figure 1),[8] are nonionic superbases ($pK_a \approx 32$) now broadly used in organic synthesis as stoichiometric bases and as catalysts.[9,10] Therefore, there is a real challenge to combine the properties of Verkade's superbases and the confinement upon specific architectures. Recently, Raymond et al. investigated the host−guest assembly of azaphosphatrane $[\mathbf{2a}\cdot\mathrm{H}]^+$ in the hydrophobic pocket of a metal−organic framework, but the effect of encapsulation could not be evaluated as experiments were run in water.[11]

The synthesis of hemicryptophane-phosphatrane $[\mathbf{3}\cdot\mathrm{H}]^+\mathrm{Cl}^-$ was performed using the experimental conditions reported for other azaphosphatranes (Scheme 1): addition of hemicryptophane

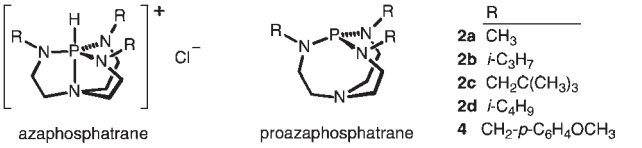
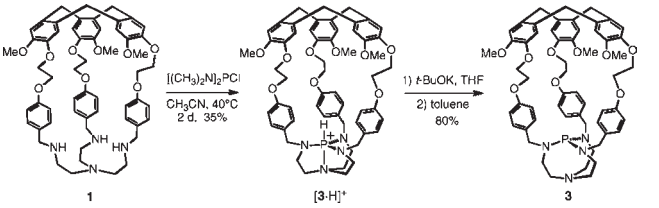


Figure 1. Structures of the azaphosphatrane and proazaphosphatrane derivatives.

Scheme 1. Synthesis of the Hemicryptophane Superbase 3



1 to a solution of $[(CH_3)_2N]_2PCl$ in acetonitrile afforded $[\mathbf{3}\cdot\mathrm{H}]^+\mathrm{Cl}^-$ in 35% yield,[12] which was then deprotonated using potassium *t*-butoxide in THF followed by extraction with toluene to give the encaged superbase **3** in 80% yield. The weak acid $[\mathbf{3}\cdot\mathrm{H}]^+\mathrm{Cl}^-$ displayed a single ^{31}P NMR signal at −32 ppm in $CDCl_3$, which is significantly highfield shifted by about 20 ppm compared to other azaphosphatranes.[10] Compound **3** showed a ^{31}P NMR signal at 125 ppm in toluene-d_8 as expected for a proazaphosphatrane derivative.

The single-crystal X-ray diffraction analysis of $[\mathbf{3}\cdot\mathrm{H}]^+\mathrm{Cl}^-$ clearly shows the phosphatrane moiety inside the molecular cavity (Figure 2). The average P−N_{eq} bond length is 1.62 Å, and the apical P−N_{ap} bond length is 1.93(2) Å, which are in the range of typical values determined on phosphatrane derivatives.[8,9c,12] The trigonal bipyramidal geometry around the phosphorus atom is characterized by the sum of the N_{eq}−P−N_{eq} angles in the equatorial plane of 359° and the average N_{eq}−P−N_{ap} angle value of 86°. A dichloromethane molecule is located inside the molecular cavity and interacts with the aromatic rings of the cyclotriveratylene (CTV) unit, emphasizing the host properties of the new hemicryptophane.

Since the phosphatrane structure was preserved in host $[\mathbf{3}\cdot\mathrm{H}]^+$, it was interesting to measure the pK_a value of the enclosed superbase. The pK_a value was estimated from competition

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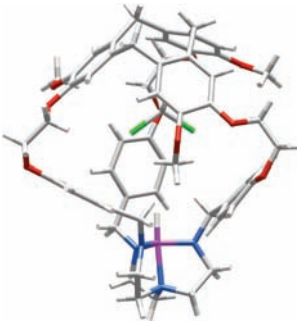

Figure 2. X-ray molecular structure of the hemicryptophane-phosphatrane cation $CH_2Cl_2@[3\cdot H]^+$.

Table 1. pK_a Values of Conjugate Acids of Proazaphosphatrane Bases in CH_3CN, and Rate Constants Values for Proton Transfers

base	pK_a	K_a	k_1 [mol L^{-1} s^{-1}]	k_{-1} [mol L^{-1} s^{-1}]
3[a]	32.99	1.03×10^{-33}	1.88×10^{-6}	1.16×10^{-5}
4[a]	32.14	7.25×10^{-33}	1.06×10^{-3}	0.93×10^{-3}

[a] Average values of at least two experiments, T = 298 K.

experiments: addition of the azaphosphatrane $[3\cdot H]^+Cl^-$ to a solution of the Verkade's superbase **2a** in CD_3CN led to an equilibrium mixture that was accurately analyzed by ^{31}P and ^1H NMR spectroscopy (Supporting Information). This afforded a reproducible value $K_a = 1.03 \times 10^{-33}$ for **3**, slightly lower than that of the Verkade's superbase **2a** ($K_a = 1.26 \times 10^{-33}$) (Table 1).[9a] This highlights that the hemicryptophane caged structure retains the strong basic character of the proazaphosphatrane. It has been shown that the basicity of the proazaphosphatranes depends on the nature of the substituents on the nitrogen atoms.[9] Thus, in order to investigate more accurately the effect of the cage structure, the K_a value was compared to that of the model molecule **4**, which lacks a cavity (Figure 1). Compound **4** was synthesized in 3 steps from tris(2-aminoethyl)-amine and *p*-anisaldehyde in 24% overall yield (Supporting Information). The K_a value for **4** was found to be 7 times that of **3**, making the encaged superbase **3** 7 times more basic than the model molecule **4** (K_a's = 1.03×10^{-33} and 7.25×10^{-33}, respectively), corresponding to a variation of $\Delta G°$ of 1.2 kcal mol^{-1}. Since the substitents in the vicinity of the phosphorus atom in **3** and **4** are identical, this enhancement can be uniquely attributed to the encapsulation of the superbase inside the host structure.

During the pK_a measurements we observed that proton transfer occurred on dramatically different time scales for the model superbase **4** and the encaged superbase **3**. When $[3\cdot H]^+Cl^-$ is added to a solution of **2a** in CD_3CN, after more than 5 h no $[3\cdot D]^+$ was observed in the ^{31}P NMR spectra, whereas under the same experimental conditions, when using $[4\cdot H]^+Cl^-$, $[4\cdot D]^+$ appeared immediately. As proton transfer between **3** and acetonitrile occurred on a time scale of hours, addition of the azaphosphatrane $[3\cdot H]^+Cl^-$ to a solution of **2a** in CD_3CN allowed the direct monitoring of the transfer kinetics by recording ^{31}P and ^1H NMR spectra as a function of time.

Two acid−base reactions are involved (Scheme 2); since, after more than 5 h, no $[3\cdot D]^+$ was observed in the ^{31}P NMR spectra,

Scheme 2. Kinetic Acid−Base Equilibriums Involved in the Proton Transfer $[3\cdot H]^+ \leftrightarrows 3$

$$[3\cdot H]^+ + {}^-CD_2CN \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 3 + CHD_2CN \quad (1)$$

$$3 + CD_3CN \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} [3\cdot D]^+ + {}^-CD_2CN \quad (2)$$

reaction 2 can be neglected at short time. Similarly, as the concentration of CHD_2CN is negligible compare to that of CD_3CN, reaction 1 can be considered as nonreversible. This allowed us to establish eq 1 and eq 2, where $K_a^{3\cdot H+}$, $K_a^{2a\cdot H+}$ and K_e are the acidity constant of $[3\cdot H]^+$, the acidity constant of $[2a\cdot H]^+$, and the autoprotolysis constant of acetonitrile, respectively, affording the k_1 and k_{-1} values.[13] Rate constants for model compound **4** were obtained using a similar method (Supporting Information).

$$\frac{d([3]/[3\cdot H^+])}{dt} = \frac{k_1 K_e}{K_a^{2a\cdot H^+}} \frac{[2a](1+[3]/[3\cdot H^+])}{[2a\cdot H^+]} \quad \text{(eq 1)}$$

$$k_{-1} = \frac{Ke}{K_a^{3\cdot H^+}} k_1 \quad \text{(eq 2)}$$

The deprotonation rate constant was found to be more than 500-fold lower with the encaged azaphosphatrane $[3\cdot H]^+$ than with the model compound $[4\cdot H]^+$ (Table 1). Despite the higher basicity of the host superbase **3**, the rate constant for its protonation is nearly 2 orders of magnitude lower than that for the model superbase **4**, where the rate constant turned out to be unrelated to the thermodynamics of proton transfer. We should note that previous studies have demonstrated the effect of encapsulation on the kinetics of proton transfer, in particular with tertiary amine derivatives.[14] However, to our knowledge, it has never been reported for such strongly basic species. Thus, confinement of the proazaphosphatrane in a molecular cavity dramatically affects the kinetics of proton transfer with CD_3CN solvent. The specific environment around the reactive site could impose a specific orientation of the acetonitrile guest inside the cavity, involving an entropic cost for proton transfer. Moreover, orbital overlap between phosphorus and the C−H bond of acetonitrile could impose the position of the acetonitrile nitrogen in the vicinity of the electron-rich aromatic rings of the CTV unit. Therefore, the appearance of a negative charge on this nitrogen atom, in the transition state, might lead to an unfavorable interaction and hence increase the enthalpic cost.

In conclusion, a Verkade's superbase has been covalently attached inside the host cavity of hemicryptophane **1** , leading to the host superbase **3** containing a preorganized cavity defined by the cyclotriveratrylene moiety above the strongly basic proazaphosphatrane. The pK_a value showed a 7-fold increase in the basicity of the encaged superbase when compared to that of the model molecule, which lacks a cavity. This enhancement was attributed to the incorporation of the highly basic species in a confined medium. The encapsulation of the phosphorus moiety was also found to strongly affect the rate for proton transfer. These thermodynamic and kinetic modifications by molecular encapsulation may provide valuable information for a better understanding of enzymes or other complex biological systems.

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■ ASSOCIATED CONTENT

Supporting Information. Additional NMR spectra, detailed experimental procedures and crystallographic analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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