# CRYSTALLOGRAPHIC IMAGING OF A MOLECULAR CRYSTAL :
## Aspirin $C_8H_5O_4$-$CH_2D$

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The nuclear density distribution of partially deuterated aspirin at 300 K and at 15 K has been determined by single-crystal neutron diffraction coupled with Maximum Entropy image reconstruction (MEM). While fully protonated and deuterated methyl groups in aspirin (acetylsalicylic acid) have been shown to be delocalized at low temperature due to quantum mechanical tunnelling, we provide here direct experimental evidence that in partially deuterated aspirin-$CH_2D$ the methyl groups are orientationally ordered at 15 K whilst randomly distributed over three sites at 300 K. This is the first observation of low temperature isotopic ordering in condensed matter by diffraction methods.

## PHYSICAL BACKGROUND

The quantum mechanical behavior of ever larger and heavier molecules and molecular subunits in condensed matter is a subject of considerable interest . The onset of quantum behavior is usually observed at low temperature. Substitution of hydrogen with deuterium leads to large isotopic effects, in fact the largest ones known in chemical physics. Spectroscopic methods such as NMR and QENS are the prevalent tools to investigate these phenomena.

The rotational dynamics of molecules or side groups such as methyl groups is a very sensitive probe of the interatomic forces in crystals. Rotating a methyl group about the bond connecting it to the rest of the molecule makes it experience a rotational hindering potential which arises from the interactions of the methyl hydrogens with their surroundings.

This potential has at least three wells due to the molecular symmetry. At moderately high temperatures, the methyl groups undergo thermally activated reorientations between all three wells, whereas at low temperature, say below 30 K, the dynamics of the methyl groups is usually dominated by rotational quantum tunnelling [1].

While the dynamics of isotopically uniform methyl groups is by now well understood, little attention has been paid so far to the isotopically mixed $CHD_2$ and $CH_2D$ groups. Due to the loss of the three fold permutation symmetry in the latter, dramatic differences in the dynamical behavior are expected.

## WHY ASPIRIN ?

A well-studied case of the dynamics of the $CH_3$ and $CD_3$ groups is that of aspirin $C_8H_5O_4$-$CH_3$ and $C_8H_5O_4$-$CD_3$. The observation of rotational tunnelling in this compound by NMR triggered a whole series of studies concerned with the potential and with the dynamics of these methyl groups. These studies show that from room temperature down to about 35 K the per-protonated, the per-deuterated as well as the

isotopically mixed methyl groups perform thermally activated stochastic reorientations between the three potential wells. Upon cooling, the rate of the reorientations naturally slows down. What happens at low temperature depends crucially on the isotopic composition of the methyl group. For $CH_3$ and $CD_3$, coherent rotational tunnelling was inferred from NMR experiments. This implies that the wavefunction describing the methyl group is such that the three protons, respectively deuterons, are completely delocalized over three sites. By contrast, partial ordering, which implies localization as well as a rapid incoherent process between the almost degenerate upper two of the three wells were suggested for $CH_2D$, again on the basis of NMR results .

As shown below, Neutron Diffraction provides a direct check of the indirect NMR hints [2-4].
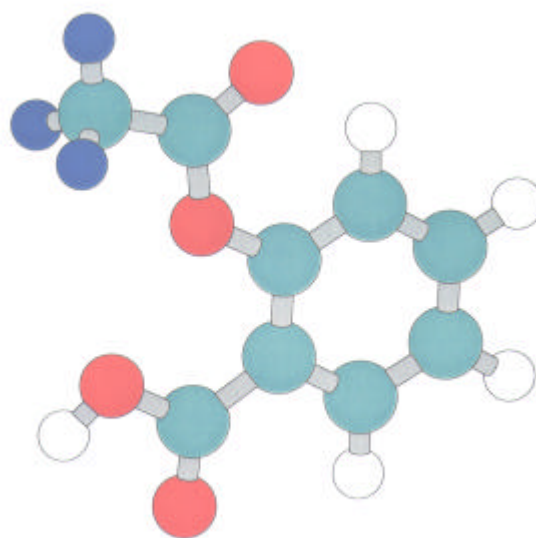


*Figure 1. The aspirin molecule. Carbon and oxygen atoms are shown in blue-green and red. The hydrogen atoms from the methyl group are shown in blue and the*

*remaining protons attached to the backbone are shown in white .*

## SINGLE-CRYSTAL NEUTRON DIFFRACTION

This technique allows us to measure the nuclear density distribution within the crystallographic unit cell. This distribution is given by the probability density function of finding a nucleus at a given position, multiplied by the coherent neutron scattering length b of that nucleus. The probability density function relates to an average over space and time, *i.e.* over the volume of the sample and over the duration of the measurement. In case dynamic processes are involved, then neutron diffraction yields a direct long time exposure of those processes. Due to the opposite signs of the neutron scattering length of protons and deuterons ( $b_H$=-3.74 fm, $b_D$=6.67 fm), the former yield a negative contribution to the nuclear scattering density, in contrast to the latter. Thus neutron diffraction is an excellent tool for distinguishing protons from deuterons, and hence for studying isotopic ordering processes such as those proposed for aspirin-$CH_2D$.

## A ZERO AVERAGE CONTRAST SAMPLE

In order to improve the visibility of the alleged H/D orientational order of the methyl groups at low temperature, we aimed at an aspirin-$CX_3$ sample with an average scattering length $<b_X>$ of zero. Consequently the single-site nuclear scattering length is expected to be close to zero for a random orientational distribution, for which there will hardly be any coherent scattering from the methyl hydrogens. On the other hand, if ordering occurs, it will then be revealed by positive bumps and negative holes in the nuclear density distribution .

## OUR EXPERIMENT

To test the above-mentioned ideas, we collected data sets from our crystal at 300 K and at 15 K on the four-circle 5C2 diffractometer ($\lambda$ = 0.8302 Å) at LLB. At both temperatures the crystal was found to be isomorphous to normal protonated aspirin, which had been examined much earlier by X-ray diffraction [5]. The crystal is monoclinic, of space-group $P2_1/c$ with 4 molecular units per unit cell. We used a crystal from a previous NMR study[3], and for which the requirement $<b_X>$ =0 is nearly met. In fact, $<b_X>$ ≈ -0.6 fm, about 11 times smaller than $<b_D>$. A further complication arises from the fact that our sample comprises approximately 70% $CH_2D$, 19% $CH_3$, 10% $CHD_2$ and 1% $CD_3$.

## LEAST-SQUARES RESULTS

The program SHELXL97 was used for refinements. As expected, neither could methyl hydrogen positions be found, nor did the calculated difference Fourier map reveal any contribution from either the methyl protons or deuterons. Any information about these latter hydrogens (which is definitely present in our data) is swamped by the inherent residual noise due to series termination effects.

Taking this model which does not include methyl hydrogens as the starting point for the LT structure refinement, two proton positions and one deuterium position are easily located by their negative and positive contributions in the difference Fourier map calculated by SHELXL97. Including these in the structural model without any bond length or bond angle constraint yields a good final agreement factor $R_1$=0.0465.

## MAXIMUM ENTROPY IMAGING

We are specifically interested in the nuclear density distribution arising from the methyl hydrogens. Since conventional Fourier syntheses would not reveal the latter when used on our room temperature data, we therefore applied the Maximum Entropy reconstruction method (MEM) to both our LT and RT data sets. We use our program GIFT (Generalized Inverse Fourier Transforms) which makes use of the Cambridge MemSys algorithm.

A projection of the 3D MEM-reconstructed nuclear density distribution along the monoclinic b-axis based on our 15 K data set is shown in Fig.2.
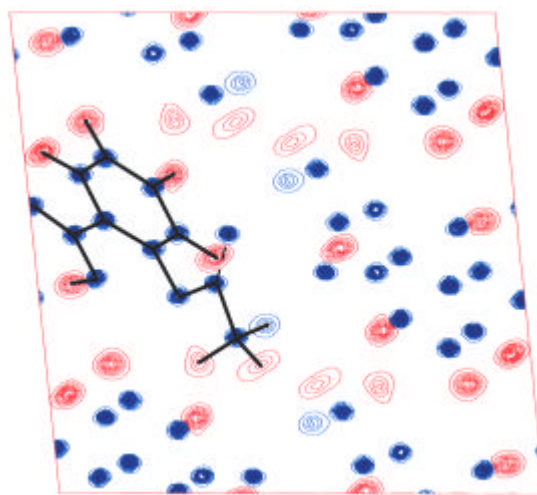


*Figure 2. : Experimental nuclear density distribution of partially deuterated aspirin (acetylsalicylic acid) at 15 K projected along the monoclinic b-axis. Red contours pertain to protons, which have a negative scattering length, in contrast to deuterium, carbon and oxygen atoms shown here in blue. The solid line delineates a single aspirin molecule.*

Similarly, the two sections shown below in Fig.3a,b are obtained from 3D scattering density reconstructions of the asymmetric unit of the aspirin

crystal by making use of MEM rather than conventional Fourier syntheses. Three dramatic improvements arise : (a) noise suppression, (b) flexibility to use non-uniform prior densities and (c) possibility to tackle partially phased data sets. In the present case, there is no phase problem : the phases of the structure factors are perfectly determined by the well-behaved atoms known from the X-ray study by Wheatley[5]. The decisive point is that MEM enables us to locate the methyl hydrogen even at room temperature. This is demonstrated in Fig.3a, in which a section of the nuclear density distribution function through the plane of the methyl hydrogens is displayed. Three holes, all negative as they should be since $<b_X> < 0$, are clearly seen. Despite being very shallow, the three minima are robustly reconstructed by MEM. No matter how the reconstruction is carried out, with or without non-uniform prior scattering length densities , the three minima are consistently reproduced. No prior knowledge about the hydrogen positions, available in principle from the 15 K data, was used in reconstructing this density distribution. It demonstrates the superior power of MEM over both standard Fourier and least-square techniques and provides clear evidence of the random distribution of the methyl protons and deuterons at 300 K over three geometrically well-defined sites.

In Fig.3b, we finally show the nuclear density distribution at 15 K for the same section as in Fig.3a, again reconstructed by MEM. The clear message of this figure is that the methyl protons and deuteron in aspirin-$CH_2D$ are well-ordered at 15 K. The deuteron obviously occupies with high preference the site associated with the large positive bump whereas the protons occupy almost exclusively the sites related to the negative holes. Truly, the localization of the methyl hydrogens at 15 K is also detectable in standard Fourier maps, albeit with a sizable background noise.

### COPING WITH THE ISOTOPIC MIXTURE

Quantitatively, the density distribution displayed in Fig.3b corresponds to the [70%-19%-10%-1%] superposition of the four isotopic species mentioned earlier. This results in **effective** occupancies for both H and D different from unity when an assumed unique species $CH_2D$ is refined using SHELXL97. We find 0.7, 0.7 and 0.53 for the two protons and the deuterium respectively. It can then be deduced that the probability of finding a deuteron from the $CH_2D$ isotopic species at the position evidenced by the positive bump seen in Fig.3b is at least equal to 0.86.

### References

[1] M.Prager, A.Heidemann, Chem.Rev. **97,** 2933 (1997)
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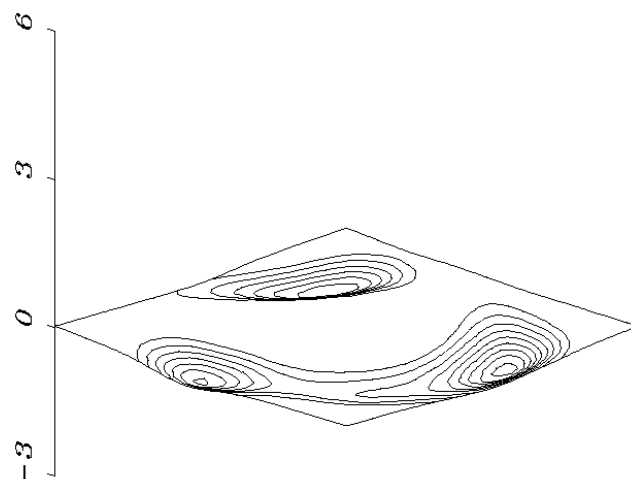[3,4] A.Detken , J.Chem.Phys.**108,** 5845,**109,**6791(1998)

*FIG.3a. MEM section of the nuclear density distribution through the methyl hydrogens of aspirin obtained from the 300 K data set. Note the three shallow minima of almost equal depth. They evidence the random occupation of the three methyl hydrogen sites by the protons and deuterons with weights corresponding to the isotopic composition of the crystal (see text). The residual (positive) contribution due to the thermal motion of the carbon atom of the $CX_3$ group has been removed numerically. (density unit : $fm/A^3$)*
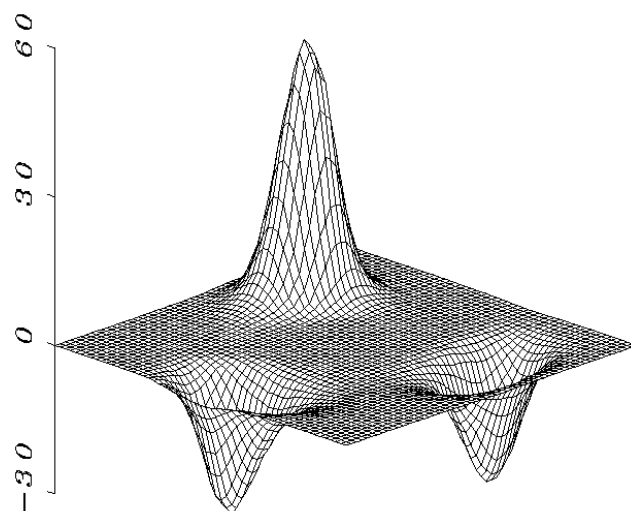


*FIG.3b. MEM section of the nuclear density distribution through the methyl hydrogens of aspirin from the 15 K data set. Note that the vertical scale has been changed by a factor of 10 in comparison with that in Fig.3a. The graph demonstrates the orientational ordering at 15 K of the most abundant methyl isotopomer, $CH_2D$ in our crystal sample. The deuteron occupies almost exclusively the site related to the (positive) bump while the protons preferentially occupy the two sites associated with (negative) holes. (density unit : $fm/A^3$)*

[5] P.J.Wheatley, J.Chem.Soc.,6036(1964)