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Probing the State of Water on the Surface of Pharmaceutical Salts by X-ray Photoelectron Spectroscopy

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Introduction

Purpose:

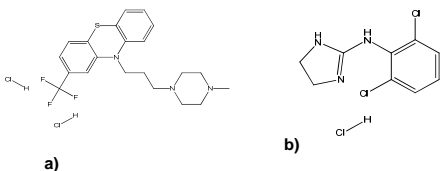
While pharmaceutical salts tend to have higher hygroscopicities than their free base or acid counterparts, knowledge of the nature of the sorbed water and the fundamental basis for variations in moisture uptake for various salts are lacking. The goal of this work was to investigate the use of x-ray photoelectron spectroscopy (XPS) to gain a better understanding of these issues. To date, there has been little if any work performed where water has been investigated via ultra-high vacuum surface techniques on the surface of organics.

Background:

Understanding if water is molecularly or dissociatively adsorbed is of critical importance because the presence or absence of dissociation will influence chemical reactions; the chemical reactivities of the species generated by dissociation of water are very different from molecular water. It is well known that water can chemically dissociate on metals and metal oxide surfaces and recent work has provided evidence for the chemical dissociation of water at surface defect sites on sodium chloride crystals². However, the chemical state of water on organic surfaces, although clearly of great importance for understanding their chemical stability, has not been investigated.

Compound Selection

- Crystalline organic hydrochloride salt
- No oxygen atoms within the drug molecule to prevent interference with the oxygen signal of potential surface water
- Stable under ultra high vacuum and high temperature conditions
- Stable under X-ray radiation.



Schematic 1. Structures of A) trifluoperazine dihydrochloride and B) clonidine hydrochloride.

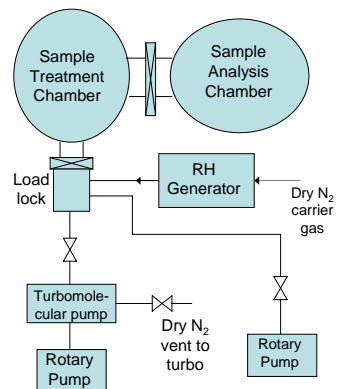


Figure 1 (above) Schematic layout of XPS experimental system.

Preliminary evidence of dissociated water

Initial studies on a powder sample of clonidine HCl, stored at 25°C/51% RH for 24 hr showed an O 1s peak at a binding energy of 531.9 eV, with an elemental composition of 1.8%. Furthermore, there was no change in the oxygen concentration or BE as the temperature was raised from 110 K to room temperature (Figure 2). This result suggests strongly bound surface water present in dissociated form as the hydroxide ion

Hypothesis: Freshly cleaved faces of recrystallized clonidine HCl would be pure of any oxygen-containing contaminants and surface water. Subsequent exposure to high relative humidity would lead to moisture adsorption and dissociation at the surface.

Single crystals of clonidine hydrochloride were grown by slow evaporation. The surfaces of both freshly cleaved faces of the crystals and a powder prepared by grinding large single crystals were analyzed. The samples were quickly transferred after processing to the LLC and pumped down. The chamber was then pumped back up to atmospheric pressure with dry nitrogen gas, followed by exposure to 90% RH from the RH generator, operated with dry nitrogen gas. This setup and procedure allowed for exposure to moisture followed by analysis with only minimal exposure to ambient air and thus contaminants. Any O 1s peak should be attributed solely to water.

Experimental Methods

Significant modification of the experimental setup was required to allow for exposure to controlled high moisture (relative humidity) conditions without introducing ambient air. The load-lock chamber of the XPS spectrometer was modified to accommodate the feed-through attached to the RH generator (Figure 1). In order to perform variable temperature experiments as low as 110 K, an apparatus using nitrogen flow through liquid nitrogen and to a coldfinger was set up for both the load lock and sample analysis chamber. A gold-plated sample holder was manufactured for stable analysis at higher temperatures.

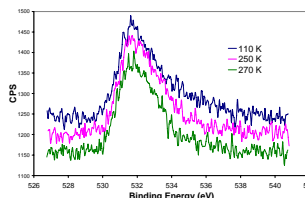


Figure 2 (above) O(1s) photoelectron spectra of powder sample of clonidine HCl, after cooling to 110 K followed by heating to room temp.

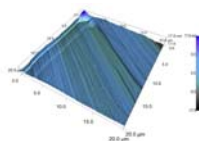


Figure 3 (above). AFM images of smooth portion of cleaved 100 face of clonidine HCl for scan areas of 20 nm

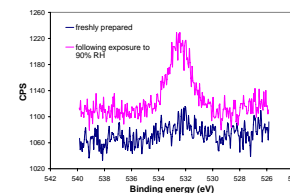


Figure 4 (above) O 1s photoelectron spectra of cleaved single crystal sample of clonidine HCl, before and after exposure to moisture

	Freshly prepared	After exposure to 90% RH for 24 h	Change	After heating to 80°C	After heating to 140°C
powder	0.07	0.45	+ 0.38	0.59	1.17
cleaved #1	0.24	0.73	+ 0.49	0.83	1.38
cleaved #2	0.09	0.51	+ 0.42	0.42	0.39

Table 1 (above) Elemental compositions (%) of O 1s for freshly prepared clonidine HCl samples before and after exposure to high RH, and after subsequent heating steps.

Results

- Powder and cleaved #2 samples initial peaks close to noise
- Change similar for all 3 samples
- Possible surface migration of hydroxide at higher temperatures

Trifluoperazine di-HCl

- Exposed to 60% RH in load lock chamber
- Evacuated with dry nitrogen gas, then immediately cooled to 110 K
- Peak position corresponds to molecular water at 110 K
- Shift in O 1s BE indicative of thermally activated dissociation as temperature increased to rt

Annealed to 100°C before exposure to moisture, then heated to 100°C again

Condition	O 1s elemental %	
	ground powder	cleaved (parallel to fast-growing face)
freshly prepared	0.43	0.17
pre-heating to 100 C (1 h)	0.26	0.24
after exp. to 90% RH (1 h)	0.59	0.87
after heating to 100 C (1 h)	0.62	0.86

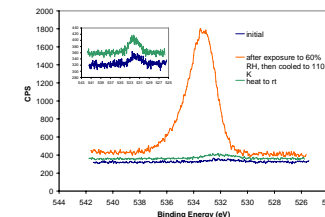


Figure 5 (above). O 1s photoelectron spectra of a recrystallized powder sample of trifluoperazine di-HCl.

Summarizing...

- The results with both trifluoperazine di-HCl and clonidine HCl provide strong evidence for dissociative adsorption of water on organic hydrochloride salts.
- This strongly bound water may act as nuclei for further moisture uptake and cause stability problems for moisture-labile salts.
- Future work will investigate:
 - Role of surface chemistry and defect density of various faces of clonidine HCl single crystals on the extent of dissociation
 - Comparison between clonidine HCl, clonidine HBr and clonidine free base

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