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Water dynamics in channel hydrates investigated using H/D exchange

Matti U.A. Ahlqvist, Lynne S. Taylor *

Solid State Analysis, Pharmaceutical and Analytical R&D, AstraZeneca R&D Mölndal, S-431 83 Mölndal, Sweden

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Abstract

The dynamics and interactions of water with different channel hydrates were studied. Caffeine 4/5-hydrate, theophylline monohydrate and sodium cromoglycate were used as model compounds. The hydrogen/deuterium (H/D) exchange of the different hydrates following exposure to deuterium oxide vapour was studied using FT-Raman spectroscopy. The aim of the work was to (1) investigate the potential for H/D exchange studies to provide information about channel hydrates and (2) correlate the mobility of the water molecules inside lattice channels with structural parameters of the specific hydrates. The rate of exchange in the three different compounds was shown to vary considerably with caffeine 4/5 hydrate undergoing exchange much more rapidly than either sodium cromoglycate or theophylline monohydrate, with exchange in the latter compound being extremely slow. Based on the known crystal structures, it was possible to rationalise the results and to draw conclusions about the mechanism of exchange for the model compounds. It was found that the mobility of the water molecules in a channel hydrate is very dependent on the dimensions of the hydrate channel. Thus H/D-exchange studies may provide very useful structural and energetic information about channel hydrates. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Theophylline monohydrate; Caffeine 4/5 hydrate; Sodium cromoglycate; H/D exchange; Raman spectroscopy; Deuterium oxide

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1. Introduction

Pharmaceutical materials are often capable of incorporating water into the crystal lattice to form a hydrate. It has been estimated that one third of all pharmaceutical substances on the market have hydrated forms (Stahl, 1980). Water may be incorporated in the lattice in several ways and the properties of the hydrate crystal will depend on how the water is bound. It is thus useful to be able to divide hydrates into a number of classes which reflect structural and/or behavioural differences. One such classification system for hydrates has been suggested by Morris and Rodriguez-Hornendez (Morris and Rodriguez-Hornedo, 1993) whereby hydrates can be structurally divided into three different groups, namely isolated lattice site hydrates, lattice channel hydrates and metal ion co-ordinated hydrates.

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* Corresponding author. Tel.: +46-31-776-1282; fax: +46-31-776-3835

E-mail address: lynne.taylor@astrazeneca.com (L.S. Taylor).

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The present work focuses on understanding water dynamics and interactions in lattice channel hydrates and to some extent metal ion co-ordinated hydrates. Lattice channel hydrates comprise an interesting class of hydrates because small differences in structural parameters may have a large effect on the stability of the hydrate (Perrier and Byrn, 1982; Byrn et al., 1999). The water molecules in lattice channel hydrates can be either localised (hydrogen bonded to specific groups in the parent molecule) or disordered. Some lattice channel hydrates may also expand or contract to host more or less water molecules as the ambient humidity is altered and these are termed expanded lattice channel hydrates (Morris and Rodriguez-Hornedo, 1993).

Hydrates are commonly investigated by hydration/dehydration experiments. However, since hydration/dehydration often leads to a change of phase, alternative methods for studying hydrates are of interest. Hydrogen/deuterium (H/D) exchange has been used in a number of studies to investigate interactions of water with cyclodextrins by monitoring the exchange of crystal water and hydroxyl groups following exposure to deuterium oxide vapour (Steiner et al., 1995; Amado and Ribeiro-Claro, 1997; Moreira da Silva et al., 1997). More recently, this method has been used to probe amorphous and crystalline sugars (Ahlqvist and Taylor, 2002). The purpose of the present study was to (1) investigate the potential for H/D exchange experiments to provide information about channel hydrates and (2) correlate the mobility of the water molecules inside lattice channels with structural parameters of the specific hydrates.

Theophylline monohydrate and caffeine 4/5-hydrate were chosen as model compounds for this investigation. They can both form lattice channel hydrates and are essentially isomorphous with very similar molecular structures (Sutor, 1958a,b). Despite the similarities, the stability of their hydrated forms are very different. While caffeine effloresces under ambient conditions, theophylline must be heated to 35–50 °C or stored at low relative humidities (RH) before dehydration takes place (Byrn et al., 1999). Sodium cromoglycate was also selected as a model compound, since it is capable of forming non-stoichiometric hydrates. Thus, when sodium cromoglycate is exposed to high RH, the crystals will expand to hold more water and at low RH, the converse occurs and the crystals contract. In addition, sodium cromoglycate contains water molecules in different chemical environments. For example, at 75% RH sodium cromoglycate contains seven molecules of water per molecule of drug, four of the water molecules are co-ordinated to the sodium ions and the other three water molecules are located in a lattice channel and held by hydrogen bonding to the parent molecule (Cox et al., 1971; Stephenson and Diseroad, 2000). The molecular structures of theophylline, caffeine and sodium cromoglycate are shown in Fig. 1. Raman spectroscopy was used to monitor H/D exchange in these model systems.

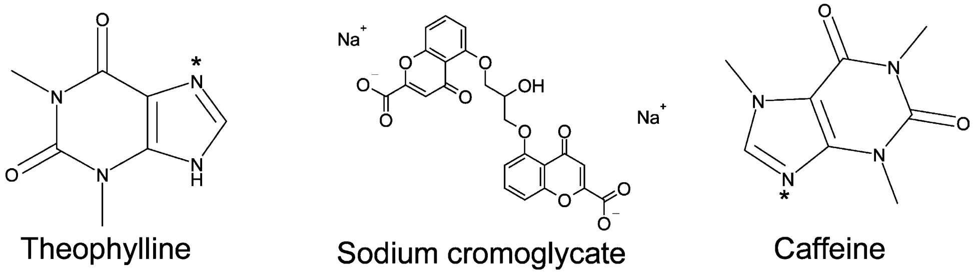

Fig. 1. Molecular structures of theophylline, sodium cromoglycate and caffeine. The asterisk on theophylline and caffeine marks the nitrogen that accepts a hydrogen bond from the water molecules in the hydrate structure.

2. Materials and methods

2.1. Materials

Anhydrous theophylline, anhydrous caffeine and sodium cromoglycate were purchased from Sigma Chemical Company (St Louis, MO). Theophylline monohydrate was obtained as needle like crystals by crystallisation from water. The sample was sieved and the 125–250 μm fraction was retained. The weight loss on heating during thermogravimetric analysis (TGA) was 9.4% (theoretical weight loss for the monohydrate is 9.1%) and X-ray powder diffraction (XRPD) pattern of the obtained hydrate was in good agreement to that reported previously (Wang, 1974). Theophylline monodeuteriate was obtained from a deuterium oxide solution and stored at ~44% RH (D_2O). The sample lost 9.9% weight on heating during TGA (theoretical weight loss for the monodeuteriate is 10.0%) and XRPD confirmed that the monodeuteriate and the monohydrate had the same crystal structure.

Caffeine 4/5-hydrate was prepared by crystallisation from a hot (80 °C) aqueous solution. The solution was slowly cooled to room temperature and the needle-like crystals were harvested by filtration. The wet crystals were dried at 44% RH for 7 days and then stored at 75% RH. The weight loss on heating during TGA was 6.8% (theoretical weight loss for the 4/5-hydrate is 6.9%). The XRPD pattern was coincident with that reported previously (Wang and Jaw, 1979). Microscopy of the material showed an approximate particle size of 100 μm. Caffeine 4/5-deuteriate was obtained by crystallisation from a hot D_2O solution. The solvent was removed under a nitrogen purge until damp crystals remained, final drying was performed at 75% RH (D_2O). The weight loss on heating during TGA was 7.4% (theoretical weight loss for the 4/5-deuteriate is 7.5%). XRPD confirmed that the crystal structure of the deuteriated sample was identical to that of the hydrated sample.

Sodium cromoglycate was equilibrated at 75% RH which corresponds to a water content of 7–7.8 water molecules per molecule of drug (Cox et al., 1971). Microscopy confirmed a particle size of around 100 μm for the bladed crystals.

2.2. Materials characterisation

A Mettler Toledo TGA 850 system was used for the TGA measurements. The heating rate was 10 °C/min and open alumina pans were used.

XRPD analysis was performed using low background sample holders and a Siemens D5000 X-ray diffractometer.

Qualitative analysis of particle size of the samples was performed on an Olympus BX50 microscope fitted with a Sony Exwave HAD digital video camera and Linksys software for Windows v.1.85.

2.3. Spectroscopic monitoring of the H/D-exchange

A Perkin-Elmer System 2000 FTIR with a Raman accessory, equipped with an InGaAs detector was used for collecting Raman spectra of theophylline.

Raman spectra of caffeine and sodium cromoglycate were collected with a Bio-Rad FTS 575C FTIR instrument with a Raman accessory, equipped with a liquid nitrogen cooled Ge detector.

For both instruments, a Nd:Yag laser (1064 nm) was used for excitation. The laser power on the sample was typically 500 mW and the spectral resolution was 4 cm^{-1}. Scattered radiation was collected at an angle of 180° and the Stokes radiation is reported. Indene was used as a standard to monitor the wavenumber accuracy. Spectra were collected as a function of time with a minimum of 1064 scans for each time point. Samples were analysed in triplicate in rotated sample vials where a constant humidity environment was provided by a saturated salt solution prepared with D_2O. These hygrostats have been described in detail previously (Ahlqvist and Taylor, 2002). The experimental variation was better than ±10% and the mean of the data are presented.

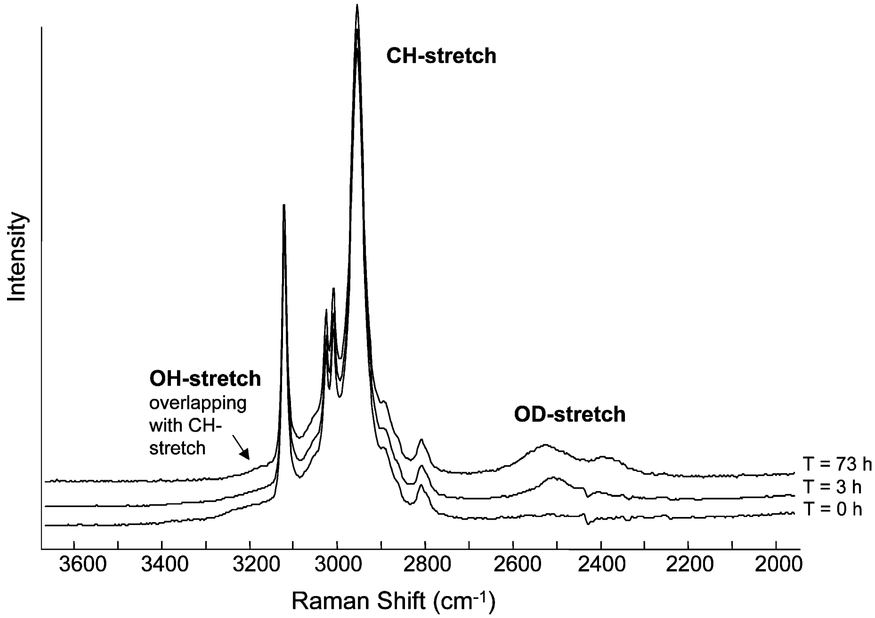

Fig. 2. Raman spectra of caffeine 4/5 hydrate as a function of time of exposure to deuterium oxide vapour (~ 75 %RH·D_2O). With time the peak due to OH stretch (3400–3100 cm^{-1}) decreases and the peak due to OD stretch (2600–2300 cm^{-1}) increases. All spectra are normalised to the CH stretching peak.

3. Results

3.1. H/D exchange in caffeine

Fig. 2 shows Raman spectra of caffeine 4/5-hydrate over the 3600–2000 cm^{-1} wavenumber region following exposure to deuterium oxide vapour (~ 75% RH) for different time periods. The peaks in this region arise from three group frequencies. At around 3300–3000 cm^{-1}, the very broad, weak peak arises from OH stretching modes of the crystal water molecules in caffeine 4/5-hydrate. Overlapping with the main part of the OH peak are the much stronger CH stretching peaks (3150–2800 cm^{-1}) of the caffeine molecule. The bands in the frequency range from 2650 to 2250 cm^{-1} are due to stretching modes of D_2O molecules that have replaced the water of crystallisation.

It is apparent from Fig. 2 that the spectrum of caffeine 4/5-hydrate changes on exposure to deuterium oxide vapour. The peak arising from OD vibrations evolves with time. The simultaneous decrease of the OH peak is not as easy to detect since it overlaps with the CH peaks and is very weak even in the fully hydrated material. However, careful examination of the spectra shows a decrease in OH intensity, indicating that water molecules in the hydrate are replaced by deuterium oxide.

The change in the peak area of the OD peak (I_{OD}) as a function of time was used to monitor the exchange process. The peak area was normalised against the area of the CH stretching peak at 2980–2900 cm^{-1} to eliminate experimental variations. Caffeine 4/5 D_2O was used as the reference to calculate the extent of exchange. The assumption was made that the OH peak will decrease at the same rate as the OD peak increase. This assumption is reasonable since the hydrate can only host a certain number of water molecules, thus the uptake of a D_2O requires the loss of a H_2O molecule.

Fig. 3 shows the increase in I_{OD} as a function of time. It can be seen that the exchange is quite rapid with 50% exchange after 175 min. Moreover, all of the water molecules are able to exchange with D_2O. Since all the water molecules in caffeine 4/5-hydrate are located within the same channel and caffeine does not have any exchangeable hydrogens, the complete exchange is as expected. This can also be confirmed by the observation that the Raman spectrum of caffeine 4/5-hydrate exposed to deuterium vapour for 4 days is virtually identical to the spectrum of caffeine that has been crystallised from D_2O (Fig. 4).

The spectra of caffeine 4/5 H_2O and caffeine 4/5 D_2O were also compared. As noted previously, the caffeine molecule is unaltered on crystallisation from D_2O, the crystal structure is the same as for the hydrate and thus the only difference is the solvent molecule. It can be seen from Fig. 5a that the two spectra are virtually identical and replacement of the water molecules with deuterium oxide causes very little perturbation of the caffeine molecule. Minor differences were, however, observed in two spectral regions as shown in Fig. 5b. In caffeine 4/5 D_2O there is an increase in peak intensity at 1493 cm^{-1} and a whilst the peak seen at 646 cm^{-1} shifts to 648 cm^{-1}. These peaks most likely arise from modes associated with the nitrogen atom which is involved in hydrogen bonding with water/deuterium oxide.

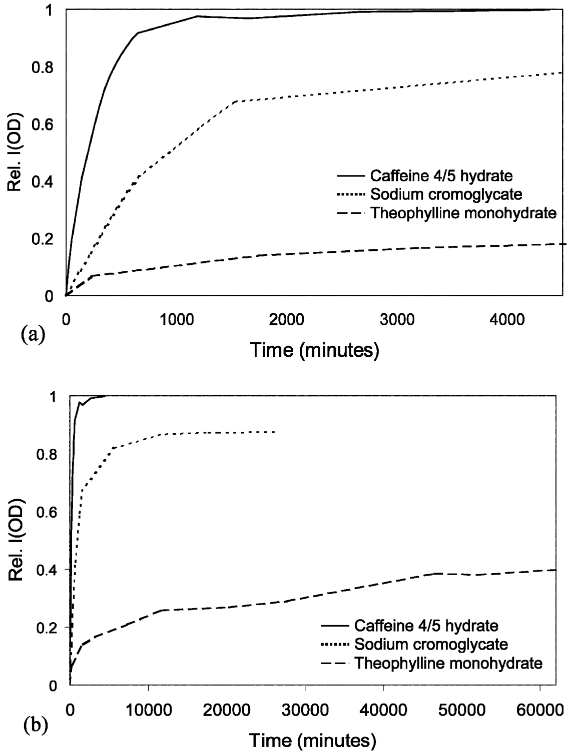

Fig. 3. Plot of the relative Raman intensity of the OD stretching peak (Rel. I_{OD}) as a function of time of exposure to deuterium oxide vapour (75 %RH·D_2O) for caffeine 4/5 hydrate, theophylline monohydrate and sodium cromoglycate. Fig. 3a shows the first 5000 min and Fig. 3b shows the exchange over 60 000 min.

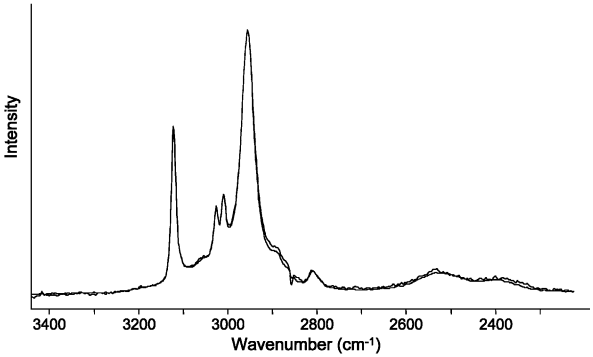

Fig. 4. Comparison of the 3400–2100 cm^{-1}region of the Raman spectra for caffeine 4/5 D_2O and caffeine 4/5 H_2O after full equilibration with deuterium oxide vapour (~ 75 %RH·D_2O).

3.2. *H/D-exchange in theophylline*

Theophylline monohydrate was also found to undergo H/D-exchange on exposure to deuterium oxide vapour. However, as can be seen from Fig. 3, the H/D-exchange in theophylline monohydrate is much slower than in caffeine 4/5-hydrate. Fig. 3b shows that the exchange is still proceeding after 60 000 min (42 days) and is nowhere close to completion, showing only around 39% exchange relative to the deuterated theophylline D_2O reference. Even after more than 6 months, exchange was not complete (it had reached approximately 40%, data not shown).

The H/D-exchange in theophylline monohydrate is more complicated than for caffeine 4/5-hydrate since the former also has an NH group that can potentially exchange a hydrogen for a deuterium. Unfortunately, the OD and ND peaks overlap so this information cannot be directly gained from a comparison of the spectra of the solvated samples. In order to see if the NH group had undergone any exchange, the sample of theophylline which had been exposed to D_2O was dried and compared with a dried sample of fully deuterated theophylline. This comparison indicated that there was a small ND peak in the spectrum of the dried exchanged sample (data not shown), indicating that some NH groups have undergone exchange. However, the intensity is much lower than for the fully deuterated sample, and from the relative intensities of the ND peak in the two samples, it can be estimated that only around 13% of the NH groups have exchanged. In other spectral regions, the exchanged sample was more similar to anhydrous theophylline than to deuterated anhydrous theophylline (the presence of a ND group changes a number of peaks in the fingerprint region of the spectrum), confirming that the NH group is largely unexchangeable.

3.3. *H/D-exchange in sodium cromoglycate*

Sodium cromoglycate will take up or give off water molecules to equilibrate with the ambient atmosphere in a non-stoichiometric manner (Cox et al., 1971; Chen et al., 1999). To enable a true H/D–exchange to take place, the samples had to be pre-equilibrated in 75% RH·H_2O prior to being exposed to ~75% RH·D_2O. At 75% RH, sodium cromoglycate hosts approximately 7 water molecules per drug molecule (Cox et al., 1971). Upon exposure to deuterium oxide, the water molecules in sodium cromoglycate were found to exchange with deuterium oxide. As can be seen from Fig. 3, the rate of the exchange process in sodium cromoglycate is slower than that in caffeine 4/5-hydrate but faster than for theophylline monohydrate with a 50% H/D-conversion after 750 min (12.5 h).

Fig. 3 indicates that exchange does not reach completion as compared with the reference sample of sodium cromoglycate crystallised from D_2O and equilibrated at 75% RH·(D_2O) atmosphere. Since all of the water molecules are found in a channel, it seems likely that this incomplete exchange may result from the inaccessibility of the hydroxyl group of the cromoglycate molecule. This was checked by comparing the spectrum of a dried sample of sodium cromoglycate, exposed for six months to D_2O vapour, with that of a dried sample of sodium cromoglycate re-crystallised from D_2O (data not shown). The sample that was exposed to D_2O vapour had a small OH peak whilst the sample crystallised from D_2O had none. This indicates that the OH group in sodium cromoglycate is not exchanged on exposure to D_2O vapour. This was also confirmed by looking at other areas of the spectrum where the dried six month sample was virtually identical to that of the dried hydrate, but different from that of the dried deuterated sample which showed a number of differences due to the presence of the OD hydroxyl function. Thus our results suggest that although all the water is exchanged, the hydroxyl group is unexchangeable and this group accounts for the residual OH intensity.

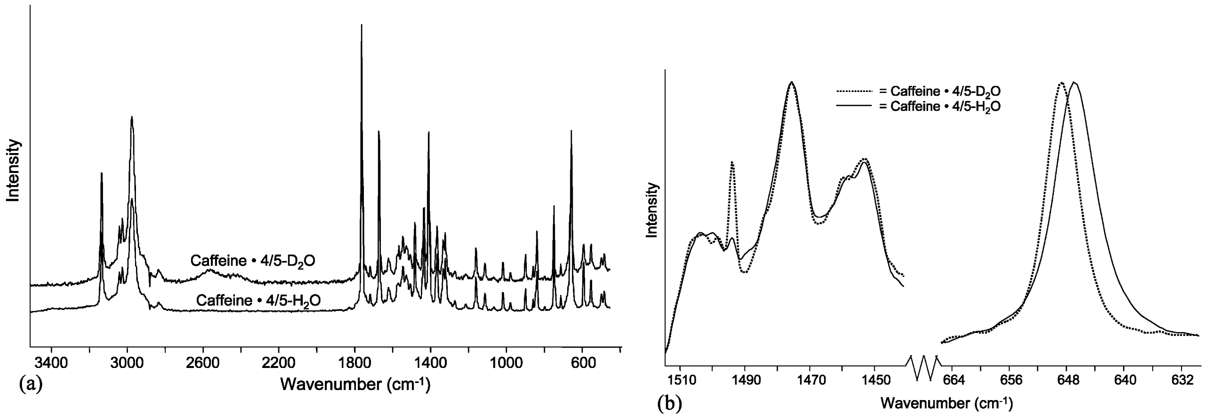

Fig. 5. Comparisons of the Raman spectra of caffeine 4/5 D_2O and caffeine 4/5 H_2O. (a) shows the entire spectra while (b) shows the regions in which differences are seen (1510–1450 cm^{-1}, 664–630 cm^{-1}).

4. Discussion

In channel hydrates, the water molecules are adjacent to other water molecules in the neighbouring unit cell and a channel of water molecules is formed along one of the crystallographic axis (Morris and Rodriguez-Hornedo, 1993). The three compounds examined in this study can all be classified as channel hydrates. Results from this study have shown that crystal hydrate water can be replaced by D_2O molecules on exposure to D_2O vapour for all three compounds although the kinetics and extent of exchange were found to vary considerably for the different compounds. The single crystal structures of caffeine 4/5 hydrate, theophylline monohydrate and sodium cromoglyclate have been published and were used to aid interpretation of the results from this study.

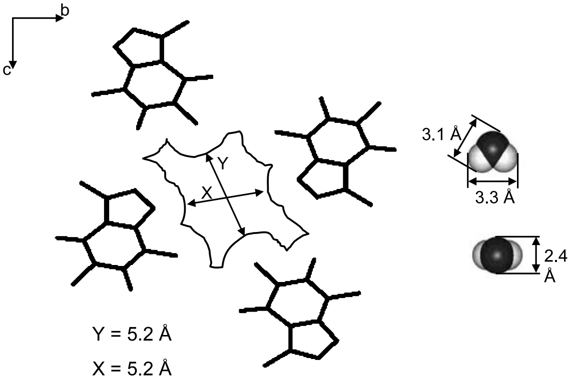

Fig. 6. Crystal structural of caffeine 4/5 hydrate (looking along the a-crystallographic axis), space group *P*21/*c*. The contours indicate the profile of the van der Waal radii of the atoms that are adjacent to the hydrate water channel. The water molecules are drawn as van der Waal representations from two perspectives and are shown next to caffeine for size comparisons. The distances, X and Y, are the shortest distances between opposite atoms (in three dimensions) forming the channel.

Despite the fact that theophylline monohydrate and caffeine 4/5-hydrate are nearly isomorphous (Byrn et al., 1999), the rate of the H/D exchange is very different for the two hydrates. In addition, the hydrates of these two compounds exhibit differing physical stabilities. Thus caffeine forms a non-stoichiometric hydrate whereby the water molecule readily effloresces through a channel in the a-crystallographic direction (space group $P2_1/c$). There is a single hydrogen bond between the caffeine molecule and water, between the iminazole nitrogen atom marked in Fig. 1 and the hydrogen of a water molecule. The water molecules form a zigzag chain which has vacancies as a result of the non-stoichiometry leading to localised disorder of the water molecules (Gerdil and Marsh, 1960). In contrast theophylline forms a stoichiometric hydrate which is stable to dehydration at room temperature. Each theophylline molecule hydrogen bonds to a water molecule through the nitrogen atom marked in Fig. 1 and the water molecules form a zigzag chain. Unlike caffeine 4/5 hydrate, the water molecules are localised. The strength of the hydrogen bonds between drug molecule and water are similar in magnitude in the two compounds, suggesting that other structural features are important in influencing the observed differences in the rate and extent of H/D exchange. Perrier and Byrn have highlighted the importance of the cross sectional area of the water channel in relationship to the dehydration behaviour of hydrates (Perrier and Byrn, 1982), and it is suggested that the size of the hydrate water channels in theophylline and caffeine will be an important factor affecting the H/D-exchange rate.

Figs. 6 and 7 show structural diagrams of caffeine 4/5-hydrate, looking along the a-crystallo-

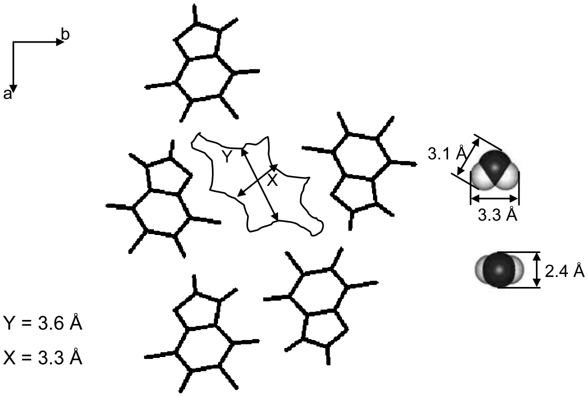

Fig. 7. Crystal structure of theophylline monohydrate (looking along the c-crystallographic axis) showing only the molecules that are in direct contact with the hydrate water channel. Other details are as for Fig. 6

graphic axis and theophylline monohydrate, looking along the c-crystallographic axis. The van der Waal radii of the atoms surrounding the hydrate water channel are represented as a contour, the parent molecules are represented as sticks. The water molecules are drawn next to the parent molecules with van der Waal radii for size comparison.

The size of the hydrate water channels were measured from crystallographic data (Sutor, 1958a,b) imported from Cambridge Crystallographic Database using WebLab ViewerPro 3.7 software. The size of the hydrate channels were estimated by measuring the two shortest distances (roughly perpendicular) across the channel. The distances were measured from the edge of the van der Waal radius of one drug atom to the edge of the van der Waal radius of the opposite drug atom (see Figs. 6 and 7). The size of the water molecule was determined in a similar way by measuring three distances between edges of the van der Waal radii of the atoms in the molecule (see Figs. 6 and 7).

By comparing the size of a water molecule with the measured size of the caffeine 4/5-hydrate water channel, it seems likely that a water molecule can enter the hydrate channel in any orientation. This means that all water molecules that approach the channel entrance in caffeine 4/5-hydrate may penetrate the hydrate and diffuse into the molecule. It can also be assumed by reference to Fig. 6 that the size of the channel may allow for one water molecule to pass by another water molecule inside the channel. This allows for diffusion of intact water molecules along the channel and the replacement of water molecules by D_2O molecules. Moreover, the vacancies in the hydrate chain discussed above will facilitate the movement of water within the channel.

In contrast, the hydrate channel in theophylline monohydrate is considerably smaller than that found in caffeine 4/5 hydrate and is approximately the same size as a water molecule as shown by Fig. 7. The packing of theophylline molecules around the hydrate water molecules is thus much closer than in caffeine 4/5 hydrate. This structural difference is the most likely explanation for the extremely low rate and incomplete extent of H/D exchange for theophylline. There is, however, around 40% exchange in theophylline monohydrate as compared with the deuterated form. It is likely that some exchange of water molecules in the channels can take place at the ends of the crystals (where the hydrate channel commences) which are in contact with D_2O atmosphere and further exchange may also occur in disordered regions of the crystals. However, given the structure of theophylline monohydrate as discussed above, it is unlikely that the majority of the H/D-exchange occurs by diffusion of intact D_2O molecules. Instead the exchange mechanism may be proton chain transfer which would provide an explanation for the extremely slow exchange process in theophylline monohydrate. Proton chain transfer involves disruption of the water covalent bonds and is, therefore, more energetically demanding and slower than the exchange of intact water molecules. Moreira da Silva et al. postulated that part of the H/D-exchange process in β-cyclodextrin occurs by proton chain transfer (Moreira da Silva et al., 1997; Steiner et al., 1995). Their assumption that the proton chain transfer is an essentially slower process than the diffusion of intact water molecules is given further support by the work done on α-cyclodextrin by Amado and Ribeiro-Claro (Amado and Ribeiro-Claro, 1997). Furthermore, the observation that the NH group undergoes very little exchange suggests that this group does not hydrogen bond with the hydrate water. Single crystal data confirms this observation; the NH group hydrogen bonds with a carbonyl group of another theophylline molecule and one of the ring nitrogens (as marked in Fig. 1) forms a hydrogen bond with the hydrate water.

As mentioned previously, sodium cromoglycate is capable of forming non-stoichiometric hydrates, i.e. to expand or contract the hydrate water channel continuously to equilibrate with different ambient humidities. Sodium cromoglycate in its hydrated form has one localised and one delocalised sodium ion per cromolyn ion. The water molecules in the structure are delocalised over eight sites but preferentially coordinated to the sodium ions (Chen et al., 1999). The H/D-exchange process in sodium cromoglycate is slower than in caffeine 4/5-hydrate even though the hydrate water channel area is considerably bigger. It is likely that this is a consequence of the water molecules being coordinated to the sodium ions as compared with hydrogen bonded with the drug substance as in the case of caffeine. The electrostatic force between a sodium ion and an oxygen atom is four to five times stronger than an ordinary hydrogen bond (Morris, 1999), thus the energy barrier for exchange of water molecules will be much higher, providing an explanation for the observed slower exchange kinetics in sodium cromoglycate. It may be further speculated that the ability of the hydrate to adapt the size of the hydrate water channel to a specific water content makes diffusion of D_2O molecules through the channel more difficult by minimizing the non-occupied volume. The observation that the hydroxyl groups in cromoglycate do not undergo H/D-exchange upon exposure to deuterium oxide vapour suggests that they are structurally or kinetically inaccessible to the water molecules, in good agreement with the crystal data which does not report any hydrogen bonding interactions between this functional group and water.

5. Conclusions

Water dynamics in three different channel hydrates has been investigated by monitoring H/D exchange on exposure to deuterium oxide vapour. The rate of the H/D-exchange process was shown to vary considerably between the three hydrates. The difference in exchange rate could be rationalised by comparing the dimensions of the hydrate channels with the size of a water molecule and in terms of the strength of the interactions holding the water molecules in the crystal lattice. These results indicate that H/D-exchange is a promising method to obtain structural information about channel hydrates, particularly where it is difficult to obtain single crystal data.

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