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A cautionary note regarding the investigation of supramolecular complexes involving secondary ammonium salts in acetone ☆

Jason W. Jones,† Feihe Huang, William S. Bryant‡ and Harry W. Gibson*

Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, VA 24061, USA

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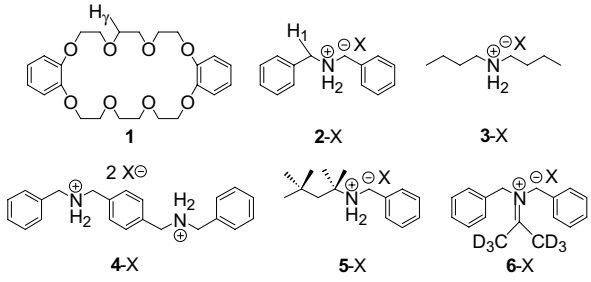
Abstract—Accompanying pseudorotaxane formation between dibenzo[24]-crown-8 and dibenzylammonium salts in acetone-d_6, iminium salts result from the well-known condensation reaction between ketones and amines, calling into question formation constants estimated by direct spectroscopic means in acetone.

1. Introduction

Of the many classes of self-assembled architectures, the pseudorotaxane and rotaxane binding motifs, which are comprised of guest ligands threaded through the cavities of macrocyclic hosts, have received much attention.[1] One such commonly employed pseudorotaxane is that fashioned between dibenzo[24]-crown-8 (DB24C8, **1**) and dibenzylammonium salts (**2**-X), in which threading is driven by H-bonding and π-cloud interactions.[2] A major advantage of this system is that formation of the host/guest complex is slow on the NMR time scale: one may readily discern the percentage of host threaded or guest bound by simple integration techniques. It has recently been shown that the strength of binding in these pseudorotaxane systems may be calculated only after careful consideration of ion-pairing of the guest salts and of the complexes.[3] The solvent's dielectric constant plays an important role, governing the extent of ion-pairing (K_{ipd}) as well as the degree of association (K_{assoc}). Wishing to extend those studies to more polar media, we undertook an investigation to quantify pseudorotaxane **1**·**2**-X formation in acetone-d_6, chosen because of its widespread use in similar complexation studies.[4] Our studies revealed surprising results, which constitute the focus of this note.



2. Results and discussion

Solutions of **1** and **2**-BF_4 in acetone-d_6 were studied by ^{1}H NMR spectroscopy at 295 K. Evolution of complex signals (labeled with a subscripted 'c'; uncomplexed resonances are labeled with a subscripted 'uc', Fig. 1) signify host/guest association under the slow exchange regime on the NMR time scale, as anticipated. However, two uncharacterized resonances at 3.0 and 5.4 ppm were noted (Fig. 1, denoted by the symbol '**'); a solvent background check confirmed the purities of solvent and starting materials. Identical complexation experiments were performed with **2**-PF_6 and **2**-TFA: once again, the same byproduct peaks were observed with nearly identical chemical shifts.

Keywords: Iminium; Ammonium; Acetone; Association constants.
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* Corresponding author. Tel.: +1-540-231-8242; fax: +1-540-231-8517; e-mail: hwgibson@vt.edu
† Present address: E.I. du Pont de Nemours and Company, Jackson Laboratory, Route 130 Chambers Works, Deepwater, NJ 08023, USA.
‡ Present address: Specialty Minerals, 9 Highland Avenue, Bethlehem, PA 18017, USA.

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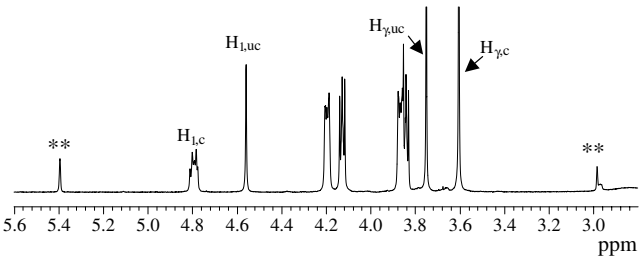

Figure 1. ^{1}H NMR spectrum (400 MHz, 295 K, acetone-d_6) of an initially 2.00 mM equimolar solution of **1** and **2**-BF_4.

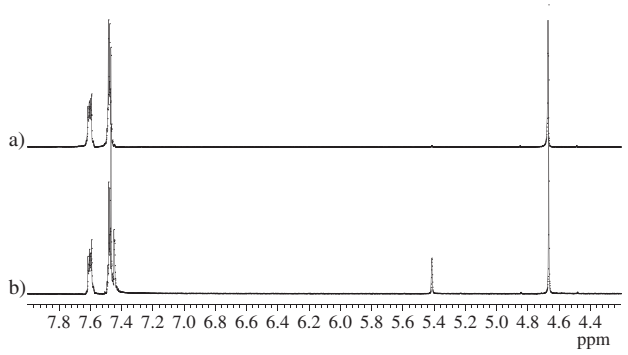

Figure 2. ^{1}H NMR spectra (400 MHz, 295 K, acetone-d_6) of **2**-PF_6, 16.0 mM, collected after (a) 5 min and (b) 24 h of solvation.

To probe the identity of the byproduct, time dependent studies were run on the pristine salt solutions. Figure 2 displays results from a 16.0 mM solution of **2**-PF_6, run 5 min (Fig. 2a) and 24 h after solvation (Fig. 2b). Note the increase in intensity of the 5.4 ppm peak, which represents a 20% conversion to the byproduct; an emerging aromatic signal is also distinguishable. This time dependency was seen at all concentrations of **2**-X investigated, regardless of counteranion. Furthermore, the evolution of byproduct was not limited solely to **2**-X: the secondary ammonium salts **3**-PF_6, **4**-2PF_6, and **5**-BF_4 also displayed time dependent byproduct evolution.

Because of the importance of clearly defining equilibrium concentrations based upon integration values for the determination of K_{ipd} and K_{assoc} the emergence of a competing reaction was of immediate concern. As a result, our focus shifted toward the underlying chemistry of byproduct evolution.

Recognizing the tendency of amines to undergo nucleophilic addition to aldehydes and ketones,[5] we believed the impurity to be an acetone condensation product. Indeed, saturating **2**-PF_6 with freshly distilled acetone-d_6, and allowing the solution to stir over molecular sieves for 24 h under N_2 resulted in nearly 95% conversion of the 2° ammonium salt to the byproduct, confirming the role of water evolution in this reaction (Fig. 3a); the chemical shifts of Figure 3a agreed well with formation of iminium salt **6**-PF_6. Addition of a drop of water to the same NMR tube resulted in complete recovery of **2**-PF_6 (Fig. 3b). Furthermore, examination of Figure 1 provides corroboration of salt formation: the evolved peaks (labeled '**') experience an upfield

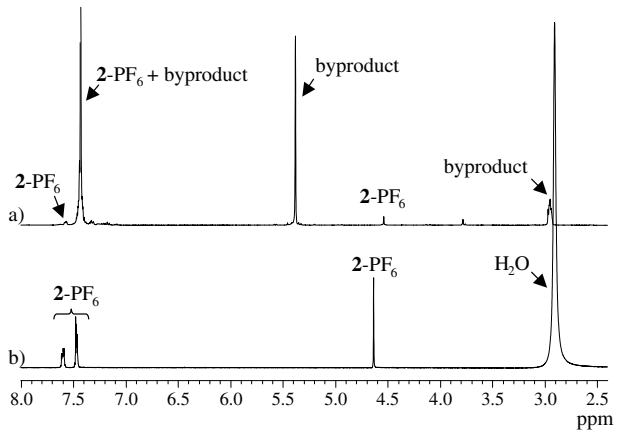

Figure 3. ^{1}H NMR spectra (400 MHz, 295 K, acetone-d_6) of **2**-PF_6 (a) 24 h after solvation in dry acetone stirring over molecular sieves and (b) sample from (a) to which a drop of H_2O was added.

shift with concentration in a manner analogous to $H_{1,uc}$, indicative of a rapidly exchanged ion pairing event on the NMR time scale.[6]

Despite such high conversion, all attempts to isolate the byproduct were fruitless: solvent extraction, thin layer chromatography (TLC), flash column chromatography, high pressure liquid chromatography (HPLC), and selective crystallization all failed. Direct detection of the byproduct by mass spectroscopy also proved futile. Our failure to isolate and identify the predicted iminium salt is not without precedent: molecules of the type $R_2C{=}NR_2^+X^-$ are notoriously difficult to isolate due to the reversible nature of the condensation.[7] Nevertheless, the existence of iminium ions has been proven by isolation from similar condensation reactions.[8]

Unable to directly prove its structure, we theorized that we should be able to indirectly prove the existence of **6**-X by irreversible formation of N,N-dibenzylisopropylamine (**7**) through the process of reductive amination. We chose sodium cyanoborohydride as the reducing agent due to its solubility and selectivity: it is well-known that at moderate pH ($5 < pH < 9$), the cyanohydridoborate anion preferentially reduces imines over ketones.[9] The reduction was allowed to proceed at room temperature in dry acetone over molecular sieves utilizing a 2:1 stoichiometric ratio of reducing agent to **2**-PF_6. After 72 h the reduction was determined to be complete by ^{1}H NMR analysis, resulting in the isolation of amine **7**, as anticipated, in moderate yields.

3. Conclusion

These results call into question K_{assoc} values calculated for the complexation of 2° ammonium salts in acetone. They do not outright reject such values, however, as evolution of the iminium salt was shown to be slow: 5 min after solvation, the concentration of **6**-PF_6 was negligible (Fig. 2a), but this is not the case after 24 h (Fig. 2b).

Importantly, this work confirms quite clearly the need to characterize new individual resonances fully in what would otherwise be considered known systems. This is particularly true when spectroscopic studies are being utilized for quantification of concentrations. It further reminds us that solvents by definition are not inert species, and that careful consideration of the molecules to be studied in solution should be made before the solvent is chosen.

Supporting Information

Supplementary experimental data is available online with the paper in ScienceDirect.

Acknowledgements

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