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SPECIAL ISSUE

Azahelicene Superbases as MAILD Matrices for Acidic Analytes**

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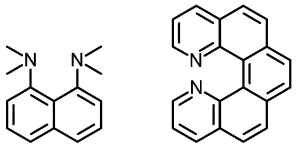
In memory of Detlef Schröder

Fast metabolite profiling, imaging and drug analysis is an indispensable tool nowadays in the discovery of biomarkers and disease diagnostic applications. Matrix-assisted laser desorption/ionisation (MALDI), developed in the late eighties, represents one high-throughput method. Initially used for the mass spectrometric analyses of large biomolecules,[1] for example, proteins, peptides and oligosaccharides, recently it has frequently been used to analyse small molecules.[2] However, conventional MALDI matrices (e.g., 2,5-dihydroxybenzoic or α-cyanohydroxycinnamic acids) produce a significant background of interfering peaks within the low-mass region; thus limiting the usefulness of MALDI-MS techniques in the analysis of low-molecular-mass analytes ($M_r < 500$ Da).[3]

To extend the MALDI-MS technique to include small-molecule analysis and to utilise this fast high-throughput screening technique for metabolomic studies,[4] we have recently developed a novel approach.[5] It is based on the usage of superbasic UV-absorbing matrices that do not undergo facile gas-phase deprotonation. Accordingly, no interfering anions are generated during the measurements. In contrast to the MALDI technique, ionisation is completed in a solution, if an acidic analyte is mixed with a super base; thus forming an ion pair. Such a phenomenon was explained by the Brønsted–Lowry acid–base theory and the new method was coined "matrix-assisted ionisation/laser desorption" (MAILD). Specifically, 1,8-bis(dimethylamino)naphthalene (DMAN; a "proton sponge")[6] was shown to obviate the problem of low-mass-region interference in MALDI-TOF/MS spectra of low-molecular-weight compounds at physiologically relevant concentrations.[5a,c] The same principle was applied to the positive-ion mode of MAILD by using 2-naphtholsulfonic acid.[5b] Recently, it was realised by us and others[7] that DMAN might desorb under experimental conditions (10^{-6} mbar) to form deposits in an ion source; these deposits might result in the appearance of interfering peaks in MS spectra. To eliminate this troublesome drawback, we have been searching for alternative MAILD matrices either by modifying the structure of DMAN or by exploring other types of organic superbases.



DMAN 1

To the best of our knowledge, azahelicenes[8] have never been tested as potential candidates for MALDI or MAILD matrices, despite the fact that some of them exhibit high proton affinities that are comparable to those of classical proton sponges.[9] Herein, we explore the potential of azahelicenes—the leading candidate is 1,14-diaza[5]helicene (**1**)[9c,10] —as MAILD matrices for the analysis of fatty acids and organic acids in a wide range of samples. The development of an efficient MAILD-MS analysis for small molecules may open up new directions in metabolomics research and diagnostic applications. We bring together our expertises in mass spectrometry, the synthesis of helical heteroaromatics, quantum chemical calculations and capillary electrophoresis not only to identify a new highly promising azahelicene matrix (**1**) for MAILD-MS and to explain differences in the efficiency of other azahelicenes, but also to shed light on the mechanisms underlying the MAILD technique.

Classical organic proton sponges, such as DMAN, are characterised both by a strong electrostatic repulsion between lone electron pairs at basic centres and by the hydrophobic shielding of these centres (as well as by the N–H$^+$–N hydrogen bond upon monoprotonation). Similar to DMAN, the conformational strain in **1** causes the lone electron pairs in nitrogen atoms to be in close proximity. Whereas protonation of DMAN (and deprotonation of DMANH$^+$) is a slow process (owing to hydrophobic shielding), helicene **1** is a kinetically active proton sponge (owing to a rapid exchange of protons between the donor and diaza[5]helicene base).[10b] It is worth noting that **1** should have a significantly lower vapour pressure under vacuum than that of DMAN because the scaffold of **1** consists of five condensed benzene/pyridine rings; thus minimising desorption.

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[**] *MAILD = matrix-assisted ionisation/laser desorption.*

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