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Multiple hydrogen bonds. Mass spectra of hydrogen bonded heterodimers. A comparison of ESI- and REMPI-ReTOF-MS

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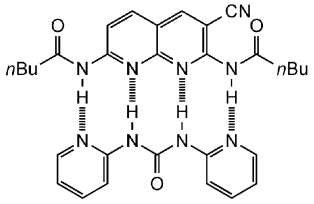
***R*esonance *e*nhanced *m*ulti-*p*hoton *i*onization - *re*flectron *t*ime *o*f *f*light *m*ass *s*pectrometry is the analytical method of choice to observe hydrogen bonded supramolecules in the gas phase when protonation of basic centers competes with cluster formation.**

The hydrogen bond is one of the most important interactions in supramolecular chemistry, connecting naturally occurring supramolecules like the DNA double helix or protein associates as well as artificial host–guest systems.[1–5] The association energy of a single hydrogen bond between one hydrogen bond donor D and one hydrogen bond acceptor A is rather small. Sartorius and Schneider[6] estimated it as *ca.* 8 kJ mol^{-1}. Therefore at room temperature, host–guest complexes which are bound by a single hydrogen bond are mostly dissociated but complexes with more hydrogen bonds are stable (for examples see:[7–14]).

After the synthesis of the first heterodimer with four hydrogen bonds (DAAD·ADDA; Scheme 1),[15] we have tried to analyze this dimer by mass spectrometry. Modern mass spectrometry methods have successfully been used in the past to observe various supramolecular clusters in the gas phase.[16–19] But even with a binding constant in chloroform of *ca.* 2000 M^{-1} for DAAD·ADDA, we were not able to observe this dimer by standard mass spectrometry methods, including ESI-MS (*e*lectro*s*pray *i*onization). Starting from the mixture of DAAD and ADDA, or investigating both partners alone, only *homo*dimers were observed in an ESI-MS. However the results prove proper conditions for the observation of clusters.



DAAD•ADDA

Scheme 1

Next we used REMPI-ReTOF (*r*esonance *e*nhanced *m*ulti-*p*hoton *i*onization - *re*flectron *t*ime *o*f *f*light) mass spectrometry.[20,21] Table 1 compares these results to the ESI-data. Good results were found using REMPI-ReTOF-MS, but the nature of the matrix is crucial. In contrast to many other applications where ions can only be detected in the mass spectrum if acid is present in the matrix, acid has to be avoided in this case. Why?

The dimer formation between DAAD and ADDA occurs *via* four hydrogen bonds between pyridine or naphthyridine nitrogen atoms as hydrogen bridge acceptors A and NH groups as hydrogen bond donors D. This reaction can be followed in solution by NMR. The considerable change of the chemical shift of the amide protons of DAAD upon complex formation was used to determine the association constant in $CDCl_3$,[15] and proves that hydrogen bond formation is responsible for the host–guest binding.

But the pyridine or naphthyridine nitrogen atoms are also the most basic centers in the molecules. Therefore, protonation will predominantly occur at these nitrogen atoms turning a DAAD pattern into DDAD, or ADDA into DDDA, respectively (see Scheme 2). If the titrations in chloroform are carried out in the presence of acid, a smaller association constant results.

Table 1 Relative intensities for ESI- and REMPI-ReTOF mass spectral data for ADDA, DAAD and DAAD·ADDA, their homodimers M_2 and the heterodimer MM′. The REMPI experiments have been carried out with matrices which contained vanillic acid (+ van) or did not (no van)

		ESI ($CHCl_3$) DAAD	ESI ($CHCl_3$) ADDA	ESI ($CHCl_3$) DAAD·ADDA	REMPI no van DAAD	REMPI + van DAAD	REMPI no van ADDA	REMPI + van ADDA	REMPI no van DAAD·ADDA	REMPI + van DAAD·ADDA
DAAD	$M^{\bullet+}$	0		0	100	0[a]			< 1	0
	$M{\cdot}H^+$	9		2		0				10
	$M{\cdot}Na^+$	100		21						
ADDA	$M^{\bullet+}$		0	0			55[b]	0	80	0
	$M{\cdot}H^+$		18	31				84[a]		56[a]
	$M{\cdot}Na^+$		100	100						
$(DAAD)_2$	$M_2^{\bullet+}$	0		0	18	0				
	$M_2{\cdot}H^+$	< 1		< 1		0				
	$M_2{\cdot}Na^+$	8		5						
$(ADDA)_2$	$M_2^{\bullet+}$		0	0			0	0		
	$M_2{\cdot}H^+$		1	< 1				9		
	$M_2{\cdot}Na^+$		20	24						
DAAD·	MM′$^{\bullet+}$			0					100	0
ADDA	MM′$\cdot H^+$			< 1						6
	MM′$\cdot Na^+$			1						

[a] When vanillic acid (van) was added, often molecular ions of van or van$_n$ were the 100% peaks. [b] The 100% peak is a fragment ion of ADDA (m/z = 94).

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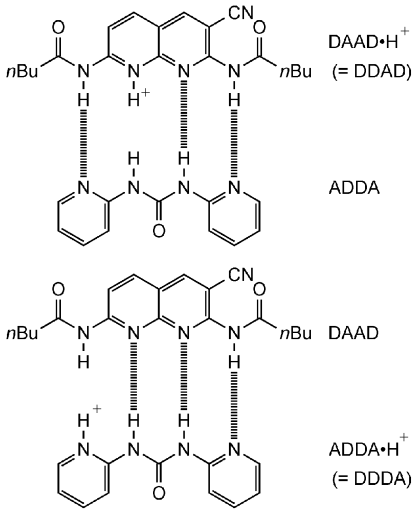

Scheme 2

Protons disturb the complementarity between DAAD and ADDA. ADDA is now facing a DDAD pattern, or DAAD faces DDDA. In protonated form, complexes with more than two hydrogen bonds are not possible any more, and comparisons with mismatch experiments argue for rather small association constants of these new couples. In chloroform, an association constant of 2000 M^{-1} was found for DAAD·ADDA (4 hydrogen bonds), while only 31 M^{-1} was measured for DAAD·DDAD (3 hydrogen bonds possible, the AAD subsequence can bind the DDA subsequence).[15] With only two hydrogen bonds, the binding constant should be even smaller. Consequently, only protonated DAAD and ADDA monomers or dimers were predominantly observed.

Such a pertubation by protonation will occur in the ESI ionization process, when the analyte picks up protons as the droplets evaporate. But protonation also occurs in the evaporation process in a REMPI machine where the substance is vaporized by a CO_2-laser beam like in a MALDI experiment.[22,23] However, the REMPI experiment selects the neutral molecules and clusters. The ions, including all protonated species, are separated from the neutral species by a repeller plate, charged at *ca.* 850 V. The ionization of the neutral molecules and clusters occurs by a second laser irradiation by an Nd:YAG-laser (model: Quanta-Ray Pro-230-30) pumped OPO (optical parametric oscillator) which forms molecular ions $M^{\bullet+}$ by a two photon process. This is the distinct difference between an ESI or MALDI experiment and the REMPI-MS. In the latter case, molecular ions $M^{\bullet+}$ are observed while protonated molecules or protonated clusters $M{\cdot}H^+$ are analyzed by the other two techniques. The chance to observe a stable heterodimer is enhanced if there is no protonation. The ionization must result from the removal of an electron out of the HOMO of the supramolecular cluster.

Often matrices like vanillic acid (van) are also used in REMPI-MS experiments, and in these cases, protonated molecules $M{\cdot}H^+$ rather than molecular ions $M^{\bullet+}$ are detected although only neutral molecules or clusters are able to pass the repeller plate. Therefore, the protonation must have occurred in the ionization process. It is highly probable that clusters of vanillic acid and the analyte pass the repeller plate in uncharged form. Then, irradiation with the OPO system results in heterolysis of the cluster.

Conclusion: Although the modern mass spectrometry methods such as ESI or MALDI have been very successful in the detection of molecular ions and clusters of varying composition,[16–19] some aggregates cannot be analyzed by these methods (yet). In cases where the most basic center of one partner of a host–guest system is involved in the formation of a hydrogen bond, an acid-free mass spectrometry method should be successful in observing the supramolecular ions. REMPI-ReTOF-MS definitely is one such method.

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