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Structural Studies of Thioredoxins and Associated Inhibitor Based Complexes

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The thioredoxin redox system, consisting of the thioredoxin protein, thioredoxin reductase and NADPH, is ubiquitous in all living cells and is known to be important in a multitude of biological functions, including cell cycle regulation and maintaining an intracellular reduced state [1]. Studies in various human malignancies and cell lines in *vitro* have shown an up regulation of thioredoxin and have demonstrated a definite link between thioredoxin and cancer [2], [3]. Thioredoxin levels have also been shown to be raised in the presence of superoxide generating drugs, thus suggesting that inhibition of this redox system may also lead to improved efficiency of these drugs.
The crystallisation of a variety of thioredoxin proteins has allowed comparisons to be made between crystal structures of mammalian and bacterial thioredoxins. Studies of existing human thioredoxin complexes have also enabled the understanding of the specificity requirements that thioredoxin has for its target proteins [4]. This has facilitated the design of potential novel inhibitors of the active site of this redox protein. There are currently two novel heteroaromatic quinol inhibitors, which have shown to have activity against thioredoxin, under development at the Cancer Research Laboratories of the University of Nottingham. These inhibitors are thought to have a novel mode of action, each containing a bis-micheal acceptor, allowing them to irreversibly bind to the active site, thus irreparably inactivating the protein.
By studying the crystal structure of thioredoxin-inhibitor complex it will be possible to apply structure-activity relationships and thus enable not only the understanding of how these heteroaromatic quinols block the activity of thioredoxin, but also to develop these drugs with the intention of improving their affinity for the binding site. N^{15} labelled NMR HSQC experiments have also provided an insite into the binding of these quinols to the thioredoxin active site and thereby facilitating further drug design to improve affinity.

[1] Powis, G., *et al. Pharmacology and Therapeutics* 68 (1) 149.
[2] Arrigo, A.P., *Free Radical Biol. and Med.,* 1999, 27 (9/10).936.
[3] Soini, Y. *et al*., *Clinical Can. Res.,* 7, 1750.
[4] Qin, J., *et al. Structure* 4(5): 613.

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Simulation of the absorption of acetone on ice at surfaces, bulk ice and small-angle grain boundaries

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The absorption of acetone on ice I_h was simulated by force field and ab-initio calculations. Three cases were investigated:
1) absorption on the surface
2) absorption into bulk ice, substituting one or more water molecules (point defect)
3) absorption on a small-angle grain boundary as example for a 2D-lattice defect
Ice I_h is the only stable ice polymorph at atmospheric conditions. When ice (snow/hail/graupel) begins to form in the troposphere, volatile organic compounds will be absorbed at the surface or incorporated into the ice crystals. Acetone is one of the most prominent organic pollutants in the atmosphere. For the force field calculations a modified Dreiding force field[1] was used.
Results:
1) An acetone molecule absorbed on the (0001) surface of ice forms two hydrogen bonds between the CO group and two dangling OH. The calculated absorption enthalpy corresponds well with experimentally determined values. This geometry was confirmed by extensive ab-initio calculations.
2) When acetone enters the ice bulk it replaces only one water molecule, and distorts the surrounding ice lattice. Preferably two acetone molecules replace three water moieties.
3) An absorption of acetone at a small-angle grain boundary or at a similar lattice defect is energetically more favourable than in bulk ice.

[1] S. L. Mayo, B. D. Olafson, W. A. Goddard III, *J. Phys. Chem.* 1990, *94*, 8897-8909.