Fast Surface Diffusion and Crystallization of Amorphous Griseofulvin

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Abstract. Among all molecular glasses studied to date, griseofulvin (GSF) is one of the fastest crystallizing. To understand this property, we have measured the surface diffusion in GSF using the method of surface grating decay. Surface diffusion in amorphous GSF is extremely fast, outpacing bulk diffusion by a factor of 10^8 at the glass transition temperature T_g (361 K). Among all molecular glasses studied (13 in all), GSF has the second fastest surface diffusion (to o-terphenyl) when compared at T_g. The GSF result fits the overall trend for molecular glasses without intermolecular hydrogen bonds, in which surface diffusion systematically slows down with increasing molecular size. This result is particularly noteworthy because GSF has many hydrogen-bond acceptors (ether and carbonyl) but no donors, indicating that so long as they do not participate in hydrogen bonding, the polar functional groups have a similar effect on surface diffusion as the non-polar hydrocarbon groups. In contrast, the formation of intermolecular hydrogen bonds strongly inhibits surface diffusion. The surface crystal growth rate of amorphous GSF is nearly proportional to its surface diffusion coefficient, as noted for other systems, supporting the view that surface crystal growth is controlled by surface diffusion. In addition, the fast surface diffusion of GSF glasses explains the fast crystal growth along fracture surfaces and provides a basis to understand fast crystal growth *in the bulk* through continuous creation of micro-cracks.

Introduction

Crystal growth in supercooled liquids and glasses is an important problem in many areas of science and technology. Work on this problem began at least a century ago, when it was proposed that the velocity of crystal growth in a supercooled liquid is limited by the rate at which diffusion (or viscous flow) rearranges molecules.[1,2] This Wilson-Frenkel model has proved reasonably accurate in describing crystal growth in many glass-forming liquids above the glass transition temperature T_g. In 1967, however, Greet and Turnbull briefly reported the "anomalously rapid" crystal growth in the molecular liquid o-terphenyl (OTP) near and below its T_g,[3] with its velocity exceeding the Wilson-Frenkel limit by 4 orders of magnitude. This fast mode of crystal growth (later termed the glass-to-crystal or GC growth mode) is now known for many molecular liquids and has received many explanations.[4,5,6,7,8,9,10] It is noteworthy that GC growth occurs in the *interior* of a molecular glass. A further progress in this area occurred in the last decade with the discovery that the velocity of crystal growth can be even faster at the *free surface* of a molecular glass than in its interior.[11,12,13] This suggests that surface molecules are highly mobile and able to crystallize even when bulk mobility is low. This notion gained support from independently measured surface diffusion coefficients,[14,15,16,17,18,19] indicating that surface diffusion can be 8 orders of magnitude faster than bulk diffusion when compared at T_g. It was also established that the growth velocity of surface crystals is approximately proportional to the surface diffusion coefficient,[15,16] further the confirming the relation between the two processes. In 2016, on the basis of this result, Powell et $al.$[10] proposed a new explanation for the now 50-year-old puzzle of GC growth. They argued that despite being a bulk process, GC growth is fundamentally linked to surface mobility because the crystal growth process continuously creates voids and free surfaces (a consequence of the higher density of the crystal than the glass), which in turn accelerates local transformation through high surface mobility.
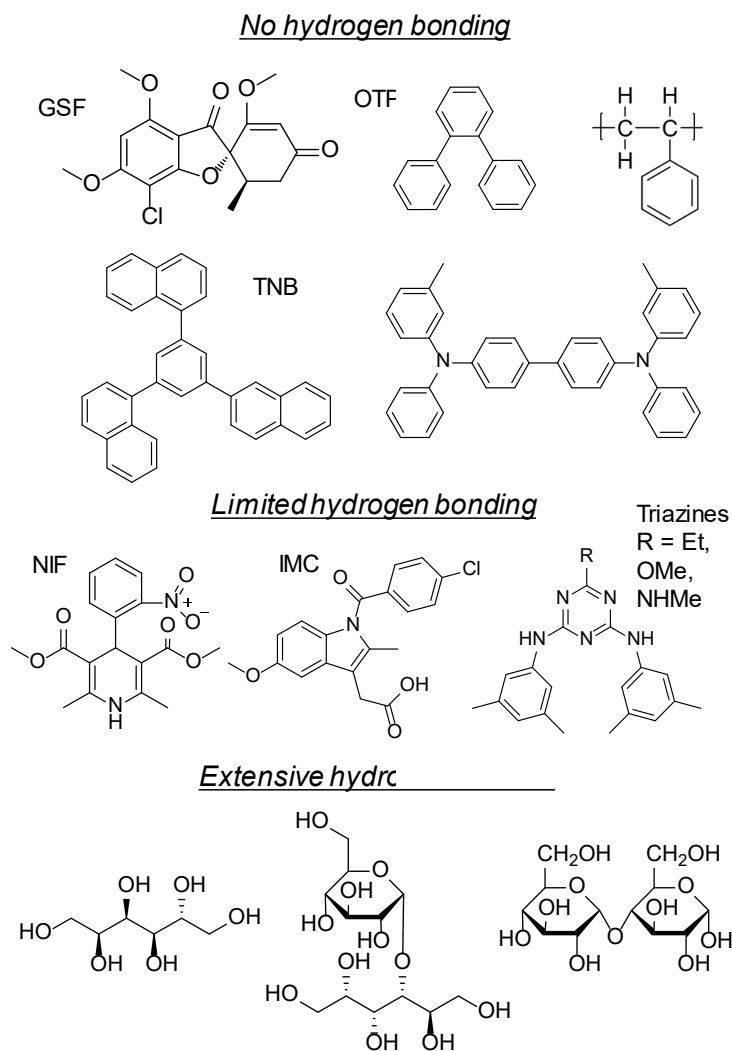
The purpose of this work is to further evaluate the current understanding of crystallization in molecular glasses using griseofulvin (GSF, see Scheme 1) as a model system. GSF is an antifungal drug and a well-studied glass-forming molecular liquid.[20,21,22,23] The glass of GSF shows remarkably fast crystal growth on the free surface;[20,21] its velocity is the second fastest on record (to OTP). This property suggests very fast surface diffusion in GSF, a hypothesis to be tested in this study. In this context, another intriguing property of GSV is that its crystallization process causes a large increase of density by 8 %;[20] this value is larger than the values reported for any other molecular glasses (5 % or less).[3,7,20] It suggests that the crystallization process can create a large amount of void space and free surfaces, which in turn accelerate local transformation. Indeed, fast crystal growth has been observed not only on the free surface of a GSF glass but also in its interior (GC growth).[21] It is noteworthy that crystal growth in a GSF glass is accelerated along artificially created cracks,[20] suggestive of a possible role of micro-cracks in bulk crystallization.

We expect GSF to play an important role in understanding the *molecular dependence* of surface diffusion in molecular glasses. Previous work[17,24] has shown that the rate of surface diffusion can vary significantly from one system to another, with two leading factors controlling the variation being the molecular size and intermolecular hydrogen bonding. For example, for a series of aromatic hydrocarbons – OTP,[15] α,α,β-tris-naphthyl benzene (TNB),[16] and polystyrene (PS) oligomers[17] (see Scheme 1), surface diffusion systematically slows down with increasing molecular size when compared at T_g. Meanwhile, for molecules of similar sizes, introducing intermolecular hydrogen bonds also slows down surface diffusion; this trend is evident by comparing OTP and TNB (no hydrogen bonds) with nifedipine (NIF),[18] indomethacin (IMC),[14] and the triazines[19] (limited hydrogen bonds) and with poly-alcohols (extensive hydrogen bonds)[24]. In this context, GSF provides a valuable new system. Similar to the simple aromatic hydrocarbons, GSF forms no hydrogen bonds (it has only acceptors but no donors); but unlike these previous molecules, GSF has many polar groups (ether and carbonyl). Is the surface diffusion of GSF fast

like that of OTP and TNB, or slow like that that of the polyalcohols? Answering this question will sharpen the understanding of the molecular factors controlling surface mobility.

We report that the surface diffusion of a GSF glass is extremely fast, outpacing bulk diffusion by approximately a factor of 10^8 at T_g. Among all molecular glasses studied to date, GSF has the second fast surface diffusion (to OTP). The fast surface diffusion of GSF is consistent with its fast surface crystal growth. The correlation plot between surface crystal growth and surface diffusion is approximately linear, indicating a fundamental relation between the processes. Despite its abundant polar functional groups, GSF has a similar rate of surface diffusion as

Scheme 1. Structures of griseofulvin (GSF) and other molecules discussed in this work. OTP: *ortho*-terphenyl; TNB: *tris*-naphthyl benzene; TPD: *N, N'* -Bis(3-methylphenyl)-*N, N'* – diphenylbenzidine; PS: polystyrene; NIF: nifedipine; IMC: indomethacin; Et/OMe/NHMe triazines: bis(3,5-dimethyl-phenylamino)-1,3,5-triazine with different functional groups R (Et, OMe, and NHMe).

a simple aromatic hydrocarbon of similar size (OTP and TNB). This indicates that as long as they are not engaged in hydrogen bonds, polar functional groups have no more influence on surface diffusion than the hydrocarbon groups, whereas the formation of intermolecular hydrogen bonds has a strong inhibitory effect on surface diffusion.

Experimental Section

Griseofulvin (GSF, purity > 99%) was obtained from J&K Scientific Co. Ltd. and used as received. To prepared a GSF glass with a surface grating, a supercooled liquid on a round silicate coverslip (diameter = 12 mm) was covered by a master grating at 408 K and was cooled to 353 K (T_g − 8 K), at which the master was detached to yield a GSF glass film with a corrugated surface. Notice that cooling to much lower temperature caused fracture of the GSF glass owing to the stress created by the coverslip's smaller thermal expansion coefficient than GSF's. The master gratings were purchased from Rainbow Symphony (wavelength λ = 1000 and 2000 nm), separated from commercial data-storage discs (1500 nm for CD and 730 nm for DVD), or duplicated from a glass grating purchased from Spectrum Scientific (550, 3300 and 8200 nm) through a UV-curing polymer (Norland Optical Adhesive 61). All masters were gold-coated to minimize the transfer of contaminants. The surface profiles of all master gratings were sinusoidal contours except for those of wavelength 3300 and 8200 nm, which had a sawtooth profile. We emphasize that the thickness of each embossed GSF glass film was *ca.* 40 μm and much greater than the wavelength of the surface grating, ensuring that the substrate had no effect on surface evolution.

The decay process of a surface grating was monitored by atomic force microscopy (AFM, Bruker Veeco Mutiple Mode IV) or laser diffraction. AFM was performed in the tapping mode at room temperature; the height profile was Fourier transformed to obtain the amplitude of the sinusoidal surface or in the case of a sawtooth profile, that of the first harmonic. In a diffraction measurement, a HeNe laser (λ = 632.8 nm, Uniphase Corp.) passed through the GSF film and the intensity of the first-order diffraction was recorded with a Si-amplified photodetector (Thorlabs) interfacing with a National Instruments LabVIEW program. The square root of the first-order diffraction intensity was shown to be proportional to the grating

amplitude. The two methods yielded consistent results at the same temperatures where both were applied. For both methods, temperature was controlled with a Linkam THMS 600 hot stage purged with dry N_2.

Results

Figure 1 shows the typical decay kinetics of GSF surface gratings recorded by AFM (Figure 1a) and laser diffraction (Figure 1b). AFM directly yielded the grating amplitude h; the laser diffraction experiment yielded the first-order diffraction intensity I, which is proportional to h^2. The decrease of h over time t is exponential, $\phi = \exp(-Kt)$, where ϕ is h/h_0 and K is the decay constant, or stretched-exponential, $\phi = \exp[(-Kt)^\beta]$, with β close to 1.

Figure 2a shows the temperature dependence of the decay constant K at $\lambda = 1000$ nm. To expand the temperature range, the K value at the highest temperature (388 K) was calculated from the decay rate of a longer wavelength grating ($\lambda = 8200$ nm), based on the wavelength dependence of K (discussed below). In total, the measured decay rates cover five orders of magnitude.
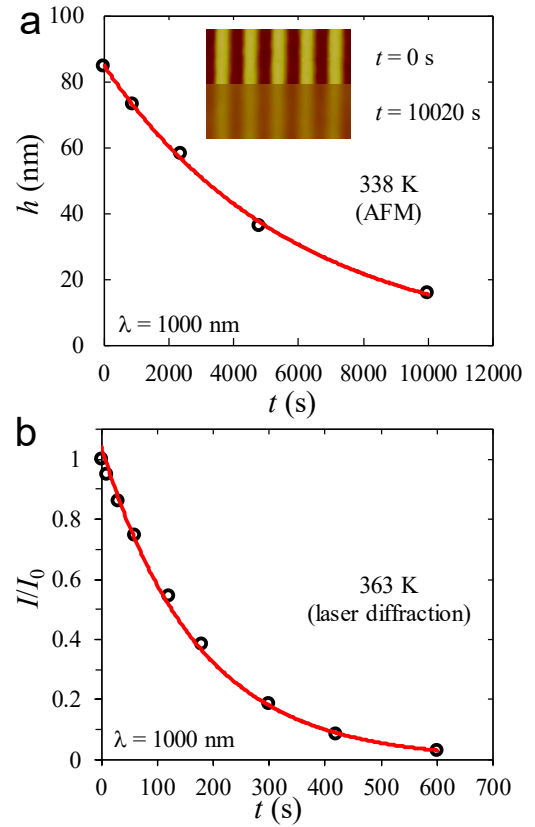

Figure 1. Typical decay kinetics of GSF surface gratings ($\lambda = 1000$ nm). (a) At 338 K recorded by AFM. Insert: AFM images at 2 time points. (b) At 363 K recorded by laser diffraction. I/I_0 is normalized diffraction intensity.

We also measured the wavelength dependence of K at different temperatures. Figure 2b shows the results at 383 K and 333 K. At 383 K ($T_g + 22$ K), the decay constant, K, is proportional to λ^{-1}; at 333 K ($T_g - 28$ K), we find $K \propto \lambda^{-4}$. These wavelength dependences of K indicate that the surface decay at 383 K occurs by viscous flow, while the process at 333 K is by surface diffusion, as we explain below.

Mullins[25,26] showed that the amplitude of a sinusoidal grating decays exponentially and the decay constant is given by

$$K = Fq + Aq^2 + Dq^3 + Bq^4 \qquad (1)$$

where $\quad q = 2\pi/\lambda$

$$F = \frac{\gamma}{2\eta} \qquad\qquad A = \frac{p_0\gamma\Omega^2}{(2\pi m)^{\frac{1}{2}}(kT)^{\frac{3}{2}}}$$

$$D = A' + C = \frac{\rho_0 D_G \gamma \Omega^2}{kT} + \frac{D_v \gamma \Omega}{kT}$$

$$B = \frac{D_s \gamma \Omega^2 \nu}{kT}$$

where λ is the grating wavelength; η is the viscosity; γ is the surface tension; p_0 is the equilibrium vapor pressure; Ω is the molecular volume; m is the molecular weight; k is the Boltzmann constant; T is the temperature; ρ_0 is the number density of vapor at equilibrium; D_G is the diffusion coefficient of the vapor molecules in the inert atmosphere; D_v is the bulk self-diffusion coefficient; ν is the number of molecules per unit area on surface. The four terms in Equation (1) correspond to different mechanisms of mass transport: viscous flow (F), evaporation-condensation ($A + A'$), bulk diffusion (C), and surface diffusion (B).

Figure 2. (a) The temperature dependence of decay constant, K, at $\lambda = 1000$ nm for amorphous GSF (solid circles). The structural relaxation time, τ_α, is shown as a black curve. (b) The wavelength dependence of K at 333 K (black) and 383 K (blue).

Notice that each term in eq. (1) has a distinct wavelength dependence. For example, the viscous flow term scales as λ^{-1} and the surface diffusion term as λ^{-4}. These are the wavelength dependences observed for GSF decaying at high and low temperatures (Figure 2b). As a result, we assign the high-temperature
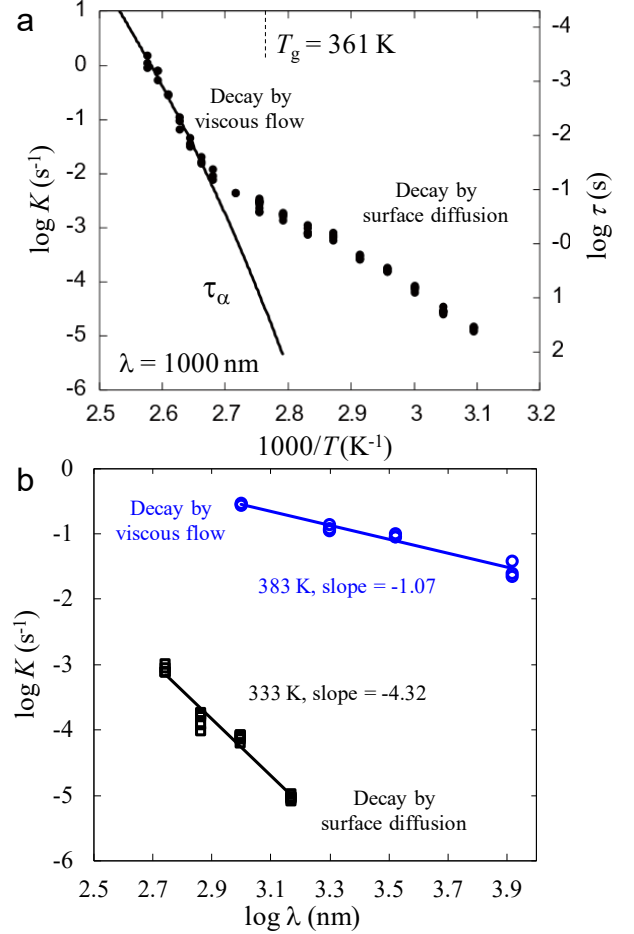
decay as occurring through viscous flow and the low temperature decay through surface diffusion. In what follows, we offer additional justification for these assignments.

Among the four terms in eq. (1), the evaporation-condensation and bulk-diffusion terms are shown to be much smaller than the observed decay constant, K, by at least 10,000 times. For this calculation, the following values are used: $p_0 = 6.8 \times 10^{-11}$ Pa (predicted by the ACD software[27]), $\rho_0 \approx 1.4 \times 10^{10}$ m^{-3} (calculated from p_0 using the ideal gas law), $\Delta H_{vap} = 86$ kJ/mol (predicted value at the boiling point by ACD[27]), $\gamma = 0.0526$ N/m (predicted by ACD[27]), $D_G \approx 0.00001$ m^2/s (typical value of organic molecules at ambient pressure[28]), and D_v is assumed to be the same as OTP[29] and TNB[30] at the same T_g–scaled temperature. In addition, Ω is calculated from $m/(\rho N_A)$, where m is the molecular weight, N_A is Avogadro's number, and ρ is the density of a GSF glass (1.35 g/mL),[20] to yield $\Omega = 4.0 \times 10^{-28}$ m^3.

The assignment that the high-temperature decay occurs by viscous flow can be tested against the expected temperature dependence of K. While there is no viscosity data on GSF, the structural relaxation time τ_α is known[22] and can be used to describe the temperature dependence of viscosity because of the relation $\eta \propto \tau_\alpha$.[31] In Figure 2a, τ_α is plotted on the second y axis. It is seen that the τ_α curve has the same temperature dependence as K at high temperatures, as expected for the viscous flow mechanism. This agreement holds above 375 K ($T_g + 14$ K) for the 1000 nm wavelength grating, but breaks down at lower temperatures (Figure 2a), indicating that a different mechanism is operative. By elimination, surface diffusion is the only mechanism remaining that is responsible for the low-temperature decay. Again, this assignment is supported by the wavelength dependence test (Figure 2b), which finds $K \propto \lambda^{-4}$, as expected for this mechanism.

Assigning surface diffusion as the mechanism for surface-grating decay at low temperatures, the corresponding surface diffusion coefficients, D_s, can be calculated. Figure 3 shows the result of this calculation, along with the previous results on simple aromatic hydrocarbons: OTP, TNB, and two PS

oligomers (M_w = 1110 and 1700 g/mol). Figure 3 also includes the D_v values of OTP[29], TNB[30], and a PS oligomer[32] (M_w = 1900 g/mol). In this plot, the temperature has been scaled by T_g. In this format, the D_v values of the various systems nearly collapse to a master curve, and it is reasonable to expect that the D_v of GSF falls close to the master curve.
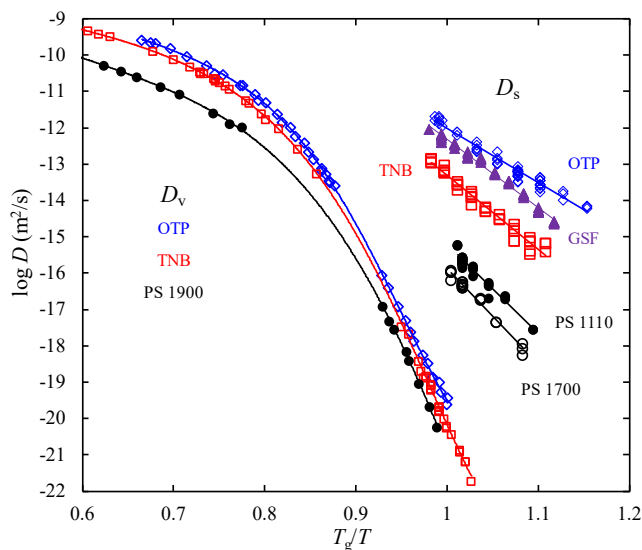

Figure 3. D_s and D_v of several glass-forming molecular liquids against T_g-scaled temperature. T_g is from DSC (onset temperature during heating): 246 K for OTP, 347 K for TNB, 307 K for PS1110, 319 K for PS1700 and 361 K for GSF).
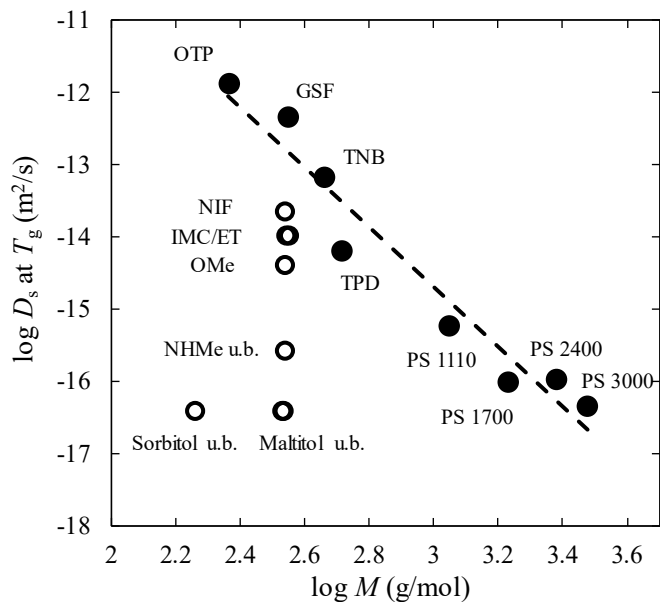
Notice that surface diffusion in a GSF glass is remarkably fast; its rate is similar to that of OTP, the fastest system on record. The ratio D_s/D_v is approximately 10^8 at T_g and increases with further cooling. The D_s of GSF has an approximately Arrhenius dependence on temperature with an activation energy of 131 kJ/mol. From OTP to GSF and to the other systems in Figure 3, surface diffusion slows down, with the D_s/D_v at T_g decreasing from 10^8 to 10^4, and the activation energy for surface diffusion appears to increase.

In Figure 4, the D_s value at T_g is plotted against the molecular weight M. To expand the range of comparison, other data points are included for molecular glasses that form intermolecular hydrogen bonds: IMC,[14] NIF,[18] three triazines[19] (Et, OMe, and NHMe), and two polyalcohols (sorbitol and maltitol).[24] All these data were

Figure 4. The surface diffusion coefficient, D_s, at T_g as a function of molecular weight. Solid symbols: no intermolecular hydrogen bonds. Open symbols: with intermolecular hydrogen bonds. "u.b." means upper bound.

obtained by the method of surface-grating decay. In addition, several data points are included that were obtained by other methods: TPD (surface evolution around a nano-particle),[33] PS 2400 (spontaneously roughening),[34] and PS 3000 (smoothing of a step)[35]. In Figure 4, solid symbols indicate systems without intermolecular hydrogen bonds, and open symbols systems with intermolecular hydrogen bonds.

In the case of non-hydrogen-bonding group (solid symbols), the D_s value decreases with increasing molecular weight. Note that the GSF point fits in this overall trend very well. This is noteworthy because GSF is the only system in this group that is *not* a simple aromatic hydrocarbon. GSF has many polar functional groups (ether and carbonyl). This result argues that in terms of its effect on surface diffusion, each polar group in GSF has no more influence than a non-polar hydrocarbon group. The molecular size dependence of D_s has been attributed to a steep and similar mobility gradient beneath the surface of molecular glasses and the deeper penetration of a larger molecule into the bulk where mobility is low.[17]

Figure 4 also shows that the correlation between D_s and molecular weight vanishes if the data points are included for hydrogen-bonded glasses (open symbols). Here, we note a different effect: compare the molecules of similar sizes but varying degrees of hydrogen bonding (the vertical column of open symbols). Observe that D_s decreases from molecules forming no hydrogen bonds (GSF) to those forming limited hydrogen bonds (NIF, IMC and the triazines) to those forming extensive hydrogen bonds (polyalcohols). This argues that hydrogen bonding is an independent effect from molecular size that controls surface diffusion.[19,24] The hydrogen-bonding effect on surface mobility has been attributed to the persistence of hydrogen bonds (in terms of the number of bonds per molecule) as a molecule is moved from the bulk to the surface environment. Assuming that hydrogen bonding controls the barrier for molecular rearrangement, this means that the barrier at the surface is substantially the same as that in the bulk.

Discussion

Motivated by understanding its fast crystallization,[20,21,23,22] this study has measured the surface diffusion in GSF glasses. We find that surface diffusion is remarkably fast in this system, making GSF the second fastest among all molecular glasses studied to date (13 in total). Here we discuss the significance of this result for understanding the crystallization of GSF glasses.

In Figure 5, the surface crystal growth rate u_s of GSF is plotted against its surface diffusion coefficient D_s, along with the literature data on 4 other molecular glasses (OTP, TNB, NIF, and IMC)[13,16] and on amorphous silicon.[36,37] For GSF and all the other molecular glasses, u_s is roughly proportional to D_s.[16] Furthermore, the data points for the different systems approximately cluster together (within one decade in u_s); the overall trend (straight line) is described by the power law $u_s \sim D_s^{0.87}$. It is significant that this trend encompasses 7
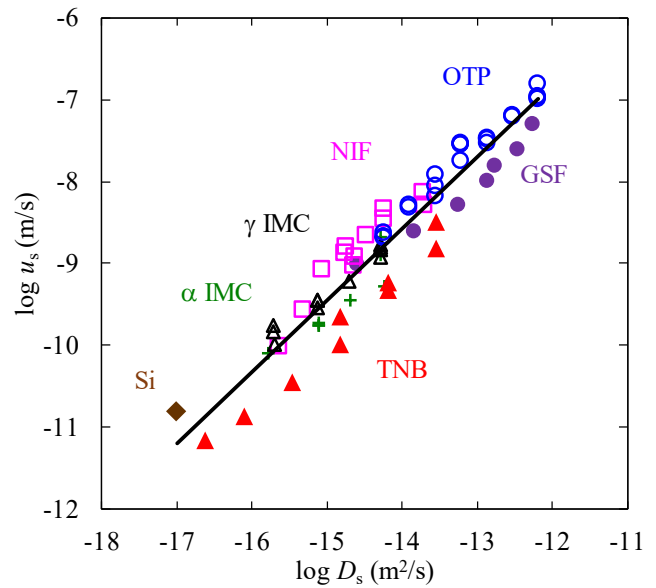

Figure 5. (a) Crystal growth rate on the surface, u_s, plotted against the surface diffusion coefficient, D_s, for molecular glasses and amorphous silicon. (b) D_s of GSF and D_v of several glass-forming molecules against T_g-scaled temperature.

different systems, organic and inorganic. It shows that at the same D_s, the rate of surface crystal growth is approximately the same regardless of the molecular details. This strong correlation between u_s and D_s argues that surface diffusion has a controlling role in the process of surface crystal growth.

In addition to fast surface crystal growth, a GSF glass is known to grow crystals rapidly *in the bulk* (the so-called GC growth).[21] This growth mode abruptly emerges as a GSF liquid is cooled near its T_g, as reported for other molecular liquids.[4,5,6] Among its various explanations, the most recent by Powell et al.[10] argues that the GC growth process continuously creates voids and free surfaces through fracture, which

in turn enables fast local transformation. Powell et al. based their model on the fact that the overall volume is conserved during crystal growth in a rigid glass. Given the higher density of the crystal than the glass, voids and free surfaces must be created during crystal growth. Small-molecule glasses generally have low fracture resistance and cannot be strained by the amount (several percent) corresponding to the glass-crystal density difference without fracture.[38] This picture seems equally valid for GSF: crystalline GSF is 8 % denser than its glass;[20] as a result, a large amount of void space must be created if the overall volume of the system is fixed during crystallization. Zhu et al. observed that crystal growth is accelerated along artificially created cracks in a GSF glass.[20] This suggests that if cracks are created during GC growth, local transformation could be accelerated through surface mobility, leading to faster bulk crystal growth.

Conclusion

Surface diffusion coefficients of amorphous griseofulvin (GSF) have been measured by the surface-grating decay method. Similar to other molecular systems, the flattening of surface grating occurs by viscous flow at high temperatures and by surface diffusion at low temperatures, with the transition occurring at T_g + 12 K for 1000 nm wavelength gratings. The surface diffusion of GSF is vastly faster than bulk diffusion, by a factor of 10^8 at T_g. The surface diffusion in GSF is faster than in any other molecular glass except for the small aromatic hydrocarbon o-terphenyl. The new result on GSF fits well with the trend formed by molecular glasses free of intermolecular hydrogen bonds where surface diffusion systematically slows down with increasing molecular size. This indicates that when not participating in hydrogen bonds, the polar functional groups in GSF (ether and carbonyl) have similar influence on surface diffusion as the non-polar hydrocarbon groups, while the formation of hydrogen bonds imposes a strong inhibitory effect. This gives credence to the idea that molecular size and hydrogen bonding can serve as

two independent leading factors that control surface diffusion. Whether other molecular attributes (e.g., shape and rigidity) influences surface diffusion warrants future studies.

We find a nearly linear relation between the surface crystal growth rate and the surface diffusion coefficient of GSF and all other molecular glasses studied to date. This strongly supports the notion that surface diffusion has a controlling role in surface crystallization. Our results on GSF are consistent with the proposal of Powell et al. that the fast crystal growth *in the bulk* of molecular glasses ("GC growth") is also enabled by surface mobility through the constant creation of voids and free surfaces as the growth front advances. This mechanism of glass crystallization could be tested by *in situ* microscopy. With its large volume change (8 %), GSF could be a suitable system for this purpose.

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