Solid-State Chemistry

DOI: 10.1002/anie.201103981

Crystallography Aided by Atomic Core-Level Binding Energies: Proton Transfer versus Hydrogen Bonding in Organic Crystal Structures**

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Crystal structure analysis by single-crystal X-ray diffraction (XRD) is the most commonly used method for determining whether Brønsted proton transfer or hydrogen-bonding take place in the solid state of organic materials.[1–3] Proton transfer is often identifiable by XRD,[1,2,4–9] especially when analyzed in conjunction with structural indicators such as bond angles and bond lengths.[1,2,4,10] However, even with high-quality crystals an unequivocal determination of atomic hydrogen or proton positions is not always straightforward, particularly with systems involving proton disorder, temperature migration, or other unusual behavior.[8] Multi-component materials, for example, formed by solid-state preparation such as milling, or an inability to obtain suitable single crystals present additional limitations. Complementary experimental methods sensitive to proton and hydrogen positions become invaluable in such cases.

Sometimes standard laboratory techniques such as vibrational spectroscopies provide the desired information[1,7] when the relevant spectral features are not too complex or broadened. More often, advanced techniques such as neutron diffraction,[1,8,10] in which proton position can be quantitatively determined, are employed. Examples for such systems are urea/phosphoric acid,[9,11,12] 4,4′-bipyridyl/benzene-1,2,4,5-tetracarboxylic acid,[13] 4-methylpyridine/pentachlorophenol,[14] and benzoic acid.[15,16] In recent years, solid-state NMR (ssNMR) methods combined with computational chemical shift analysis[3,17,18] have also been used.

Here we show that X-ray photoelectron spectroscopy (XPS), a technique hitherto rarely used[17,19,20] in crystallographic studies, is a simple and reliable means for probing H-bonding and protonation in organic materials. Perhaps because XPS is traditionally associated with studies of surface chemistry and thin films it is not normally considered a tool for obtaining bulk information from crystals. However, for organic compounds the photoemission signals excited by standard laboratory Mg and Al K_α sources derive from a region several nanometers deep below the surface, resulting in information that is dominated by bulk properties.[21]

We carried out a systematic study determining the N 1 s core-level binding energies of nitrogen acceptor moieties in 15 different organic solid-state donor–acceptor structures for which the crystal structure was known. These systems cover a wide range of pK_a differences between the donor and acceptor components. To demonstrate the practical value of the approach for applied research we also included several development pharmaceutical compounds.

The sensitivity of XPS to Brønsted interactions is illustrated in Figure 1, for two acid–base structures containing 3,5-dinitrobenzoic acid as the Brønsted donor. With 4-aminobenzoic acid as the acceptor base, two photoemission peaks arise, associated with the two types of nitrogen moieties present, namely the NH_2 acceptor and the NO_2 groups of the donor molecules (Figure 1a). The N1s binding energy of the NH_2 group occurs around 399.5 eV, which is the characteristic value[24,25] for an unprotonated amino group. The spectrum with 3,5-diaminobenzoic acid exhibits an additional peak at a

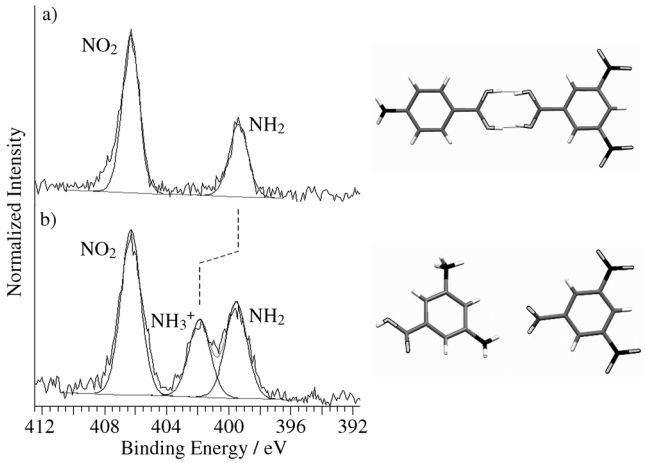

Figure 1. N1s XP spectra of a) 4-aminobenzoic acid/3,5-dinitrobenzoic acid[22] and b) 3,5-diaminobenzoic acid/3,5-dinitrobenzoic acid,[23] showing the positive shift with hydrogen donation to nitrogen. Atoms in the molecular structures are colored as follows: black = N, white = H, grey with black outline = O, gray = C.

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[**] We thank the EPSRC and Sanofi-Aventis for financial support for J.S.S. through a DTA/CTA studentship. J.S.S. currently also holds an EPSRC PhD + fellowship. We gratefully acknowledge support for S.L.M.S. and R.J.D. through an EPSRC Critical Mass Grant (EP/I013563/1).

binding energy of 401.9 eV (Figure 1b), which is representative of a protonated amino group.[17,25] Proton transfer from the Brønsted acid to half of the amino groups has resulted in a substantial core-level binding energy shift of +2.4 eV (Figure 1).

The rationale for selecting further members of a series of 15 acid/base phases was to cover a very wide range of pK_a differences (ΔpK_a) between Brønsted acid and base components. The investigated systems exhibited ΔpK_a values from −3.9 to +17.7 (Table 1). For all non-development materials it had previously been established[17,19,20,22,23,29,30] whether they were characterized by proton transfer or H-bond formation. For the five active pharmaceutical ingredients (APIs) an unambiguous assignment had been made from the crystal structures and ssNMR measurements. Plotting the N1s binding energy values of the N-acceptors[17,19] of all 15 acid–base structures as a function of ΔpK_a (Figure 2) clearly traces the expected transition[1] from H-bonding (here associated with cocrystal formation) to proton transfer (salt formation) as the pK_a difference increases through the region between 0 and +3. Recently, pK_a matching has been used as a tool for predicting H-bond strengths[31] (including the proposed pK_a slide rule[32]). A correlation between bond lengths in crystals and ΔpK_a values was shown for N–H···O/O–H···N bonds.[32] In line with this work we find a clear separation between a cluster of N1s XPS binding energies around 399.6 eV for the H-bonded cocrystals and at approximately 401.7 eV for the protonated salts (Figure 2). Measurement of the N1s binding energy unambiguously determines whether protonation has occurred, with a mean N1s binding energy difference of +2.1 eV.

Table 1: ΔpK_a values for the 15 studied materials, where ΔpK_a = pK_a(base) − pK_a(acid) based on pK_a values.[1,26–28] Pharmaceutical development compounds are indicated as API (active pharmaceutical ingredient) structures.

Materials (base/acid)	Proton transfer (P) or not (N)	ΔpK_a
theophylline/5-sulfosalicylic acid dihydrate	P[17]	2.3[1]
theophylline/5-sulfosalicylic acid monohydrate	P[29]	2.3[1]
theophylline/oxalic acid	N[30]	0.3[1]
theophylline/maleic acid	N[30]	−0.2[1,26]
theophylline/malonic acid	N[30]	−1.1[1,26]
theophylline/citric acid	N[19]	−1.4[1,26]
theophylline/glutaric acid	N[30]	−2.6[1,26]
3,5-diaminobenzoic acid/ 3,5-dinitrobenzoic acid	P[23]	2.5[27]
4-aminobenzoic acid/ 3,5-dinitrobenzoic acid	N[22]	−0.3[27,28]
4-aminobenzoic acid/ 4-hydroxy-3-nitrobenzoic acid	N[23]	−3.9[27,28]
API 1/di-HCl	P	11.3, 3.3[28]
API 1/fumaric acid	N	0.3[28]
API 2/fumaric acid	P	7.2, 4.6[28]
API 3/HCl	P	15.4[28]
API 4/HCl	P	17.7[28]

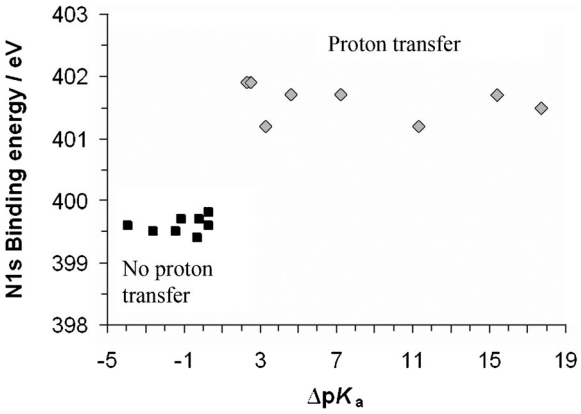

Figure 2. Correlation between N1s binding energy and ΔpK_a, illustrating that XPS clearly distinguishes between protonated and unprotonated nitrogen. ΔpK_a = pK_a(base) − pK_a(acid).[1,26–28] The measurement error on the N1s binding energies is about ±0.1 eV.

The analytical value of XPS for determining the oxidation state of atoms through their core-level binding energies is well-established and routinely used.[33–37] In contrast, the high sensitivity of core-level binding energies to Brønsted transfer, which is not associated with a change in formal oxidation state, has not been put to practical use for crystallographic studies, even though a strong chemical shift associated with protonated amino groups was already evident in early XPS studies of zwitterionic amino acid crystals.[38] Since these studies, N1s shifts due to protonation in organic systems have been noted occasionally, for example, in a study of inter- and intramolecular interactions,[39] and one of H-bonding in adsorbed molecules.[40] Core-level binding energies of molecular species in aqueous solution have also been shown to be sensitive to protonation and H-bonding in the surrounding hydrate shell.[41–43]

In molecular crystals, initial-state electrostatic effects tend to dominate over final-state relaxation contributions to core-level binding energies observed by XPS.[44,45] Core-level chemical shifts thus reflect primarily the influence of the most immediate atomic neighbors on the electronic state of the photoexcited atom.[24,33,34] Long-range order is therefore not a pre-requisite for XPS analysis of the chemical state, and even amorphous samples can be analyzed.[46] The effect of strong local intermolecular interactions such as ionic and H-bonding dominates over the comparatively weaker van der Waals and dipole interactions. It is for this reason that the core-level binding energies reported in Table 1 and Figure 2 are so universally sensitive to the protonation state. It should be noted that the sensitivity to local structure is also a drawback of XPS because the technique lacks spatial resolution at the molecular level. When a crystal structure contains too many structurally inequivalent Brønsted donors and acceptors in a similar chemical state (for example in the form of the same types of functional group) then XPS may not be able to resolve site-specific information.

In summary, measurements for a wide range of different solid-state donor–acceptor systems strongly suggest that the XPS identification of H-bonding versus Brønsted proton transfer is generically applicable to a wide range of systems.

Intermolecular hydrogen (proton) transfer from the acid to the base component leads to core-level binding energy shifts that clearly separate protonated from unprotonated nitrogen acceptors. This provides a straightforward method for pinpointing the location of hydrogen atoms and protons when crystallographic analysis is ambiguous or when a single crystal is not available. The chemical shifts of core-level binding energies provide a simple and reliable tool for determining the location of protons and hydrogen atoms, through a laboratory instrument that is commonly available in research institutes for chemistry, physics, and materials science.

Experimental Section

Materials: Acid–base materials were formed as described previously[19,20,22,23,30] or supplied from Sanofi-Aventis, Alnwick, UK.

X-ray Photoelectron Spectroscopy: XP spectra were recorded with a Kratos Axis Ultra instrument employing a monochromatic Al K_α source (1486.69 eV).[19,46] High-resolution spectra were measured within the spectral range of interest (ca. ± 20 eV around core-level emission peaks) with a 20 eV pass energy, 0.1 eV steps, and 500 ms dwell time per data point.

Analysis of the data was carried out with Casa XPS software[47] using a linear background and GL(30) line shape.[47] Samples were referenced following the procedure outlined previously,[17,19,25] giving the nitro group (NO_2) at 406.3 eV for benzoic acid materials. Repeatability of the peak positions was ± 0.1 eV.

Received: June 10, 2011
Published online: September 16, 2011

Keywords: hydrogen bonds · photoelectron spectroscopy · protonation · solid-state structures · X-ray diffraction

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