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Free Transport of Water and CO_2 in Nonporous Hydrophobic Clarithromycin Form II Crystals

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The transport of water to and from the interior of cells is essential for cellular physiological function. Water molecules diffuse through cell membranes by two general pathways.[1,2] The first, the lipid pathway, is universal in all cells in the human body. Water simply diffuses through the fluid lipid bilayer by a dynamic process with relatively slow velocity.[1] The water transport process can thus be facilitated by the presence of specific channels in the cell membrane such as aquaporins.[2,3] These are a family of proteins that associate as tetramers to form cylindrical transmembrane filters that are 2 to 3 nm long, and about 0.3 nm wide at their narrowest point. In each of these pathways, the simple notion of water transport through any matrix implies the presence of suitably sized channels defined and constricted by van der Walls surfaces.[4] Recent work with crystals composed of calixarene molecules has revealed that small and mobile molecular species, such as water, can diffuse into the hydrophilic pockets of the host lattice without evidence of channels.[5] This finding raised questions about conventional conception of crystal porosity that assumed transport of guests in solid media requires suitably sized channels. Herein, we report the transport phenomena of water and CO_2 molecules within seemingly nonporous crystals of the antibiotic clarithromycin (6-*O*-methylerythromycin A, **1**), despite a lack of channels in the crystalline state.

Clarithromycin is known to exist into at least five crystalline polymorphs, termed form 0, I, II, III and IV.[6a−e] Crystals of pure guest-free **1** were prepared by sublimation at 200 °C under reduced pressure. A fresh block-shaped crystal was selected for single-crystal X-ray diffraction analysis (SCXRD). The crystals are in an orthorhombic cell and the structure was solved in the space group $P2_12_12_1$. Within the extended structure, the molecules are arranged in a densely packed zigzag arrangement that is isostructural to the methanol solvate reported by Iwasaki and co-workers,[7] although in this case in the absence of solvent molecules (Figure 1a). In comparison to the reported X-ray powder diffraction patterns of various forms, the sublimate was found to be pure form II crystals.[6c] To the best of our knowledge, this represents the first report of a single crystal structure of guest-free **1** form II. Unlike the methanol solvate, the large uniform lattice voids (84 Å^3, Figure S1, Supporting Information) are unoccupied in the sublimed phase. These voids are isolated within the crystal lattice and cannot merge into channels. Although there are a few exceptions, large lattice voids are rarely observed in organic crystals due to the phenomenon of close packing.[5c,8]

Upon performing SCXRD studies on the same crystal after exposure to air for two days, structural analysis revealed significant electron density in the lattice voids while the overall structure remained unaltered. In contrast, structural analysis of a freshly sublimed crystal of **1** did not reveal appreciable residual electron density at this site. This observation implied that the crystal adsorbed air/moisture from the surroundings while stored under atmospheric conditions. This electron density can be modeled as a partial occupancy (25%) water molecule, which shows strong hydrogen bonding interactions with molecules of **1**. Based on this observation, we performed water diffusion studies on single crystals of **1**.

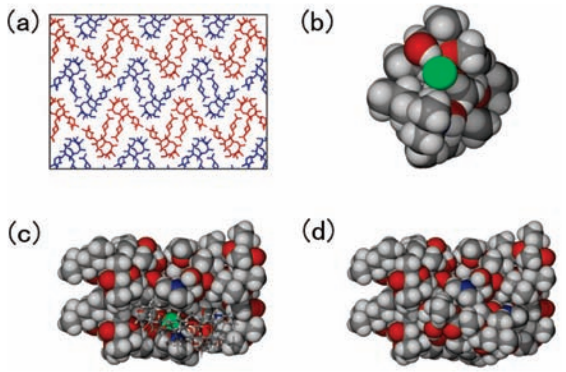

Figure 1. Views of the crystal structure of **1** form II and **1** form II·$(H_2O)_{0.5}$. (A) Densely packed zigzag arrangement of molecules of **1** form II in a *bc* cross-section. (B) Hydrogen bonding interaction between a molecule of **1** and the partial occupancy water molecule in **1** form II·$(H_2O)_{0.5}$. (C) Partial space-filling representation of the extended structure of **1** form II·$(H_2O)_{0.5}$ showing the embedded water molecule. View down the *b*-axis. (D) Full space filling representation of (C) stressing the densely packed nature of the structure.

A fresh single crystal was chosen and mounted at the top of a glass fiber. Following collection of SCXRD data, the crystal was immediately immersed in water for ~30 h. Data (SCXRD) were recollected and structure solution revealed the same arrangement and conformations of molecules of **1**. Structure solution showed significant electron density in the lattice voids in an analogous way to the aforementioned crystal that was exposed to air. This electron density was modeled as a partial occupancy water molecule (50%). This water molecule is stabilized by hydrogen bonds to and from surrounding molecules of **1** (partially shown in Figure 1b, Figure S2, Figure S3, Supporting Information). Thermogravimetric analysis (TGA) of carefully dried crystals, after submersion in water, indicated the water:clarithromycin ratio of 1:2 (Figure S4, Supporting Information). Interestingly, soaking the crystal in water for up to 6 days did not result in any further uptake of water, which was verified by TGA and crystal structural analysis. All of these experiments support the conclusion that guest-free form II crystals of **1** can uptake water via a single crystal to single crystal transformation, resulting in a new crystalline form of this well-known drug: clarithromycin hemihydrate. It is also noted that this

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hemihydrate is metastable at room temperature. After exposed to air with midhumidity, the water occupancy decreases to about 25%, identical to the water content of form II crystals stored in the same environment (Figure S5, Supporting Information). This implies water transports freely within the crystals without disrupting crystal integrity.

It remains to discuss the mechanism of water transport process in these guest-free crystals. Carefull scrutiny of the packing mode of **1** reveals that the lattice voids are surrounded and isolated by five nearest host molecules (Figure 1c and d). The radius of the largest sphere capable to pass through the narrow window of this "pentamer" is 0.93 Å (note that the van der Waals radius of a hydrogen atom is often taken to be ~1.17 Å).[9] The host framework is nonporous and no rational route can be traced for guest diffusion. In this regard, the ingress of water molecules must involve a two-step process. We propose that water diffuses through the nonporous hydrophobic lattice via a momentary window, which might be created by the cooperation of host molecules in a dynamic and concerted fashion. Following this, water molecules hop between voids until residing in the thermodynamically favorble hydrophilic pockets, bound by molecules of **1**. Even though the size of one single pocket is suitable to accommodate two water molecules, the crystals are saturated by half a molecule per pocket. This is consistent with crystals of **1** obtained when crystallizing from water-saturated solvent mixture, which also have a water/host ratio of 1:2 revealed by SCXRD studies (see Supporting Information).

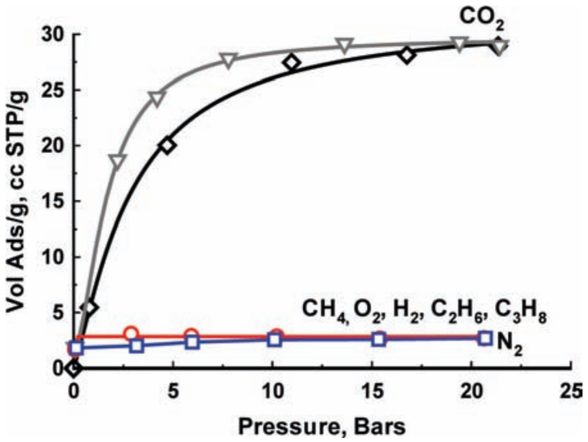

Figure 2. Sorption of various gases in **1** form II crystals at 298 K.

Given that water was found to diffuse through the seemingly nonporous crystals, we studied the general availability of these voids for gas molecules. Absorption capacities of this type of nonporous crystal were measured volumetrically at room temperature for several gases including N_2, O_2, H_2, CH_4, C_2H_6, C_3H_8 and CO_2. The activated powders show highly selective sorption values for CO_2. The sorption isotherm at 298 K is a type I curve, characteristic of the microporous material, and uptake is saturated at 10 atm. At this point, 30 mLg^{-1} CO_2 (6 wt %) is stored in the solid. This value is high for organic crystals,[8] but is relatively low compared to those of metal-organic frameworks.[10] The nonporous crystals can store up to 1.01 mol of CO_2 per mol of **1**, indicating complete filling of the available lattice voids in the structure. Little hysteresis is observed in the desorption measurement and the presence of CO_2 in the solids can be further verified by solid state NMR study with a peak of 125.2 ppm (Figure S6, Supporting Information). These studies show molecules with diameters larger than water, such as CO_2 (3.3 Å), can be transported within the channel-free host lattice with ease.

Interestingly, the solid shows little or no sorption with the other gases tested, despite the use of high pressure. The caculated BET surface area from N_2 sorption at 77 K is less than 10 m^2/g (Figure S7, Supporting Information), suggesting very little uptake of N_2. Hydrocarbon gases, such as CH_4, C_2H_6 and C_3H_8, are also not appreciably retained. Crystalline **1** form II represents a rare sorbent which is highly selective for CO_2. It can potentially be used for natural gas purification and flue gas separation. Several factors appear to account for the high affinity and selectivity for CO_2. The gas molecules with larger diameter than CO_2 may not be able to penetrate the lattice, and should they do so, there are no strong interactions between them and the walls of the void which are hydrophilic and antiaromatic. Furthermore, the size of the pocket excludes the possiblities of uptaking larger molecules (i.e., with volumes > 50 Å^3).

To conclude, we have shown that water molecules can freely pass within a pharmaceutical crystal without evidence of suitably sized channels in the crystal structure, resulting in a new crystalline pseudopolymorph. These channel-free crystals can also selectively uptake CO_2 from a mixture of various gases. These findings further imply that crystals may not be as rigid as generally presumed, but may be mobile, dynamic and capable of significant guest diffusion.

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Supporting Information Available: Experimental procedures, X-ray crystallographic data for **1** form II and **1** form II·$(H_2O)_{0.5}$ crystals, TGA, and solid state NMR study of CO_2 uptake. This material is available free of charge via the Internet at http://pubs.acs.org.

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