Well-defined Ion-pair Clusters of Alkyl- and Dialkylammonium Salts of a Sterically-hindered Carboxylic Acid. Implication for Hydrogen-bonded Lys Salt Bridges

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Ion-pair clusters of simple alkylammonium carboxylates in solution and in the crystalline state were described as a model of Lys salt bridge. *tert*-Butylammonium triphenylacetate gives a well-defined tetrameric cluster by a cubic hydrogen bond (H-bond) network, and diisopropylammonium triphenylacetate gives a dimeric cluster by a cyclic network.

Ion pairs between oppositely charged ionic groups play an important role for molecular assembly and molecular recognition. Especially, in non-polar media, both electrostatic interactions and polarized hydrogen bonds produce well-defined supramolecular assemblies *via* hydrogen bonds.[1] For example, guanidinium or amidinium salts of carboxylates or phosphates have been reported to form well-defined ion-pair complexes like Arg salt bridges in proteins.[1b] However, to our surprise, there have been few examples of hydrogen-bonded complexes based on primary or secondary ammonium carboxylate salts in the non-polar solvents,[2] while 1:1 ion-pairing in the polar solvents have been widely documented.[3] A few solution studies in non-polar media as weak electrolytes demonstrated that they form higher aggregates or conjugated species by the strong electrostatic interactions,[4] and role of hydrogen bonding for the ion-pairing and the aggregation of the salts remained unclear.[2–4] In this report, we describe that the primary and secondary ammonium salts of a bulky carboxylic acid produce ion-pair clusters *via* hydrogen bonds. In our knowledge, this is the first example of the well-defined complexes of the ion-pairs in the crystalline state and in the non-polar solvents.

Sterically hindered salts (**1a** and **1b**) were prepared by mixing triphenylacetic acid (**1**) with equimolar *tert*-butylamine (**a**) or diisopropylamine (**b**) in THF, respectively. They were crystallized from benzene to yield single crystals for X-ray analysis as shown in Figure 1.[5] The most striking feature is core-shell structures. In the cores, the carboxylate anions and the ammonium cations are arranged alternatively and connected by hydrogen bonds. In the primary salt, the four cations and the four anions assemble into a $4+4$ ion-pair cluster with a cubic hydrogen bond network (Figure 1b). The three NH's of the primary ammonium form three hydrogen bonds with the adjacent oxygen atoms of three different carboxylate anions. The twelve hydrogen bonds connect the eight ions to give the tetramer of the ion-pairs. On the other hand, in the secondary ammonium salt, the two cations and two anions construct a $2+2$ ion-pair aggregate with a cyclic hydrogen bond network as shown in Figure 1d. The two NH's of the secondary ammonium form two hydrogen bonds with two neighboring carboxylate anions to yield the cyclic dimer of the ion-pairs.[6] Their different aggregation numbers are attributed to the numbers of the hydrogen atoms on the ammonium nitrogen. In the shell, triphenylmethyl groups extend from the core, and the steric hindrance inhibits extending the infinite hydrogen bond networks,[7] and the cyclization of the network produces the discrete hydrogen-bonded clusters.[8]

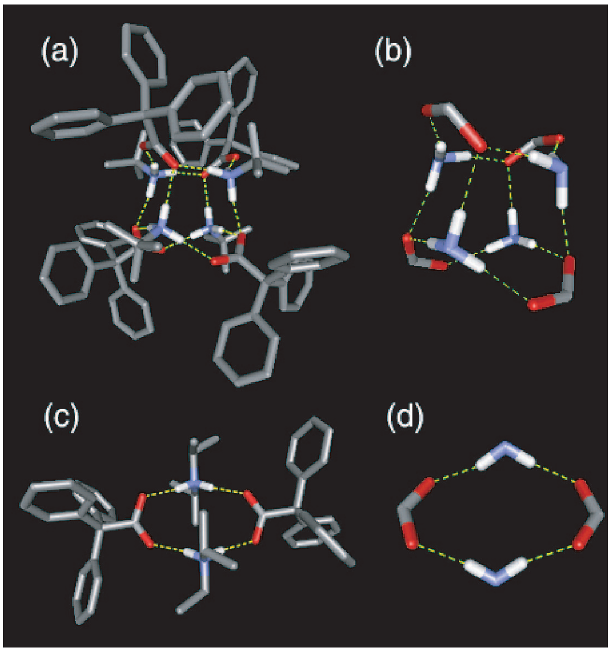

Figure 1. (a) Crystal structure and (b) hydrogen bond network of **1a**, and (c) crystal structure and (d) hydrogen bond network of **1b**. Yellow broken lines represent hydrogen bonds.

Then, we further investigated the formation of the ion-pair clusters in the non-polar solvents by ^{1}H NMR and osmometry. First, they were more soluble ($> 50\,\text{mmol dm}^{-3}$) than the corresponding acid **1** ($< 5\,\text{mmol dm}^{-3}$) in benzene. The high solubility is probably due to the formation of the discrete molecular assemblies covered by the lipophilic groups. Secondly, concentration effects on the ^{1}H NMR chemical shifts of **1a** in benzene-d_6 suggest the aggregation of the ion-pairs as shown in Figure 2. When the concentration of **1a** was raised from $2\,\text{mmol dm}^{-3}$ to $50\,\text{mmol dm}^{-3}$, the *t*-butyl proton resonance moved upfield from 1.001 to 0.865 ppm due to deshielding of the methyl groups by the triphenylmethyl groups owing to closer association, and the NH proton resonance shifted downfield from

4.488 to 8.406 ppm due to stronger hydrogen bonding. Moreover, diffusion NMR measurements[9] of **1a** in benzene-d_6 (22 mmol dm^{-3}) at 298 K showed that the self-diffusion coefficient of the aggregates was 4.9×10^{-10} m^{2}s^{-1}. According to the Stokes–Einstein formalism, the hydrodynamic radius at this concentration is about 6.5 Å. This value is much larger than those of the free acid (**1**) as well as the free amine (**a**) and similar to that of the tetramer estimated from X-ray crystallography. Thirdly, we tried to confirm the ion-pair clusters by measuring their molecular weights. However, all trials for the detections by mass spectra, such as FAB–MS, MALDI–TOF, and ESI–MS, were unsuccessful, because the ion-pair clusters themselves had no charges. Then, we examined number-averaged molecular weights by VPO (benzene at 313 K). The molecular weights of **1a** and **1b** were saturated around 1125 ± 150 and 705 ± 150, while the calculated molecular weights for the tetramer of **1a** and dimer of **1b** are 1444 (361 per one ion-pair) and 778 (389 per one ion-pair), respectively. The molecular weights are in good agreements to those of the corresponding ion-pair clusters in the solid state. Difference of the observed molecular weights is explained by the different aggregation numbers, which supports the formation of the hydrogen-bonded ion-pair clusters. Finally, the salt formations were confirmed by IR spectrum. The carbonyl stretching band of **1a** in $CHCl_3$, (*ca.* 100 mmol dm^{-3}) was observed at 1589 cm^{-1}, and this is similar to that in solid state (1586 cm^{-1} in KBr disk). They are assigned to the carboxylate anion, indicating that **1a** exists as ionized state in chloroform under the high concentration. Therefore, in non-polar solvents, **1a** and **1b** form aggregated ion-pairs with self-solvated structures, which correspond to the ion-pairs clusters in the crystalline state.

We demonstrate that the primary and secondary ammonium carboxylates provides the well-defined the tetramer or the dimer of the ion-pairs, rather than the single bifurcated 1:1 ion-pair. The supramolecular structures are controlled by the number of hydrogen atoms on the ammonium nitrogen. Importance of hydrogen bonding is understood by the fact that the positive charge of NH_3^+ or NH_2^+ are localized, not on the nitrogen atom, but on the hydrogen atoms.[10] The positively charged NH's should act strong hydrogen bond donors, and all of them have to form hydrogen bonds.

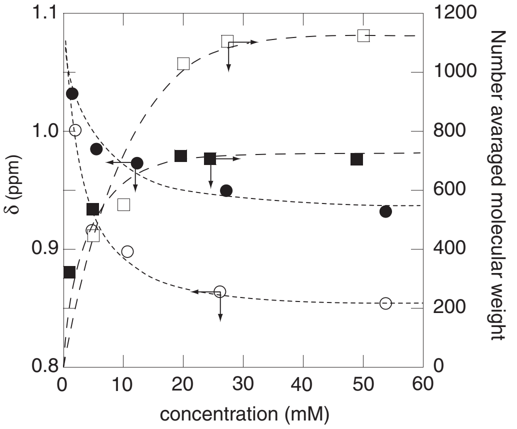

Figure 2. Concentration dependence of chemical shift changes of *t*-butyl group of **1a** (○) and **1b** (●) and number-averaged molecular weights of **1a** (□) and **1b** (■).

Moreover, these results suggest a new role of Lys residues as a strong hydrogen bonding residue with three hydrogen bond donors. One of the three NH's constructs the hydrogen bond with a counter anion, that is, a salt bridge, and the other two form with surrounding hydrogen bond acceptors such as waters, carbonyl groups of main chains, and polar side chains. Indeed, the statistic analysis of 3-D protein structures revealed that a Lys residue has 2.64 hydrogen bonds on average.[11] They act as the three-way junctions of the hydrogen bond networks in the proteins.[12] When Lys resides and acidic resides are precisely arranged within the distances and angles suitable for hydrogen bonding, they would insure formation of a single hydrogen bond in water to increase protein stability as effective salt bridges on the surface.

Finally, wide variations of amines and acids would provide various well-defined hydrogen bonded ion-pair clusters, and the use as supramolecular building blocks is now under investigation.

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