Remarkable Amine-TFA Self Assembly

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Supramolecular assemblies that are formed between amines and trifluoroacetic acid were studied using electrospray ionization mass spectrometry. Distinctive association behavior of primary, secondary, and tertiary amines with trifluoroacetic acid upon identical experimental conditions is observed and indicates that steric effects dominate in the formation of these protonated clusters. Extraordinary complexation behavior is observed in the case of R−(+)-α-methylbenzylamine and 4-*tert*-butyl-cyclohexylamine that form high-order clusters. The strong relation between stereochemistry and assembly results in the specific association characteristics of *trans* 4-*tert*-butyl-1-phenylcyclohexylamine when compared with the *cis* isomer. The *cis* isomer gives rise to a highly abundant $[M_4TFA_3 + H]^+$ ion (M = amine molecule, TFA = trifluoroacetic acid), as observed for other primary amines. However, the *trans* isomer generates higher $[M_nTFA_m + H]^+$ cluster ions, the largest and most abundant being an $[M_7TFA_6 + H]^+$ ion. Collision induced dissociation spectra that were recorded for several $[M_nTFA_m + H]^+$ cluster ions typically show the consecutive losses of M·TFA moieties. Density functional theory calculations indicate that the highly abundant $[M_4TFA_3 + H]^+$ clusters are macrocycles and support the formation of these structures with TFA and not with acetic acid.   (J Am Soc Mass Spectrom 2004, 15, 356–362) © 2004 American Society for Mass Spectrometry

Non-covalent complexes can be analyzed in solution using electrospray ionization (ESI) and mass spectrometry [1–3]. The clustering of such compounds depends on the choice of solvent and concentration but most of all on the structure and functionalities of the components. Thus noncovalently bound DNA duplex, triplex, and quadruplex structures, have been detected by electrospray ionization (ESI) mass spectrometry [4, 5]. Quantification of noncovalent interactions in diastereomeric aggregates has also been studied using mass spectral techniques that even allow, in some cases, the evaluation of enantiomeric excess [6–21]. It has been shown that the moderate preference in the formation of one diastereomeric, cation bound, heterodimer can be quantitatively used upon careful calibration. Another supramolecular phenomenon studied using ESI-MS is the formation of micelles [22–24]. Electrospray spectra of various bile acids and other surfactants show a distinct pattern of aggregation, with ions evenly separated [25]. Several studies provide insight into the complexation of inorganic substances. Salt cluster ions of alkali metal chlorides ACl (A = alkali cation) and sodium salts NaB (B = I$^-$, HCOO$^-$, CH$_3$COO$^-$, NO$_2^-$, and NO$_3^-$), formed by electrospray ionization, were studied by mass spectrometry. For example, complexes with the general formulas, A$_x$ (ACl)$_n^{x+}$ and Cl$_x$ (ACl)$_n^{x-}$ where x ≥ 1 and n > 100 were detected for A=Na or K and B=Cl [26].

Special stabilization, in the form of a supramolecular assembly was reported for the zwitterionic form of arginine. It has been demonstrated that it is possible to stabilize the zwitterionic form in cyclic arrays, based on guanidinium and carboxylate interaction [27]. These neutral arrays are detected as anionic or cationic complexes. The authors report a possible preference for homochirality in molecular clustering.

Supramolecular assemblies are produced in solution when the intermolecular interactions are strong enough. However, when these interactions are too strong, desolvation and precipitation might occur instead. In the field of supramolecular chemistry it is a great challenge to recognize the basic units that are most suited as building blocks in the design of advanced materials such as liquid crystals and gel-forming agents. Amine based organic compounds are among the important functionalities involved in supramolecular assemblies. Along with the interacting group, namely the amine itself, an important characteristic of the components of such clusters is their spatial structure, hence the tendency to form aggregates is a stereochemical issue.

Trifluoroacetic acid was shown to form dimeric and trimeric complexes with some amines and amino acids [28–30], while sodium trifluoroacetate self-assembles to form clusters of mass as high as 6000 Da [31]. Here we report the study of supramolecular assemblies that are

formed between amines and trifluoroacetic acid (TFA) under electrospray ionization conditions.

Experimental

Mass Spectrometry

All ESI/FTICR experiments were carried out using a Bruker BioAPEX III 47e FTICR spectrometer (Bruker Analytical Systems, Inc., Billerica, MA) equipped with a 4.7 T superconducting magnet, an external source (Apollo ESI Source), and an infinity analyzer cell. The samples were dissolved in CH_3OH/TFA (0.01%, ca. 10^{-3} M TFA, ca. 10^{-5} M amine) and introduced into the ESI source at a flow rate of 0.3 mL h^{-1}. Ions were generated using an end plate voltage of −3.0 kV, capillary voltage of −3.5 kV and minimal capillary exit voltage (<10 V). The accumulation time in the hexapole (d1) was 1–2 s and ion ejection time 2.5 ms. Ions were detected using the broadband detection mode covering a mass range from 50 to 5000 Da. Typically, eight individual transients were accumulated to improve the signal-to-noise ratio. For CID experiments precursor ions were isolated using swept frequency ejection pulses of 250–500 μs duration to eject all other ions. A pulsed valve introduced the argon collision gas prior to ion activation. With the pulsed valve open for 30 ms, a peak pressure of ca. 8 exp-7 mbar (indicated) was obtained relative to a backpressure of ca. 3 exp-10 mbar. The precursor ions were excited using a variable amplitude off-resonance excitation pulse.

Materials

R−(+)-α-methylbenzylamine, 1-adamantylamine, and dicyclohexylamine were purchased from Aldrich Chemical Company, Inc. Piperidine, 2,2,6,6-tetramethylpiperidine, decylamine and 4-tert-butyl-cyclohexylamine were purchased from Fluka Chemical Corp, Milwaukee, WI, USA. Cis and trans -4-tert-butyl-1-phenylcyclohexylamine (1-cis and 1-trans) were synthesized using known procedures [32, 33] and characterized by ^{1}H NMR. NOE was used to confirm which is the trans isomer, on the basis of the interaction between the phenyl hydrogen atoms and the hydrogen atoms at positions 3 and 5 of the cyclohexyl ring.

Theoretical Methods

Calculations were carried out using Gaussian 98 package of programs [34]. The clusters and molecules under study were optimized at B3LYP/6-31G* hydride density functional level of theory and the optimized structures were analyzed using analytical frequencies calculations.
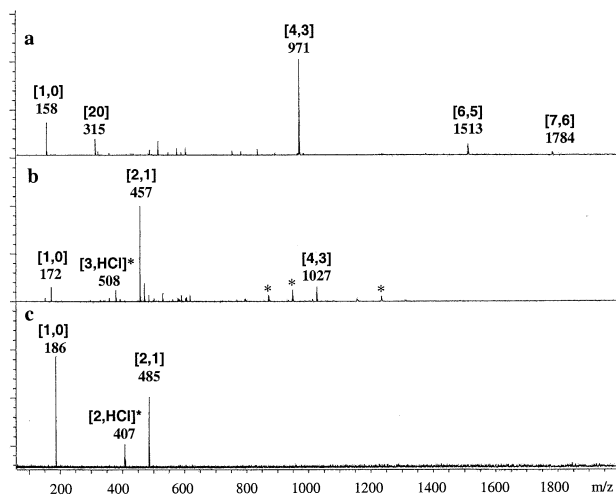

Figure 1. ESI spectra of decylamine (**a**), N-methyldecylamine (**b**), and N,N-dimethyldecylamine (**c**) in MeOH/TFA. The $[M_nTFA_m + H]^+$ ions are designated as [n,m], and asterisks correspond to $[M_nHCl_m + H]^+$ ions, some indicated as [n,HCl].

Results and Discussion

ESI mass spectra were measured for a variety of amines in a methanolic solution of TFA (MeOH/TFA, 0.01%). A series of cluster ions of the general formula $[M_nTFA_m + H]^+$ (M = amine molecule) were detected with a specific composition depending on the structure of the amine and the experimental conditions. Figure 1 shows the ESI mass spectra measured for n-decylamine (Figure 1a), N-methyl-n-decylamine (Figure 1b), and N,N-dimethyl-n-decylamine (Figure 1c). Decylamine gives rise to a series of cluster ions upon ES-ionization ranging from the proton bound dimer at m/z 315 with a relative abundance (RA) of 20% to a $[M_7TFA_6 + H]^+$ complex at m/z 1784 (RA < 5%, Figure 1a). The most abundant ion in the ESI mass spectrum of decylamine in MeOH/TFA is a $[M_4TFA_3 + H]^+$ cluster at m/z 971 (RA = 100%). On the other hand, secondary N-methyl-decylamine exhibits a highly abundant $[M_2TFA + H]^+$ ion at m/z 457 (RA = 100%, Figure 1b) under the same ESI conditions and the tertiary N,N-dimethyl-decylamine exhibits both an $[M_2TFA + H]^+$ ion at m/z 485 (RA = 70%) and a most abundant MH^+ ion at m/z 186 (RA = 100%, Figure 1c). Other ions in the spectra that are labeled with asterisks correspond to $[M_nHCl_m + H]^+$ species.

The different association behavior of the primary, secondary, and tertiary amines upon identical experimental conditions indicates that steric effects are involved. More pronounced structural effects are observed in the ESI mass spectra of other amines, listed in Table 1. For example 2,2,6,6-tetramethylpiperidine in MeOH/TFA gives rise to an abundant $[M_2TFA + H]^+$ ion at m/z 397 but no other clusters could be detected while the corresponding $[M_2TFA + H]^+$ ion in the ESI spectrum of nonsubstituted piperidine, in MeOH/TFA (m/z 285, RA = 100%), is accompanied by $[M_3TFA_2 +$

Table 1. RA of $[M_nTFA_m + H]^+$ complexes and other ions (RA > 5%) of a variety of amines that were measured in MeOH/TFA using ES ionization

	$[M_nTFA_m + H]^+$		
	n	m	RA (%)
R−(+)-α-methylbenzylamine	6	5	100
"	4	3	60
Other ions	$[M_5TFA_5 + Na]^+$ (40%); $[M_5TFA_5-H + 2Na]^+$ (15%)		
4-*Tert*-butyl cyclohexylamine	10	9	25
"	9	8	40
"	7	6	45
"	6	5	100
"	4	3	80
Other ions	$[M + TFA + Na]^+$ (20%); MH^+ (70%)		
Adamantylamine	7	6	10
"	6	5	80
"	5	4	25
"	4	3	100
Other ions	$[M_7TFA_7 + Na]^+$ (7%); $[M_6TFA_6 + Na]^+$ (10%); $[M_5TFA_5 + Na]^+$ (25%); $[M_4TFA_4 + Na]^+$ (15%); $[M_3TFA_3 + Na]^+$ (27%); MH^+ (60%)		
n-Decylamine	6	5	10
"	4	3	100
"	M_2H^+ (20%); MH^+ (33%)		
Dicyclohexylamine	5	4	55
"	2	1	100
2,2,6,6-Tetramethylpiperidine	2	1	100
Piperidine	4	3	50
"	3	2	60
"	2	1	100
1-*cis*	4	3	100
"	3	3	18
Other ions	$[M_4TFA_4 + Na]^+$ (15%)		
1-*trans*	7	6	100
"	6	5	52
"	5	4	14
"	4	3	25
"	3	2	22
Other ions	M_2H^+		

$H]^+$ (RA = 60%) and $[M_4TFA_3 + H]^+$ (RA = 50%) ions, at *m/z* 484 and 683, respectively.

We find that primary amines exhibit a high tendency to form large $[M_nTFA_m + H]^+$ complexes and the most abundant cluster ion in their ESI mass spectra corresponds to a complex composed of four amine and three TFA molecules ($[M_4TFA_3 + H]^+$). Nevertheless, there are specific structural effects that result in the favored formation of high-order clusters. Specifically, it is evident that R−(+)-α-methylbenzylamine and 4-*tert*-butyl-cyclohexylamine (Table 1, Figure 2) exhibit an extraordinary complexation behavior. R−(+)-α-methylbenzylamine gives rise to an $[M_6TFA_5 + H]^+$ ion (RA = 100%) while 4-*tert*-butyl-cyclohexylamine affords a series of ions, the highest corresponding to $[M_{10}TFA_9 + H]^+$.

The tendency to produce clusters from solution in the electrospary source may serve as an indication for a more general structural competence of specific building blocks to associate. ESI mass spectrometry is found to be advantageous as a method for the recognition of basic units for the design of advanced materials that are based on such interactions. R−(+)-α-methylben-
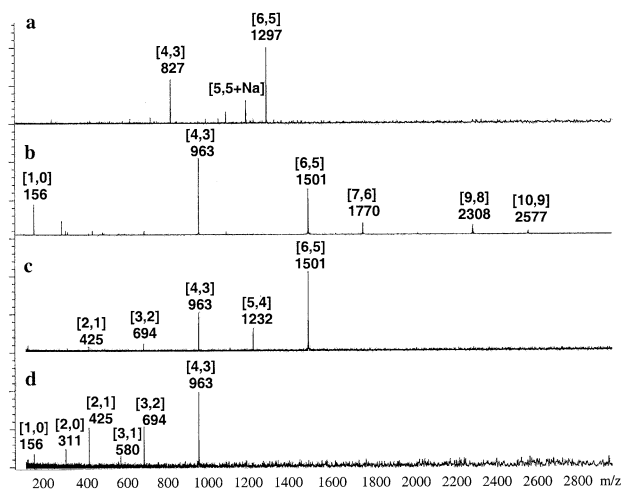

Figure 2. ESI mass spectra of R−(+)-α-methylbenzylamine (**a**), 4-*tert*-butyl-cyclohexylamine (**b**), MS/MS Spectrum of the $[M_6TFA_5 + H]^+$ cluster ion at *m/z* 1501, M=4-*tert*-butyl-cyclohexylamine (**c**) and MS³ spectrum of an $[M_4TFA_3 + H]^+$ ion that is generated upon collisional activation of $[M_6TFA_5 + H]^+$ (**d**). $[M_nTFA_m + H]^+$ cluster ions are designated as [n,m].
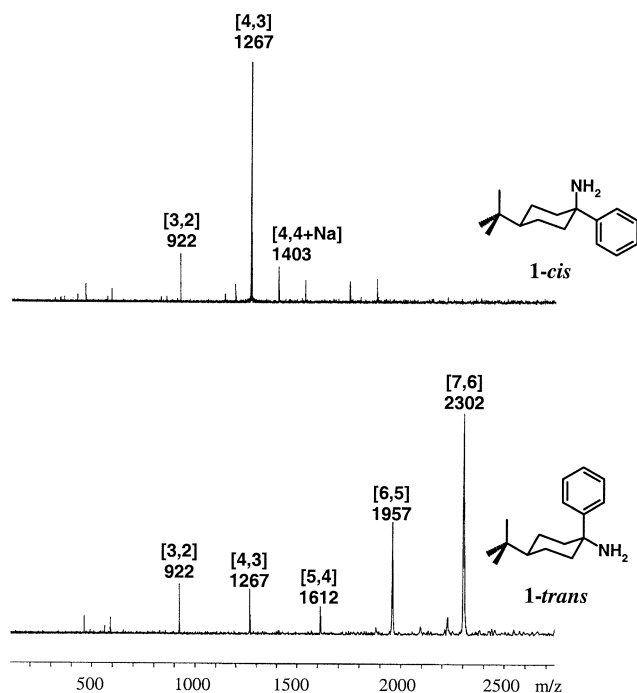
Figure 3. ESI mass spectra recorded for **1-cis** and **1-trans**, in MeOH/TFA. $[M_nTFA_m + H]^+$ cluster ions are designated as [n,m].

zylamine and 4-*tert*-butyl-cyclohexylamine are primary amines possessing approximately the same basicity as decylamine and other primary amines. Their different tendency to form aggregates must therefore result from the differences in their sterical shapes rather than different acid-base interactions.

The strong relation between stereochemistry and assembly results in the specific association characteris-

tics of one geometric isomer when compared with another. For example, solutions of *cis* and *trans* 4-*tert*-butyl-1-phenylcyclohexylamines **1-cis** and **1-trans**, in MeOH/TFA form a series of $[M_nTFA_m + H]^+$ clusters and two distinct mass spectra were recorded for the two isomers (Figure 3). The *cis* isomer **1-cis** gives rise to a highly abundant $[M_4TFA_3 + H]^+$ ion, as observed for other primary amines. However, the *trans* isomer **1-trans** generates higher $[M_nTFA_m + H]^+$ cluster ions, the largest and most abundant being an $[M_7TFA_6 + H]^+$ ion. It is worth adding that the specific composition of cluster ions in the ESI mass spectrum depends on the experimental conditions at the ion source. The variation between the RAs of the ions in an electrospray spectrum can be very large. Nevertheless, the compared mass spectra were recorded under identical conditions and consecutive measurements are reproducible within 10%.

Contrarily, product ion mass spectra that were recorded for M_2H^+ proton bound dimers of **1-cis** and **1-trans** (not shown) are practically identical. CID spectra were also recorded for the ions at *m/z* 1267 that correspond to $[M_4TFA_3 + H]^+$ complexes (Figure 4). The two isomeric parent ions at *m/z* 1267 give rise to resembling CID spectra, however, one ion corresponding to $[M_3TFA + H]^+$ at *m/z* 808 is present in the CID spectrum of **1-cis** but not in the one of **1-trans**. CID spectra were recorded for several $[M_nTFA_m + H]^+$ clusters that were generated from the amino compounds in study (e.g., Figure 2c, d and Figure 4). These CID spectra show that higher $[M_nTFA_m + H]^+$ clusters dissociate to afford lower $[M_nTFA_m + H]^+$ complexes, including the ones that are not formed in the electrospary source or in solution.
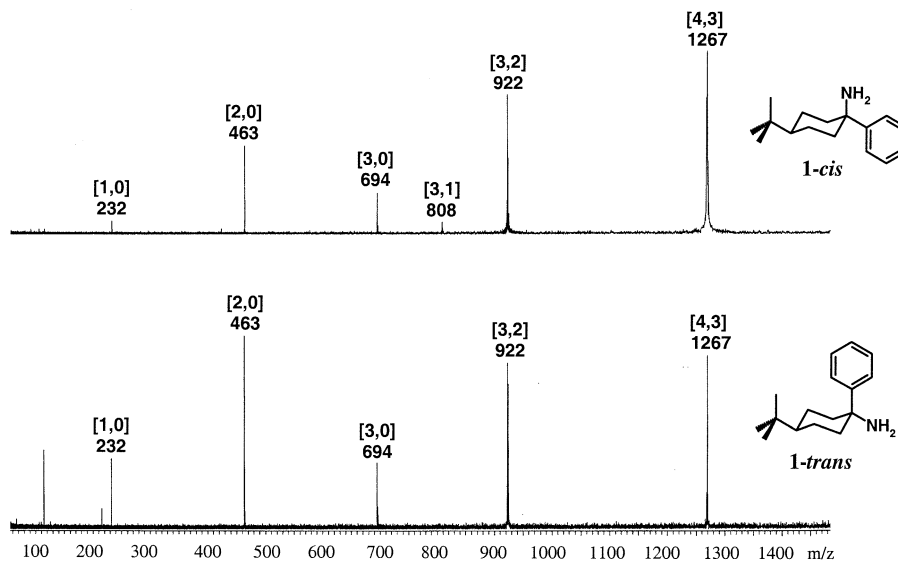
The application of mass spectrometry to organic

Figure 4. CID spectra recorded for the ions at *m/z* 1267 that were generated upon ESI of **1-cis** and **1-trans** in MeOH/TFA, argon was used as collision gas. $[M_nTFA_m + H]^+$ cluster ions are designated as [n,m].
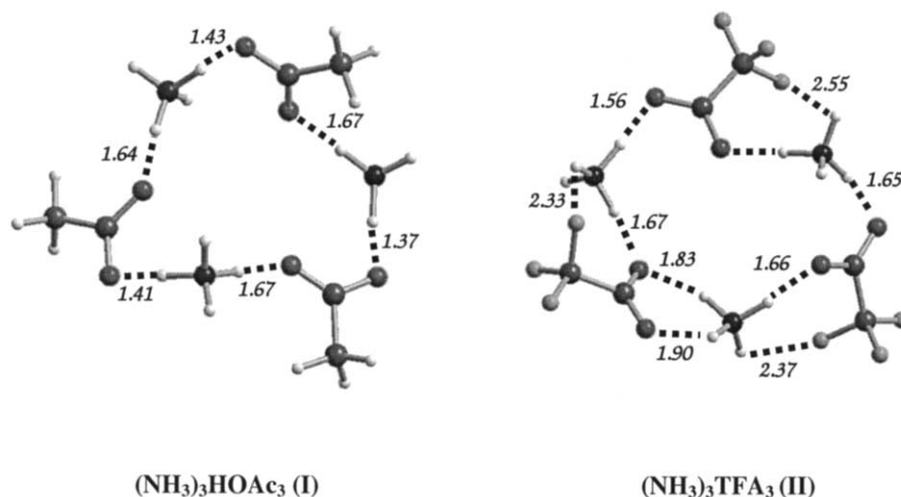
Figure 5. Calculated geometries of $(NH_3)_3TFA_3$ and $(NH_3)_3HOAc_3$ clusters (B3LYP/6-31G*).

stereochemistry was studied extensively [35]. Some isomeric structures show distinct fragmentation behavior and thus their mass spectrum can allow stereochemical identification. In many cases, however, mass spectra of isomers are much alike and stereochemical distinction is not possible. An alternative approach to achieve stereochemical assignment using mass spectrometry is to record a complexation spectrum such as the ones recorded for **1-cis** and **1-trans**. It is worth adding that amines **1** were not chosen arbitrarily. The *trans* alcohol analog 1-phenyl-4-*tert*-butyl-cyclohexanol is a known gel forming agent while the *cis* is not [36]. This indicates that the *trans* configuration allows such intermolecular interactions that result in the formation of assemblies that subsequently form a gel. It was our intention to observe whether the capability of one isomer over the other to self-assemble will be manifested by a different behavior upon ESI MS.

There are many possible structures that correspond to the compositions of the observed clusters, linear or cyclic in nature. Theoretical calculations were used in order to assess the stability of cyclic and open chain clusters of acid-bound ammonia. The geometries of several structures that correspond to $(NH_3)_3TFA_3$ and $(NH_3)_3HOAc_3$ complexes were minimized. Many such complexes probably exist in solution differing by specific bond length and/or an angle and are all but one meta-stable minima. We found that cyclic complexes are more stable than sheet or linear analogs in the case of $(NH_3)_3TFA_3$ and $(NH_3)_3HOAc_3$ (Figure 5).

Calculations were conducted in order to obtain theoretical support for the observed special ability of the fluorinated acid to complex amines. It is therefore reasonable to compare acetic acid and TFA. Ammonia is a good model for primary amines and the systems of interest are already as large as possible considering the time required for such calculations.
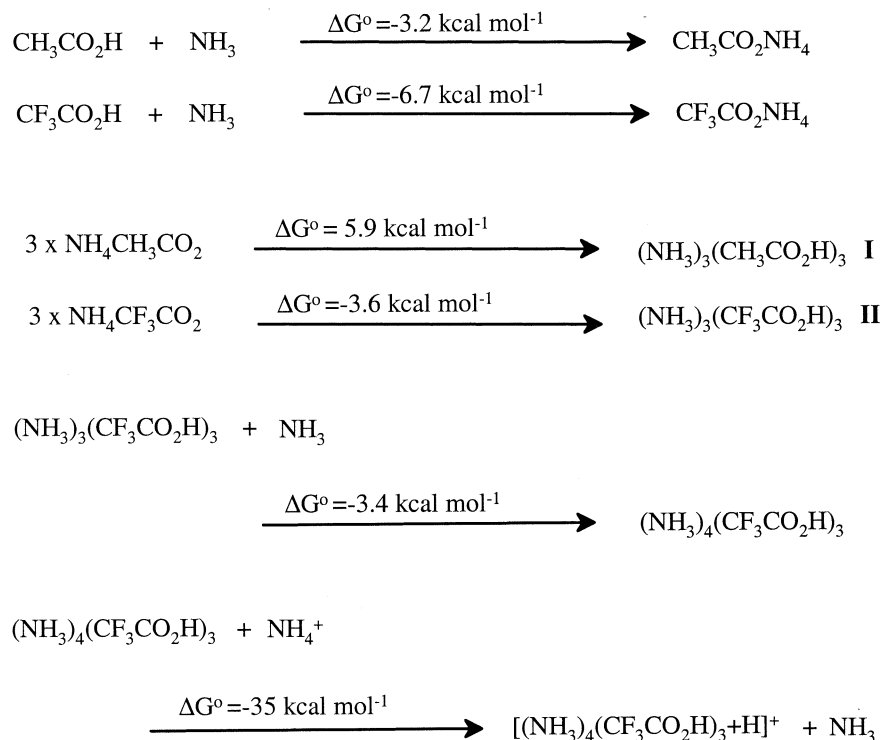
A comparison between the reactivity of TFA and that of acetic acid in the formation of supramolecular structures requires the deduction of the trivial effect of the higher acidity of TFA. This is why the informative chemical processes are the formation of $(NH_3)_3TFA_3$ and $(NH_3)_3HOAc_3$ heteroclusters from the corresponding RCO_2NH_4 salts (Scheme **1**). DFT calculations agree with the experimental results as the formation of $(NH_3)_3(RCO_2H)_3$ macrocycle is only exoergic when RCO_2H is TFA and not for acetic acid (Scheme **1**).

The calculations above were conducted for $(NH_3)_3(RCO_2H)_3$ clusters that correspond to $[(NH_3)_3(RCO_2H)_3 + NH_4]^+$ ions that are present in the ESI spectra of primary amines. Alternatively we considered the protonation of $(NH_3)_4TFA_3$. It is found that the formation of $(NH_3)_4TFA_3$ from $(NH_3)_3TFA_3$ and ammonia is exoergic by 3.4 kcal mol^{-1}. However, enhanced stability is achieved by protonation of the $(NH_3)_4TFA_3$ complex. The gas-phase basicity of the $(NH_3)_4TFA_3$ cluster is 35 kcal mol^{-1} higher than that of ammonia. This is in accordance with the experimental results that indicate the preferential formation of $[M_4TFA_3 + H]^+$ ions in the ESI mass spectrum of primary amines.

Conclusions

A remarkable complexation allowing the formation of amine-TFA composed clusters has been identified by using ESI mass spectrometry. Different clusters, most of which are $[M_nTFA_m + H]^+$ ions in which n = m + 1 are formed with pronounced tendency of specific groups towards the formation of certain clusters, depending on the stereochemistry and the nature of the amine. Thus primary amines afford highly abundant $[M_4TFA_3 + H]^+$ ions and some *cis* and *trans* isomers give rise to distinctive complexation spectra. DFT calculations demonstrate the relative stability of macrocycles composed of ammonia and TFA units and provide an explanation for the experimental results. Further calculations will present a general overview on the composition of ammonia-TFA solutions.

$$CH_3CO_2H \; + \; NH_3 \xrightarrow{\Delta G^o = -3.2 \; kcal \; mol^{-1}} CH_3CO_2NH_4$$

$$CF_3CO_2H \; + \; NH_3 \xrightarrow{\Delta G^o = -6.7 \; kcal \; mol^{-1}} CF_3CO_2NH_4$$

$$3 \times NH_4CH_3CO_2 \xrightarrow{\Delta G^o = 5.9 \; kcal \; mol^{-1}} (NH_3)_3(CH_3CO_2H)_3 \quad \mathbf{I}$$

$$3 \times NH_4CF_3CO_2 \xrightarrow{\Delta G^o = -3.6 \; kcal \; mol^{-1}} (NH_3)_3(CF_3CO_2H)_3 \quad \mathbf{II}$$

$$(NH_3)_3(CF_3CO_2H)_3 \; + \; NH_3$$

$$\xrightarrow{\Delta G^o = -3.4 \; kcal \; mol^{-1}} (NH_3)_4(CF_3CO_2H)_3$$

$$(NH_3)_4(CF_3CO_2H)_3 \; + \; NH_4^+$$

$$\xrightarrow{\Delta G^o = -35 \; kcal \; mol^{-1}} [(NH_3)_4(CF_3CO_2H)_3 + H]^+ \; + \; NH_3$$

Scheme 1. Calculated standard free energy values for the formation of $(NH_3)_3TFA_3$ and $(NH_3)_3HOAc_3$ heteroclusters.

Acknowledgments

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