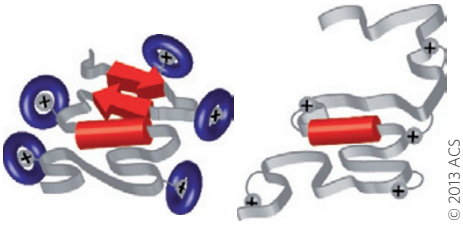
ION-MOBILITY SPECTROSCOPY

Crowning achievement

J. Am. Chem. Soc. **135,** 1177–1180 (2013)



Proteins exist and function in an aqueous environment and their structures are heavily dependent on solvent interactions. Techniques such as mass spectrometry (MS) and ion-mobility spectrometry (IMS) provide much useful information on the structural and biophysical properties of macromolecules, but are gas-phase techniques that require the solvent to be evaporated off before analysis. The extent to which proteins retain their native (solvated) structure during these processes is therefore not clear. Now, Kevin Pagel and colleagues at the Fritz Haber Institute of the Max Planck Society, Berlin, have highlighted the significant structural differences that can be present between native and non-solvated proteins and have developed a technique that may lessen the effects of solvent loss.

They studied the effects of non-covalently attaching crown ethers (18-crown-6) on the structure of cytochrome *c*. Crown ethers (CEs) are known to co-ordinate to protonated lysine side-chains and can act as a substitute for the absent solvent molecules. Using IMS and MS they showed that the effect of adding an increasing number of CE molecules to cytochrome *c* differed depending on its original charge. Adding CEs to high charge (>9+) or low charge (<6+) cytochrome *c* caused the proteins to become progressively bigger (larger collision cross-sections) — as might be expected because of the CEs they now carry. Those of intermediate charge, however, surprisingly shrunk in size. Next the team looked at what happened when the CEs were removed using a collision-induced fragmentation technique, and saw a reversal of the behaviour — the cytochrome *c* proteins of intermediate charge increased in size.

Pagel and colleagues attribute the changes in size of the intermediary cytochrome *c* to CEs inhibiting the collapse of the protein on removal of the solvent. When no CEs are present and the solvent is removed, the groups that were previously stabilized by solvent begin to interact intramolecularly, destabilizing secondary and tertiary structures and causing partial unfolding. The CEs inhibit such intramolecular interactions, leaving the protein more compact and in a state more similar to the native protein. *GA*

ANCIENT MEDICINE

Two-millennia-old tablets

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Our knowledge of ancient medicine typically comes from contemporary texts or other works written in the first century AD. Scientists have now had the opportunity, however, to directly characterize what seem to be medicinal samples found in a shipwreck dating back from the second

RNA CLEAVAGE

A radical solution

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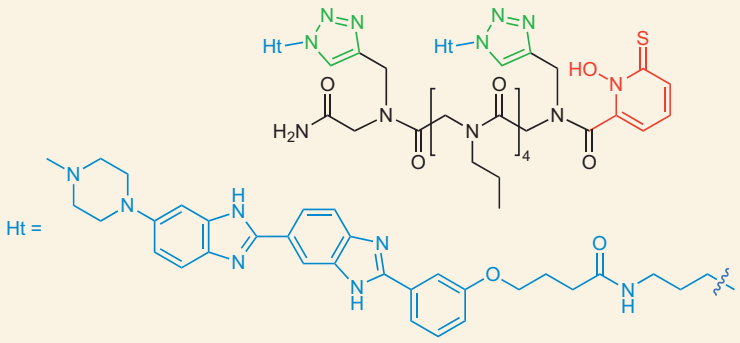
The production of a faulty protein or of too much of a particular protein is the root cause of many diseases. A common approach to treatment is to attempt to modulate the effect of that protein, but an alternative would be to change how much is produced in the first place. This is the basis of ongoing research in small-interfering RNAs (siRNA) — short double-stranded RNA molecules that bind to messenger RNA and interfere with the translation process that results in protein production. Poor cellular permeability for siRNAs is a problem, however, and so Lirui Guan and Matthew Disney from the Scripps Research Institute in Florida are developing an alternative approach by designing small molecules that can bind to and induce cleavage of specific RNA sequences.

Myotonic dystrophy type 1 is a chronic disease that is caused by the presence of a repeating CUG base sequence in messenger RNA. This structure binds to and inactivates important proteins and ultimately results in the disease symptoms. The Disney research group has previously described a therapeutic strategy in which small molecules can bind to the CUG repeat unit and displace the proteins that would otherwise bind there. Their strategy (pictured) relies on the use of a peptoid backbone (black) to display two bis-benzimidazole binding units (Ht, blue) that are appended to the backbone through the use of copper(I)-catalysed Huisgen cycloadditions to form the triazoles (green). In this latest work they incorporate an *N*-hydroxypyridine-2(1*H*)-thione (red) — a structure known to generate hydroxyl radicals on photolysis — with the aim of not just binding to the problematic RNA structure, but cleaving it as well.



Using controls that omit the RNA binding group (Ht) and the radical generating unit, Guan and Disney then tested the effectiveness of their design. The addition of the radical-generating hydroxypyridone structure was found to slightly decrease the strength of binding to the RNA, but on photolysis the potency was increased approximately six-fold. The modular nature of this RNA-cleaving molecule should enable the rapid development of improved cleavage agents that can target a variety of RNA sequences. *SD*