

# Origins and predictability of the hydrostatic limit of molecular liquids

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Loss of hydrostaticity limits high-pressure experiments, as pressure transmitting media solidify under compression. Here, we report a strong and positive correlation between the increase of molar density with pressure ( $\zeta$ ) and the hydrostatic limit (HL) associated with the vitrification of isothermally compressed molecular liquids. This correlation is derived using molecular dynamics simulations and is validated against experimental values of  $\zeta$  and HL. The positive  $\zeta$ –HL correlation can be rationalized by writing  $\zeta$  as a function of the molar density ( $\rho$ ) and the pressure-induced decrease in molar volume ( $v$ ):  $\zeta = \rho^2 v$ . While liquids are seen to not exhibit large  $\rho$  and  $v$  simultaneously, we find that large HL values originate mostly from large  $\rho$ , or, to some extent, from a large  $v$ . At the molecular level, large  $\rho$  and large  $v$  are linked to small molecular sizes and to low characteristic frequencies of intermolecular vibrations ( $\omega$ ), respectively.

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## I. INTRODUCTION

The study of materials under high pressure provides access to mechanical properties and phases of matter with potentially transformative properties [1–5]. In general, static high-pressure experiments require conditions under which no gradient in thermodynamic pressure exists within the sample. In opposed-anvil geometries, this necessitates an environment that ensures hydrostaticity throughout the sample chamber [6,7]. To achieve this, solid samples are typically embedded in a liquid or gaseous pressure-transmitting medium (PTM).

The PTM choice faces experimental challenges, including chemical reactivity, solvation, and penetration into the sample [8]. Another relevant limitation is the pressure range over which the PTM can maintain hydrostatic conditions. The upper limit of this range is referred to as the hydrostatic limit (HL) and is commonly associated in the literature with the solidification of the PTM [9–13]. The solidification can occur either through crystallization or via vitrification (liquid-to-glass transition); thus, the HL is associated with either the crystallization pressure or the glass transition pressure ( $P_G$ ).

A common strategy to bypass crystallization is the use of mixtures as PTMs [7,9,14–16]. Vitrification, albeit reportedly occurring at different pressures for a given liquid, cannot ultimately be bypassed. Thus, it is desirable to identify PTMs that can sustain higher pressures before vitrifying. Yet, a

straightforward route to do so remains elusive. For example, a clear mathematical relationship between ambient-condition macroscopic properties of a liquid and its  $P_G$  is currently lacking. The relaxation time  $\tau$  of a liquid has been linked to temperature and specific volume via relationships such as  $\log \tau \propto T^{-1}V^{-\gamma}$ , where  $\gamma$  is a constant [17,18]. However, the exponent  $\gamma$  is not universal: it varies from liquid to liquid and encodes much of the chemical specificity of the system. Consequently, these relations do not provide a general guideline to predict the vitrification pressure [17,18].

In this work, we investigate  $\approx 100$  organic liquids using classical molecular dynamics simulations, with the goal of finding robust correlations between their macroscopic properties and their HL. In particular, we identify a robust correlation between their HL at ambient temperature ( $T = 300$  K) and the isothermal variation of their molar density at ambient conditions ( $T = 300$  K,  $P = 1$  atm), which is a readily accessible macroscopic property. This provides a practical, experimentally accessible criterion for screening PTM candidates. Additionally, the underlying physical origin of the correlation identified is interpreted at the molecular level. In light of the link between solidification and the ability of a given liquid to explore its potential energy landscape (PEL) proposed in previous works [19,20], we argue that some of the macroscopic properties investigated here can act as experimentally accessible proxies for how compression modifies the ability of a molecular liquid to sample its energy landscape. This does not amount to a direct characterization of the landscape topology, but it does provide a practical route for linking ambient-condition observables to the molecular mechanisms underlying loss of hydrostaticity.

This paper is organized as follows: Sec. II (Methods) discusses how hydrostaticity was quantified in our work, the simulation methods and analysis, and how the previously mentioned correlation was experimentally validated. Section III (Results) discusses the correlations found in our

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work, their validation, and their interpretation at the molecular level. Section IV (Conclusion) summarizes the main findings of this work.

## II. METHODS

### A. Quantifying hydrostaticity

Pressure is a scalar quantity defined as the ratio between the magnitude of a force in one or more specific direction(s) and the area of the surface on which the force acts [21,22]. A common example is the thermodynamic pressure, which is linked to the force in the direction normal to the surface of a thermodynamic system. Another example is the pressure tensor in Cartesian coordinates, whose elements are associated with forces in the  $x$ ,  $y$ , or  $z$  direction acting on a plane normal to one of these same directions [23,24]. For a system composed of  $N$  atoms, the expression for the value of  $P_{ij}$ , where  $P_{ij}$  is the average value of an element of the pressure tensor in Cartesian coordinates associated to a force in direction  $j$  acting in a plane normal to direction  $i$ , is [25]

$$P_{ij} = \frac{1}{V} \left\langle \sum_{k=1}^N \frac{p_{ki} p_{kj}}{m_k} \right\rangle + \frac{1}{V} \left\langle \sum_{k=1}^N r_{ki} f_{kj} \right\rangle, \quad (1)$$

where  $m$ ,  $\mathbf{r}$ ,  $\mathbf{p}$ , and  $\mathbf{f}$  indicate the mass, position, momentum, and force, respectively, associated with a given atom of index  $k$ ; subscripts  $i$  and  $j$  each indicate a specific direction,  $V$  indicates the average volume of the system at the given thermodynamic state, and  $\langle \dots \rangle$  indicates the ergodic average over several microstates [25].

The second term on the right-hand side of Eq. (1) can be written as  $\frac{1}{V} \langle \sum_{k<l} r_{kl}^i f_{kl}^j \rangle$ , i.e., as the ergodic average of the sum of the products of (i) the distance between a pair of atoms in direction  $i$  and (ii) the magnitude of the force the pair experiences in direction  $j$ , divided by the volume [26]. Thus, if one were to split the system into subdomains of a certain size, introducing any disturbance in a subdomain's structure would lead to a pressure there that differs from the pressure in the other subdomains, as atoms experience difference forces and are characterized by different pair distances. In fact, most likely, the structural units (i.e., atoms, molecules or ions) in the perturbed subdomain experience nonzero net force at their (originally) equilibrium sites due to the broken local symmetry (or broken isotropy). The structural disturbance and the development of the nonzero net force picture are illustrated for a generic 2D system in Figs. 1(a) and 1(b).

If, however, the disturbed system is in the liquid or gas state, the structural units are generally capable of a significant degree of translational motion. As a consequence, the structural units respond to the perturbation by progressively rearranging in space so that the net forces at the new equilibrium sites and local structural disturbance are dissipated, as shown in Fig. 1(c). Therefore, in this case, the structure of a liquid/gas is usually isotropic and homogeneous at equilibrium. Consequently, a state where  $P_{xx} = P_{yy} = P_{zz}$  in any and all subdomains is ensured at all times. As the thermodynamic pressure ( $P$ ) can be written as a function of  $P_{xx}$ ,  $P_{yy}$ , and  $P_{zz}$ , this also ensures that no gradient in  $P$  occurs. This ability to respond to the perturbation makes it impossible for

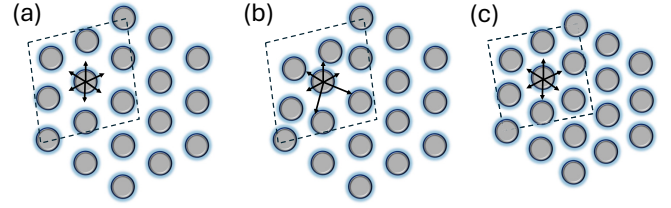


FIG. 1. Schematic of pressure-induced relaxation in a 2D system of interacting beads, which can represent atoms, molecules, or ions if the compound is atomic, molecular, or ionic, respectively: (a) equilibrium configuration with zero net force on each bead; (b) a local structural perturbation breaks local isotropy, generating nonzero net forces; (c) the beads rearrange to restore equilibrium. The dashed box marks the subdomain of interest, and the arrows are forces coming from interactions between bead pairs.

any local pressure gradient to develop, and is referred to as “hydrostaticity” or “pressure transmission.”

On the other hand, solids, whose structural units lack significant translational motion, cannot rearrange in space in response to the above-mentioned perturbation. This is the reason why solids are not hydrostatic, as well as maybe the reason why loss of hydrostaticity is commonly associated with solidification (either via crystallization or vitrification) in the literature [9–13]. We note, however, that this argument might be debatable: although crystals and glasses are necessarily nonhydrostatic, a liquid may become unable to evenly transmit pressure under some specific conditions before solidification can be unambiguously identified [13]. In static high-pressure diamond anvil cell (DAC) experiments, pressure is typically increased stepwise, with the PTM allowed to relax from minutes to days between pressure increments [7,13]. To remain hydrostatic, the PTM must then dissipate the structural perturbations induced by compression, and hence any associated pressure gradients, within this experimental timescale. Alternatively, a value of  $\tau$  in the range of 100 to 1000 seconds is accepted by many as a threshold for the liquid-to-glass transition [27]. However, besides being in principle arbitrary, there is no precise consensus about how large  $\tau$  or how low the ability of translational must be for a system to be considered solid [28,29]. This complicates the association of loss of hydrostaticity with solidification in scenarios where a crystal structure cannot be readily identified: the system may be after all regarded as a liquid with large  $\tau$ .

Experimentally, loss of hydrostaticity is commonly assessed from spatial pressure gradients by using the pressure distribution measured by ruby fluorescence across the sample chamber. An analogous criterion can be defined in molecular simulations by monitoring the nonimposed normal components of the pressure tensor under uniaxial compression. If the liquid transmits pressure efficiently, the equilibrium structure after compression will be isotropic ( $P_{xx} = P_{yy} = P_{zz}$ ). As the elements of the stress tensor can be easily computed in molecular simulations via Eq. (1), we can define a parameter  $\sigma$ :

$$\sigma = \sqrt{\frac{(P_{zz} - P_{xx})^2 + (P_{zz} - P_{yy})^2}{2}}, \quad (2)$$

to quantify hydrostaticity at an imposed  $P_{zz}$  value.

In previous work, we showed that the pressure dependence of  $\sigma$  mirrors the behavior of its experimental analog, defined within methods based on the distribution of ruby spheres [7]. In particular, loss of hydrostaticity is associated with a sharp increase in  $\sigma$ , which has an onset typically near  $\sigma = 0.1$  GPa.

A limitation of unbiased molecular dynamics simulations is their relatively limited timescale: whereas DAC experiments allow the PTM to relax over minutes to days, atomistic simulations generally span at most a few hundred nanoseconds. As a result, relaxation processes associated with large  $\tau$  values cannot be sampled directly. Loss of hydrostaticity is therefore expected to occur at lower pressures in simulation than in experiment, and it need not coincide with vitrification on the experimental timescale. Crystallization is also extremely unlikely to be observed in such unbiased simulations, since crystal nucleation in this context is classed as a rare event [30]. Thus, the simulated HL should not be interpreted as a quantitatively exact estimate of the experimental HL. Instead, its worth lies in identifying trends across different liquids: in terms of correlations, the relative ordering of HL values is more important than their absolute magnitude, particularly when crystallization can be suppressed experimentally.

## B. Molecular simulations

A total of 99 organic liquids (at ambient temperature and pressure conditions), listed in Table S1 of the Supplemental Material (SM) [31], were considered. These compounds were investigated via classical atomistic molecular dynamics simulations, performed using LAMMPS [32]. To ensure the robustness of our results, two simulations, differing solely by the force fields used, i.e., OPLS-AA or CGenFF (version 4.6) [33,34], were performed in general per compound. The main exception to this is not using CGenFF for compounds for which virtual sites are needed, as they are not supported straightforwardly within LAMMPS (see Table S1 [31]). The simulations involved stepwise  $P_{zz}$  increases of 0.2 GPa every 2 ns, starting from 1 atm (i.e.,  $\approx 0$  GPa) up to 10 GPa. Ambient temperature is enforced throughout the whole of the simulations using a Nosé-Hoover thermostat (chain with length three) [35,36]. The pressure was enforced via a Nosé-Hoover barostat (thermostated by a chain of length three) [35,36]. During the compression, the barostat allowed changing the simulation box length in the  $z$  direction only. Further details on the simulation setup can be found in the SM [31].

For each simulation performed, microstates collected within the last 1 ns at each pressure condition were used to estimate several properties and their standard errors (via block averaging). A total of 10 000 microstates sequentially spaced by 100 fs were considered. The properties estimated were molar density ( $\rho$ ), its inverse (i.e., molar volume  $\bar{V}$ ),  $P_{xx}$ , and  $P_{yy}$ . A subcollection of 2000 of these microstates was also used to compute radial distribution functions (RDFs) and confirm that no crystallization occurred. These were built based on the center of mass of the molecules and used the 2000 configurations in the trajectory. Since the results obtained when using OPLS-AA and CGenFF are very similar, we have considered the RDF analysis for OPLS-AA alone. Additionally, one microstate collected at each  $P_{zz} = 0.2, 0.4,$

0.6, 0.8, 1, 2, 3, 4, 5, 6, 7, 8 GPa, as well as at ambient pressure, was used to start a new, shorter simulation to compute the velocity autocorrelation function (VACF). The VACF was then used to compute self-diffusion coefficients and a function proportional to the vibrational density of states.

### 1. $P_{xx}$ and $P_{yy}$ : estimating hydrostaticity

For each simulation performed, the values of  $P_{xx}$  and  $P_{yy}$  determined at each pressure condition were used in conjunction with the imposed value of  $P_{zz}$  to compute  $\sigma$  [Eq. (2)]. This calculation is carried out for all imposed  $P_{zz}$  values in the simulation setup. Following our previous work, the HL was defined as the value of  $P_{zz}$  for which  $\sigma = 0.1$  GPa [7]. In this context, we identified the first imposed  $P_{zz}$  for which  $\sigma$  exceeded this threshold, and then linearly interpolated between this point and the preceding one to estimate the  $P_{zz}$  for which  $\sigma = 0.1$  GPa.

Note that replica simulations were not performed systematically for each compound and force-field combination, and therefore compound-specific uncertainties on the HL are not available. However, duplicate simulations carried out for three representative compounds showed run-to-run variations of approximately  $\pm 0.6$  GPa. This value should therefore be regarded as an indicative scale for the uncertainty associated with the simulated HL values.

### 2. Estimating the variation of $\rho$ and $\bar{V}$ with pressure

From each simulation performed, we estimated the derivatives of  $\rho$  with respect to  $P_{zz}$ ,

$$\zeta = \left( \frac{\partial \rho}{\partial P_{zz}} \right)_T, \quad (3)$$

and of  $\bar{V}$  with respect to  $P_{zz}$ ,

$$\nu = - \left( \frac{\partial \bar{V}}{\partial P_{zz}} \right)_T, \quad (4)$$

for each value of  $P_{zz}$  via the central differences method ( $\Delta P_{zz} = 0.2$  GPa, defined by the stepwise pressure increase in the simulation setup) [37]. Standard errors associated to  $\rho$  and its inverse (i.e.,  $\bar{V}$ ) were duly propagated.

We note that the average value of all normal elements of the stress tensor,  $P_{ii}$ , coincides with the thermodynamic pressure  $P$  in hydrostatic conditions. This can be concluded from how  $P$  is calculated as a function of  $P_{xx}$ ,  $P_{yy}$ , and  $P_{zz}$ . In other words, while the partial derivatives in Eqs. (3) and (4) are evaluated with respect to a uniaxial pressure,  $P_{zz}$ , for hydrostatic liquids one can write

$$\zeta = \left( \frac{\partial \rho}{\partial P_{zz}} \right)_T = \left( \frac{\partial \rho}{\partial P} \right)_T, \quad (5)$$

and

$$\nu = - \left( \frac{\partial \bar{V}}{\partial P_{zz}} \right)_T = - \left( \frac{\partial \bar{V}}{\partial P} \right)_T. \quad (6)$$

### 3. Determining self-diffusion coefficients and vibrational density of states

Additional simulations were launched from microstates extracted at  $P = 1$  atm and at  $P_{zz} = 0.2, 0.4, 0.6, 0.8, 1, 2, 3, 4,$

5, 6, 7, and 8 GPa. These simulations used the same time step, equations of motion, target temperature, and target pressure as the corresponding segment of the parent trajectory. For each target pressure, 100 VACFs based on molecular center-of-mass velocities were calculated sequentially [38]. Values of each VACF were output every 5 fs for a total simulation length of 10 ps. These 100 VACFs were then averaged to obtain a representative and less noisy VACF. The latter, in turn, was used for computing the (i) self-diffusion coefficient ( $D$ ) and (ii) a function proportional to the intermolecular vibrational density of states (VDoS) for intermolecular oscillations at each pressure condition. Details on how  $D$  and the VDoS were computed can be found in the SM [31].

To reduce each VDoS to a single descriptor, we defined a characteristic intermolecular oscillation frequency  $\omega_{\text{ave}}$  as the first moment of the VDoS (i.e., the average frequency of vibration):

$$\omega_{\text{ave}} = \frac{\int \omega g(\omega) d\omega}{\int g(\omega) d\omega}, \quad (7)$$

$$\omega_{\text{ave}} = \sum_i \lambda_i \omega_i, \quad (8)$$

with

$$\lambda_i = \frac{g(\omega_i) \Delta \omega_i}{\sum_j g(\omega_j) \Delta \omega_j}. \quad (9)$$

Here,  $\omega_i$  is the frequency associated with bin  $i$ ,  $g(\omega_i)$  is the corresponding VDoS value, and  $\lambda_i$  is the normalized contribution of that bin to the total VDoS [39–41].

### C. Experimental validation

Because the correlation between  $\zeta$  at 300 K and 1 atm and the HL at 300 K is central to this work, we compared the simulation results with available experimental data for both quantities. For the HL, we considered only experimental values not explicitly attributed to crystallization, since the latter is not expected to occur in unbiased simulations. Experimental HL values for mixtures were also included, because mixtures that avoid crystallization often exhibit  $P_G$  values close to that of their most abundant component [7,10,11,42–46]. Additionally, a new high-pressure experiment, using the same methodology described in Ref. [7], was performed to determine an HL for acetone, a reasonably promising PTM—according to the results of our simulations. Different acetone-based mixtures were investigated for their ability to bypass acetone crystallization: acetone/methanol at a 4:1 volume ratio and acetone/butanone at 9:1, 4:1, and 1:1 volume ratios. To the best of our knowledge, this is the first time the HL of acetone is studied. Finally, reference values of  $\zeta$  were determined from experimental values of  $\kappa_T$  and  $\rho$  (see Appendix) at ambient conditions, taken from the literature for a subset of liquids.

## III. RESULTS

### A. Experimental validation

To assess whether the correlation identified in simulations between the HL at 300 K and  $\zeta$  at 300 K and 1 atm is consistent with experiment, we compared simulated and

TABLE I. Range of HL values observed experimentally for methanol, isopentane, acetone, n-propanol, 2-propanol and glycerin alongside the HL obtained in the simulations via either OPLS-AA or CGenFF. The experimental value for acetone was determined in an experiment carried out in this work. The reference(s) for (i) methanol are [7,11,19,42], (ii) isopentane are [10,43], (iii) n-propanol is [47], (iv) 2-propanol is [11], (v) glycerin are [48,49], and (vi) perfluoropentane, commercialized under the name FC-87, is [50]. The value of HL determined by Angel *et al.* (2007) in Ref. [60] for glycerin has not been included, as it is much lower than the usually reported range (1.4 GPa vs 3–5.5 GPa), which could be an indication of crystallization instead of vitrification.

| System           | Exp.      | HL [GPa]       |               |
|------------------|-----------|----------------|---------------|
|                  |           | Sim. (OPLS-AA) | Sim. (CGenFF) |
| methanol         | 8.6–11.37 | 6.122          | 5.82          |
| isopentane       | 7–7.4     | 3.104          | 2.878         |
| acetone          | 4.45–5.66 | 4.598          | 4.438         |
| n-propanol       | 5         | 2.847          | 2.852         |
| 2-propanol       | 4.3       | 2.21           | 2.446         |
| glycerin         | 3–5       | 0.630          | 1.75          |
| perfluoropentane | 2.2       | 1.71           | 1.31          |

experimental values of both quantities. Table I summarizes the range of HL values reported experimentally for methanol [7,11,19,42], isopentane [10,43], 2-propanol [11], n-propanol [47], glycerin [48,49], and perfluoropentane [50]. Table I also contains an HL range for acetone, determined based on our experiment with the 4:1 volume ratio acetone/methanol mixture. The HL values obtained for these liquids when using either OPLS-AA or CGenFF are also presented in Table I. On the other hand, Fig. 2 shows the values of  $\zeta$  at ambient conditions obtained from the simulations *versus* the experimental value for a subset of 23 liquids studied here. The liquids are methanol, ethanol, acetone, pyridine, cyclohexane, n-pentane, chlorobenzene, toluene, propan-2-ol, glycerin, diethyl ether, benzene, pentanol, octanol, carbon disulfide, acetic acid, ethylene glycol, ethyl acetate, 1,2-dichloro ethane,

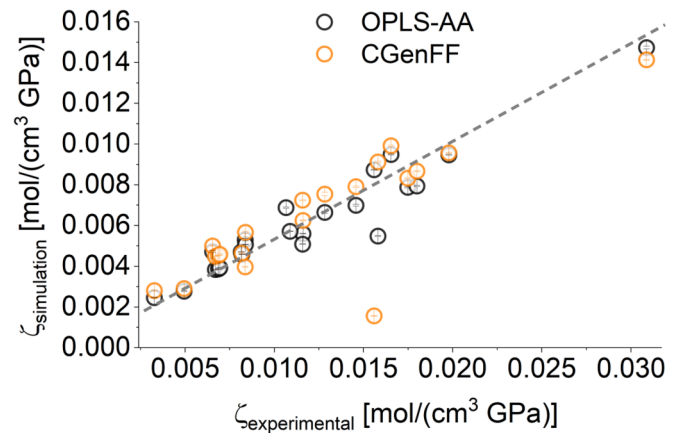


FIG. 2. Experimental  $\zeta$  (x axis) plotted against the  $\zeta$  values obtained from our simulations (y axis) for selected compounds considered in our study at ambient conditions. The gray dashed line shows that the simulation reproduces the experimental trends.

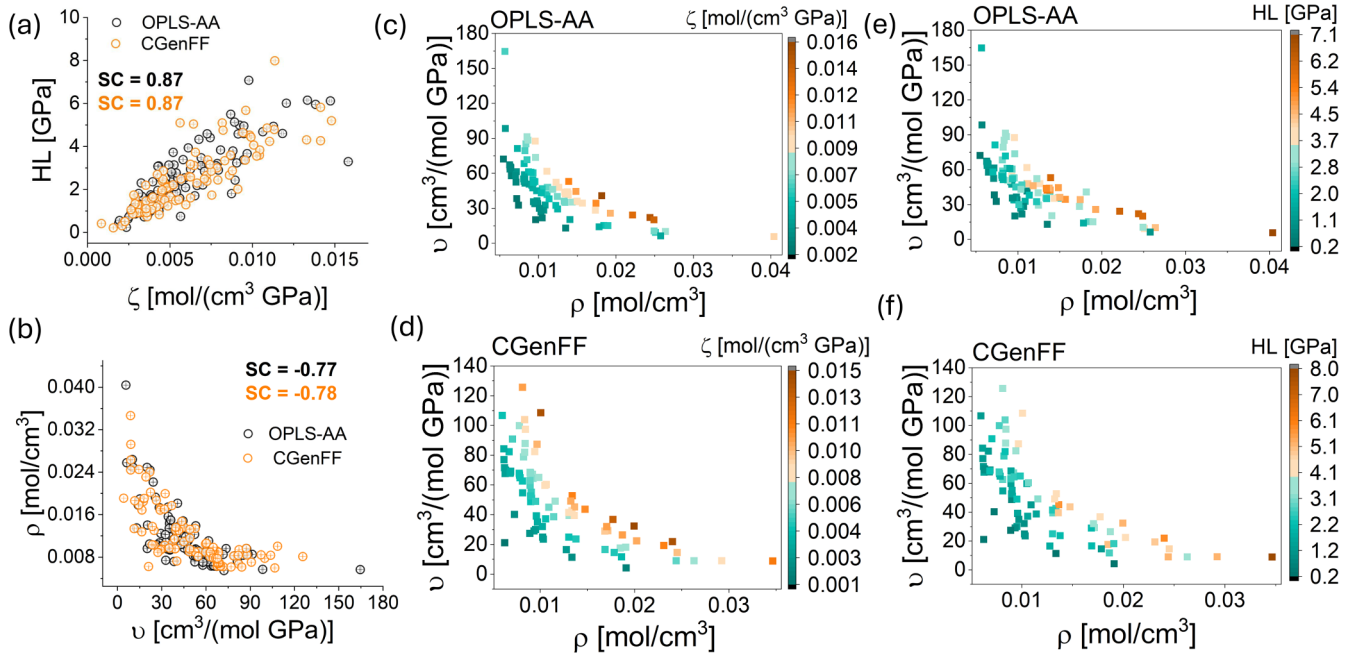


FIG. 3. Scatter plots of the values of (a) HL at 300 K vs  $\zeta$  and (b)  $\rho$  and  $\nu$ . The Spearman correlation coefficient (SC) is also reported. Scatter plots of  $\rho$ ,  $\nu$ , and  $\zeta$  obtained via (c) OPLS-AA or (d) CGenFF. Scatter plots of  $\rho$ ,  $\nu$ , and HL at 300 K obtained via (e) OPLS-AA or (f) CGenFF. Values of  $\rho$ ,  $\nu$ , and  $\zeta$ , in all panels were evaluated at 1 atm, 300 K.

carbon tetrachloride, o-xylene, m-xylene, and p-xylene. These form around 23% of the total amount of liquids considered in our study and span a great chemical diversity. To determine  $\zeta$  via Eq. (A7), values of  $\kappa_T$  were taken from Refs. [51–58], while experimental  $\rho$  values were taken from Ref. [59].

Overall, the simulated HL values are systematically lower than the corresponding experimental values, as expected given the much shorter relaxation times characterizing our simulations (Sec. II A). Nevertheless, the simulations broadly reproduce the experimental HL trend across the different compounds, in particular identifying methanol and acetone as high-HL liquids. Isopentane is the singular exception to this trend. A possible explanation for this discrepancy is that molecular simulations are limited in reproducing the experimental  $P_G$  due to the timescale they span: i.e., liquids that stop relaxing efficiently within 2 ns (that is, our simulation time at each pressure) at a given pressure  $P_1$  still relax efficiently in experimental timescales up to a different pressure  $P_2$ . As different classes of liquids can have  $\tau$  change differently with pressure, values of  $\Delta P = P_2 - P_1$  can be different for different liquids, leading to some outliers in the ordering of HL observed experimentally versus via the simulations.

A similar picture emerges for  $\zeta$ : as shown in Fig. 2, both force fields reproduce the experimental ordering of low- and high- $\zeta$  compounds reasonably well, although the absolute values are underestimated. Here, the offset is likely associated with the numerical approximation of  $\zeta$ : for all compounds,  $\rho$  increases most steeply at the earliest stages of compression, so the derivative obtained over a finite pressure interval is expected to be smaller than the ambient-pressure limiting value. Taken together, Fig. 2 and Table I show that the simulations capture the relevant experimental trends in both HL and  $\zeta$ , supporting the use of the

simulated data to analyze the correlation between these two quantities.

Additionally, it is worth noting that the 4:1 acetone/methanol mixture we have experimentally investigated in this work has an HL (4.45–5.66 GPa) equivalent to or superior to some PTMs currently used in high-pressure experiments (glycerol, 2-propanol, n-propanol). When using acetone/butanone mixtures, butanone was observed to be unable to significantly prevent the crystallization of acetone. More specifically, the 4:1 acetone/butanone and 9:1 acetone/butanone mixtures crystallized at pressures (2.59 and 2.15 GPa, respectively) only slightly higher than pure acetone (1.14 GPa). Increasing the volume ratio significantly towards butanone seems to have suppressed the crystallization: a 1:1 acetone/butanone mixture lost hydrostaticity at 4.58 GPa, in a similar range to the 4:1 acetone/methanol mixture. However, a more acetone-concentrated mixture, such as the 4:1 acetone/methanol, should be considered preferable to ensure an HL closer to that of the dominant component [7].

## B. Correlation between $\zeta$ and the HL

Figure 3(a) shows a scatter plot of  $\zeta$  values at ambient conditions and the HL at ambient temperature obtained via molecular simulations for the liquids considered in our work. The lack of ordering observed in the RDFs built for liquids where OPLS-AA was used confirmed that no crystallization occurred, as reported in the SM [31]. Values of  $\zeta$  and HL reported in Fig. 3(a) are available in Tables S2 and S3 of the SM [31]. Figures equivalent to Fig. 3(a) but where the identity of the liquids corresponding to each point is explicitly reported are also presented in the SM (see Figs. S5 and S6) [31].

In Fig. 3(a), strong correlations are observed in the case of both force fields. Specifically, we see that liquids having a large HL also have a large  $\zeta$  and vice versa. To further investigate the correlation found between  $\zeta$  and the HL, we write (see Appendix):

$$\zeta = \left( \frac{\partial \rho}{\partial P_{zz}} \right)_T = \rho^2 \nu. \quad (10)$$

It is clear from the expression on the right-hand side that  $\zeta$  increases the most when having simultaneously large  $\rho$  and  $\nu$  values. Yet, an assessment of the values of  $\nu$  and  $\rho$  at ambient conditions revealed that, in general, liquids with a large  $\rho$  do not seem to have, simultaneously, a large  $\nu$ . This is shown in Fig. 3(b) for both force fields. Thus, in the interest of maximizing  $\zeta$ , it is necessary to assess whether the compounds exhibiting large  $\zeta$  are the ones with large  $\rho$  or with large  $\nu$ . As  $\zeta$  depends on the square of  $\rho$ , a larger  $\rho$  is expected to have a higher impact than a larger  $\nu$  [see Eq. (10)]. Figures 3(c) and 3(d) show scatter plots of the values of  $\rho$ ,  $\nu$ , and  $\zeta$  exhibited by the compounds at ambient conditions considering both force fields. Within both force fields, it is possible to see that regions of larger  $\rho$  values overall coincide with those of larger  $\zeta$ , but that large  $\zeta$  values in conjugation with large  $\nu$  values are also possible.

To assess the relative importance of the  $\rho$  and  $\nu$  contributions to the HL, Figs. 3(e) and 3(f) show HL values in the  $\rho$ - $\nu$  plane. It is evident that large HL values can be obtained through different combinations of  $\rho$  and  $\nu$ , indicating that a large value of one quantity can partly compensate for a smaller value of the other. However, often the largest HL values overlap most consistently with the large- $\rho$  region, suggesting that  $\rho$  is the stronger individual correlate of HL. Regardless, we stress that it is not meaningful to assess the influence of  $\rho$  and  $\nu$  separately on the HL since these two quantities are correlated to each other. The negative correlation between  $\rho$  and  $\nu$  implies that large HL can be obtained throughout the entire range of  $\nu$  in Figs. 3(e) and 3(f) because for small  $\nu$  values a large HL is ensured by a large  $\rho$ . Similarly, large values of HL can be obtained throughout most of the range of  $\rho$  in Figs. 3(e) and 3(f) (except very small  $\rho$ ) because at small  $\rho$ , a large HL can be ensured by a large  $\nu$ . Additionally, it is interesting to note that the fact that  $\rho$  and  $\nu$  contribute differently to the HL can lead to some of the scattering reported in Fig. 3(a). The fact that there may be other structural or dynamical descriptors (other than the ones we have identified in this work) that contribute to the loss of hydrostaticity can also contribute to the aforementioned scattering.

An insightful example that illustrates the role of a large value of  $\nu$  over a large value of  $\rho$  on the HL is isopentane versus 2-propanol, for which experimental values of  $\nu$ ,  $\rho$ , and HL are available. Experimentally, isopentane has a smaller  $\rho$  at ambient conditions ( $0.0086125 \text{ mol cm}^{-3}$  [59]) compared to 2-propanol ( $0.01301 \text{ mol cm}^{-3}$  [59]), but the value of  $\nu$  for the former (ranging from  $255$  to  $270 \text{ cm}^3 \text{ mol}^{-1} \text{ GPa}^{-1}$  [61,62]) is found to be much larger compared to that of 2-propanol ( $85.47 \text{ cm}^3 \text{ mol}^{-1} \text{ GPa}^{-1}$  [56]). Despite the lower  $\rho$ , the experimental HL of isopentane ( $7$ – $7.4 \text{ GPa}$  [10,43]) is significantly superior to that of 2-propanol ( $4.3 \text{ GPa}$  [11]), as shown in Table I. Experimentally, n-propanol ( $\rho = 0.01333 \text{ mol cm}^{-3}$  [59],  $\nu = 75.46 \text{ cm}^3 \text{ mol}^{-1} \text{ GPa}^{-1}$

[51], and HL =  $5 \text{ GPa}$  [47]) acetone ( $\rho = 0.01353 \text{ mol cm}^{-3}$  [59],  $\nu = 90.38 \text{ cm}^3 \text{ mol}^{-1} \text{ GPa}^{-1}$  [53], and HL =  $4.45$ – $5.66 \text{ GPa}$ ) and glycerin ( $\rho = 0.01371 \text{ mol cm}^{-3}$  [59],  $\nu = 18.52 \text{ cm}^3 \text{ mol}^{-1} \text{ GPa}^{-1}$  [57], and HL =  $3$ – $5 \text{ GPa}$  [48,49]) fall in a scenario similar to that of 2-propanol relative to isopentane. Isopentane thus illustrates the relevance of the correlations found in our work when it comes to potentially identifying useful PTMs.

Finally, the correlations shown in Fig. 3 still hold at  $P_{zz} = 0.2 \text{ GPa}$ ,  $0.6 \text{ GPa}$ , and  $1 \text{ GPa}$  (see Figs. S1–S3 of the SM [31]). The only significant change at higher pressure is that the values of  $\zeta$  and  $\nu$  span a narrower range. This, in turn, decreases the sensitivity of the correlations involving these properties.

### C. Molecular-level interpretation of $\zeta$

At this stage, we can attempt to interpret the correlation between the HL and  $\zeta$  at the atomistic scale. We found that  $\rho$ , on which  $\zeta$  depends, is negatively correlated with the number of atoms a molecule has ( $n_{\text{atoms}}$ ). This means that liquids generally having lower molecular size tend to have a higher HL. This correlation between  $n_{\text{atoms}}$  and the HL is perhaps to be expected from what is currently already known within the field of glass transitions. Structural relaxation in molecular liquids can proceed through local rearrangements of molecular segments between neighboring environments, as molecules go from one equilibrium site to another [63]. Molecules containing fewer atoms may undergo these rearrangements more readily, because fewer internal degrees of freedom must be reorganized to reach a new local configuration. Additionally, liquids with large  $\rho$  generally display small  $\nu$  values [see Figs. 3(b) and S1 [31]], meaning that their molar volume decreases to a lesser extent upon compression. In this case, the free volume available for molecular rearrangements should also deplete less strongly with increasing pressure, allowing structural relaxation to remain accessible up to higher pressures. In this sense, pressure-induced jamming arising from increased molecular packing (a common ingredient in many descriptions of the glass transition) [17,18] is delayed, resulting in a larger HL. In a PEL picture, this corresponds to more efficient crossing of the barriers between neighboring basins, and provides a molecular-level rationale for the trend we are observing,

$$\uparrow HL \rightarrow \uparrow \rho \rightarrow \downarrow n_{\text{atoms}}.$$

The interpretation of the correlation between  $\nu$  and the HL at the atomistic scale is, however, more complex. At first sight, large  $\nu$  might be expected to lower the HL: since  $\nu$  quantifies the pressure-induced decrease in molar volume, liquids with large  $\nu$  values should lose free volume more rapidly upon compression, making structural rearrangements progressively more difficult. However, as the simulations show that large  $\nu$  values can also be associated with large HL values, another molecular factor must compensate for this loss of free volume.

The molecular origin of the link between  $\nu$  and the HL can be understood by considering the response of a liquid to isothermal compression. Static high-pressure experiments, mimicked by our simulations, can be viewed as a series of isothermal compressions, each featuring a constant, externally

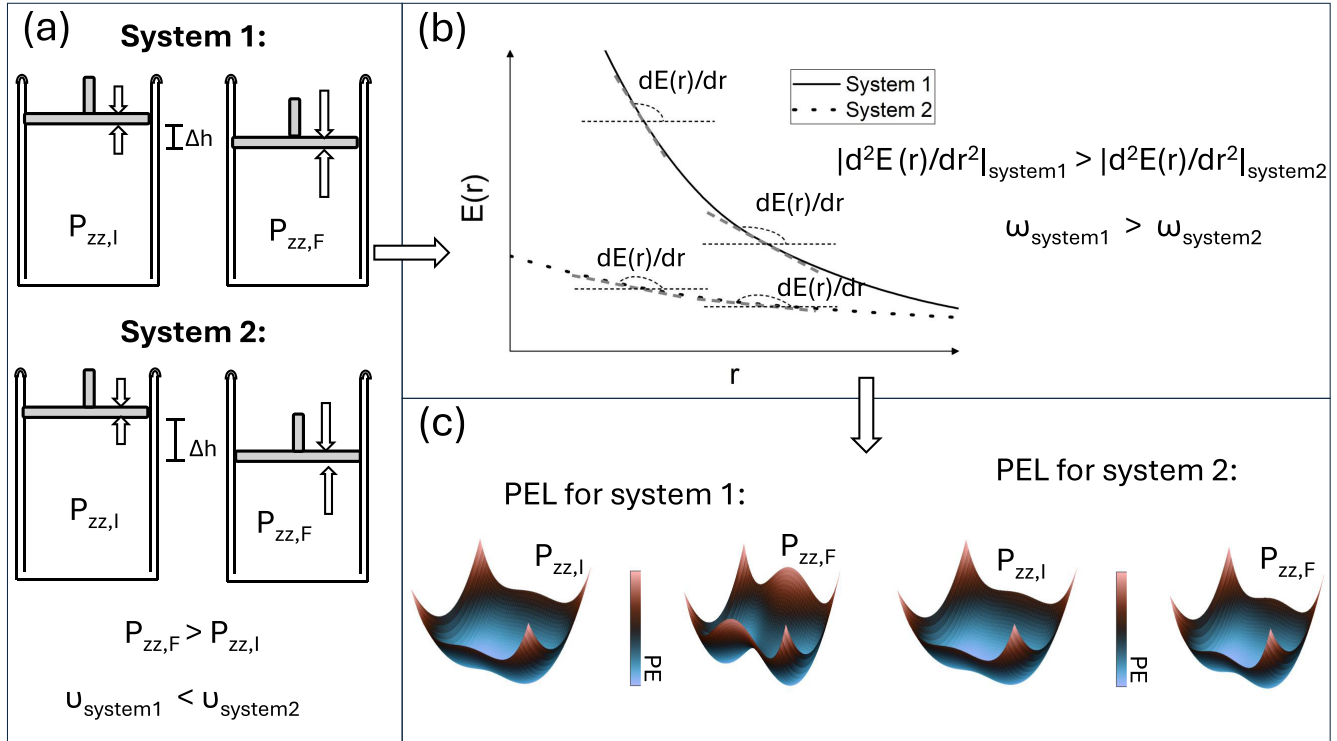


FIG. 4. Schematics qualitatively illustrating two fictitious thermodynamic systems, the link between larger  $\nu$  and lower intermolecular frequencies of vibration, along with how the PEL is expected to change with pressure. Panel (a) illustrates the compression of the two systems from an initial state at pressure  $P_{zz,l}$  to a final state at pressure  $P_{zz,F}$ . At the molecular level, panel (b) illustrates the expected profile of the function  $E(r)$  for system 1 relative to system 2. Only the repulsive part of  $E(r)$  is illustrated. Note that system 1 has stronger repulsive forces which change to a greater extent within a given  $\Delta r$ , while system 2 is characterized by weaker interactions. Finally, panel (c) shows the expected sharper increase in the activation energy separating basins of the PEL for system 1 compared to system 2.

applied  $P_{zz}$ . Each  $P_{zz}$  value is associated with an external force of a given magnitude acting along the  $z$  direction on the top boundary of the system. In response to the applied  $P_{zz}$ , the system shrinks in volume until the magnitude of the external force trying to pack the structural units closer together is no longer sufficient to overcome the forces originating from their (repulsive) interactions (see Fig. S4 [31]). At that point, the system is at mechanical equilibrium with the surroundings. Because different compounds have different compressibilities, this shrinking (quantifiable by  $\nu$ ) that occurs in response to a given applied  $P_{zz}$  is case-specific.

In this picture, we may consider a function that quantifies the potential energy stemming from the interaction between a pair of structural units  $E$  as a function of their distance  $r$ . Correspondingly, within classical mechanics, the force experienced by the structural units is associated with  $-dE/dr$ . We note that different functions  $E(r)$ , optionally of different forms (including nonanalytical), can be considered in this picture. Moreover, the framework here could be extended to include the effect of many-body interactions (a starting point could be to theoretically consider that  $E(r)$  for different pairs can change continuously as a function of one another—or of time—during the dynamics, to mimic the effect of many-body interactions).

Atomistically, shrinking translates necessarily into a reduction of the distances between pairs of structural units, with a high  $\nu$  implying that pair distances decrease to a

greater extent. Thus, compounds requiring larger  $\Delta r$  values to balance the force underlying  $P_{zz}$  must necessarily have a less steep variation in  $|-dE/dr|$  within that specific interval  $\Delta r$  compared to other compounds. A function that quantifies the variation in  $dE/dr$  is, naturally, its second derivative  $d^2E/dr^2$ .

To now connect  $d^2E/dr^2$  to the present picture, we consider that structural units vibrate in both solid and liquid states [64,65]. Examples of theories for liquids that encapsulate the concept of such vibrations are the theory by Robert Zwanzig (1983) [66] and the phonon theory of liquid thermodynamics (2012) [66–69], with the latter having been extensively experimentally validated and expanded to account for more complex liquids [65,67,69–72]. In the context of both harmonic and damped harmonic oscillations, large or small values of  $|d^2E/dr^2|$  imply large or small oscillation frequencies for the structural units  $\omega$ , respectively. This is expected to hold true for coupled oscillators, as is the reality for many-body systems. Thus, large values of  $\nu$  imply that pair distances change significantly under compression, which requires small magnitudes of  $d^2E/dr^2$  for consistency; this, in turn, implies small characteristic  $\omega$  (and vice versa). This connection is illustrated in Fig. 4, which links the curvature of the intermolecular interaction profile to the characteristic frequencies of intermolecular oscillations.

To validate the link between  $\nu$  and low  $\omega$ , we attempted to identify a correlation between  $\omega_{\text{ave}}$  (calculated from the

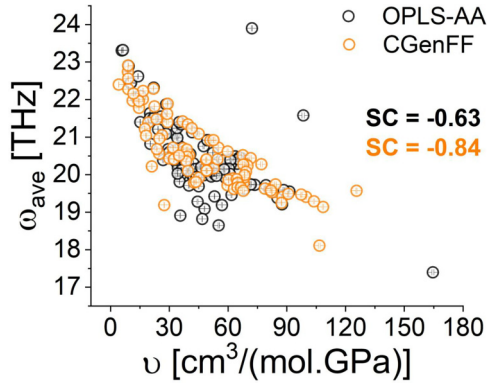


FIG. 5. Scatter plots of the values of  $\omega_{\text{ave}}$  vs  $v$  exhibited by the compounds at ambient conditions. The Spearman correlation coefficient (SC) is also reported.

VDoS, see Sec. II B) and  $v$ , both at ambient conditions as illustrated in Fig. 5. The values of these properties are available in Tables S2 and S3 of the SM [31]. Interestingly, while a correlation is observed within both force fields, it is stronger in the case of CGenFF; we cannot speculate why this is, at this stage. Furthermore, Fig. S7 in the SM [31] shows that  $\omega_{\text{ave}}$  can be safely used together with  $\rho$  as an alternative for  $v$  to correlate as expected with  $\zeta$ . This broadens the scope of the connection between  $v$  and  $\omega_{\text{ave}}$ , which ultimately suggests that liquids characterized by a larger number of low  $\omega$  values at ambient conditions have a large HL: “large HL  $\rightarrow$  large  $v \rightarrow$  low  $\omega$ ”.

Notably, the trend “high HL  $\rightarrow$  low oscillation frequencies” is consistent with recent works. It has been previously shown that a larger excess in low vibrational frequencies is associated with lower activation barriers separating the basins of the PEL [73,74]. It has also been shown that structural units whose motion is characterized by a low vibrational frequency are more prone to participate in shear deformations when a stimulus is applied [75,76]. Additionally, we note that the behavior of the VDoS of superpressed liquids and glasses found in our work is also aligned with what is observed in other works [77–80]. Evolution of the unnormalized VDoS for ethanol and trans-1,2-dichloroethene with pressure found in our work is shown in Fig. S8 as case examples. Generally, the VDoS profiles progressively shift from having one well-defined, high peak with a mode at low frequencies to a profile with lower VDoS values where the peak mode is at higher frequencies and is followed by a shoulder. Exceptionally, for some compounds, the shoulder either (i) does not develop or (ii) evolves into a second peak.

Still in the physics that links  $v$  and  $\omega$ , it is worth noting that the link between  $v$  and HL lies in the link between  $v$  and the “strength” of the interactions between structural units. Here, strong interactions can be defined by large  $E(r)$  and by how rapidly  $E(r)$  changes with intermolecular separation  $r$ . Stronger interactions give rise to forces  $-dE/dr$  that increase rapidly as neighboring structural units are brought closer together. Softer interactions, by contrast, produce forces that vary more gradually with decreasing  $r$ . A large  $v$  is therefore consistent with either or both a smaller number of interactions or weaker interactions, because larger changes in

intermolecular separation are required to generate the restoring forces needed to balance the applied pressure. In the PEL picture for solidification, softer intermolecular interactions would, in turn, be expected to make the barriers between neighboring basins less sensitive to compression than in liquids with stiffer interactions. This is because the repulsive force experienced by the structural units during their rearrangement is not as large. As a result, the activation barriers that control structural rearrangement may increase less strongly with pressure, allowing the liquid to remain dynamically able to relax, and hence to transmit pressure, up to higher pressures. This interpretation is also illustrated in Fig. 4(c).

Finally, it is important to stress that the correlations “low  $\omega_{\text{ave}} \rightarrow$  large HL” and “low  $n_{\text{atoms}} \rightarrow$  large HL” are to be interpreted as trends rather than laws. This reflects the fact that  $\rho$  and  $v$  are negatively correlated properties which are both linked to features of the PEL that can favor metastability under pressure. As a result, neither quantity should be interpreted as a standalone predictor of the HL. In other words, while the physics underlying the correlations found between (i)  $\rho$  and the HL and (ii)  $v$  and the HL are, we argue, universal in nature, one of them may override the other. Overall, our results suggest that loss of hydrostaticity reflects the combined effect of several molecular features. In this context, the correlation between large  $\zeta$  and large HL provides a useful aggregate descriptor, because  $\zeta = \rho^2 v$  combines the effects of both  $\rho$  and  $v$ .

#### D. Correlations involving $D$

The existence of correlations between  $D$  and  $\omega_{\text{ave}}$ , which would imply a link between the extent of translational and oscillatory motion displayed by the structural units, was also investigated. Figure S9 [31] shows the scatter plot of  $D$  and  $\omega_{\text{ave}}$  at ambient conditions: no correlation is found. It may be tempting to argue that a strong inverse relation between  $D$  and  $\omega_{\text{ave}}$  should be expected. This is because a large HL, which we have previously linked to low  $\omega_{\text{ave}}$  values, implies a good ability to escape the minima of the PEL in the atomistic picture of solidification [19,20], which in turn may be linked to a large  $D$ . It is, however, necessary to account for the fact that  $D$  can change with pressure by different extents for different compounds, and so a correlation between  $\omega_{\text{ave}}$  and  $D$  is not necessary. Additionally,  $D$  and  $\omega_{\text{ave}}$  probe very different aspects of the dynamics. The former reflects long-time translational transport, whereas the latter characterizes short-time intermolecular oscillations around local configurations.

To show that a large  $D$  at ambient conditions does not imply a large HL, correlations between  $D$  and the HL are presented in Fig. 6(a). The data indicates there is only a very weak positive correlation between the HL and  $D$  at ambient pressure. We note that all values of  $D$  at ambient conditions computed in our work can be found in Tables S2 and S3 [31] together with the values of other properties. Interestingly, the correlation between the HL and  $D$  improves significantly when  $D$  is assessed at higher pressure conditions, as shown in Figs. 6(b) and 6(c). This suggests that any factor causing the poor link between  $D$  and HL is weakened with increasing pressure. We cannot argue at this stage why that is.

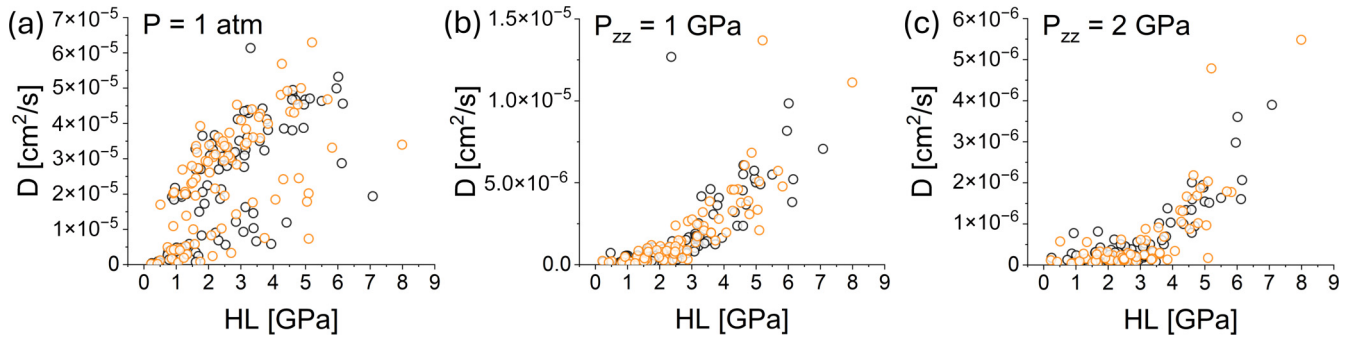


FIG. 6. Scatter plots of values of  $D$  at 300 K and (a)  $P = 1$  atm, (b)  $P_{zz} = 1$  GPa, (c)  $P_{zz} = 2$  GPa exhibited by the compounds when using OPLS-AA (black) or CGenFF (orange).

#### IV. CONCLUSIONS

In this work, we have investigated correlations between macroscopic properties and the HL of molecular liquids using molecular simulations and interpreted them at the molecular level. In particular, we have shown a strong and positive correlation between the change of molar density with respect to pressure,  $\zeta$ , at 300 K and 1 atm—an easily measurable, macroscopic property—and the HL at 300 K. This result provides a physically grounded selection criterion for liquids that remain hydrostatic up to higher pressures, and can thus better serve as a PTM, without relying on costly high-pressure screening. The correlation found between  $\zeta$  and the HL via simulations was validated by comparison with experimental results. In this context, we note that the experimental HL determined here for a 4:1 volume ratio acetone/methanol mixture (4.45–5.66 GPa) is superior to that of other commonly used PTMs.

Furthermore, we find that large  $\zeta$  is associated with large  $\rho$  and compressibility values  $\nu$ . Although it is in general not possible to find liquids that have, simultaneously, large  $\rho$  and  $\nu$ , we have shown that a large HL can be obtained by having a large value of one of them in detriment of the other, with larger  $\rho$  being more important for a larger HL. Crucially, the correlation between  $\zeta$  and the HL can be interpreted within the potential-energy-landscape framework, where vitrification or very large relaxation times reflect the reduced ability of the liquid to move between distinct basins. In this context,  $\zeta$  provides an experimentally accessible proxy for the extent to which a liquid can retain configurational mobility under compression. Although this does not amount to a direct characterization of the PEL topology, it provides a practical link between ambient-condition macroscopic observables and the molecular features that govern pressure-induced loss of hydrostaticity.

We also provided a molecular-level explanation of how  $\rho$  and  $\nu$  are linked to loss of hydrostaticity. In that process,  $\nu$  was found to be connected to intermolecular oscillation frequencies  $\omega$  with liquids having larger  $\nu$  also having lower characteristic  $\omega$ , consistent with recent work. Notably, studying the character and correlations of intermolecular vibrations in liquids might provide further insight into understanding mixtures characterized by an anomalously high HL (e.g., methanol/ethanol mixtures). We also note that, in crystalline

solids, it is well known that the compressibility and elastic constants are both related to the sound velocity, which in turn is governed by the energy of long-wavelength lattice vibrations. This may be a route to further our knowledge on what makes a compound withstand higher pressures before solidifying.

In terms of dynamical properties, we have shown that (i) no significant correlation exists between  $D$  and the average intermolecular vibrational frequencies and (ii) a (positive) correlation between  $D$  and HL exists only at higher pressures. The fact that no correlation exists between  $D$  at ambient pressure and the HL reflects, we argue, the fact that the value of  $D$  of different compounds at ambient conditions is impacted differently by pressure.

In future work, we intend to investigate correlations between further macroscopic properties and the HL, and ultimately leverage them to build a predictive model that can identify liquids with sufficiently large HL that are chemically compatible (e.g., not reactive) with specific samples. By crafting such a model, liquids having a large HL might be identified by using as input a database containing the relevant properties. Such a predictive model can thus serve as a straightforward tool to identify PTMs.

#### ACKNOWLEDGMENTS

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#### DATA AVAILABILITY

The data that support the findings of this study are available in the Supplemental Material [31] accompanying this article and in the Zenodo repository [81].

# APPENDIX: RELATION BETWEEN $\zeta$ AND OTHER MACROSCOPIC PROPERTIES

Here, we show equations relating  $\zeta$  to other properties:

$$\frac{\Delta\rho}{\Delta P_{zz}} = \frac{n\left(\frac{1}{V+\Delta V} - \frac{1}{V}\right)}{\Delta P_{zz}}, \quad (\text{A1})$$

$$\frac{\Delta\rho}{\Delta P_{zz}} = \frac{n}{\Delta P_{zz}} \left( \frac{-\Delta V}{V(V+\Delta V)} \right), \quad (\text{A2})$$

$$\frac{\Delta\rho}{\Delta P_{zz}} = \frac{n^2}{V(V+\Delta V)} \left( \frac{-\Delta V}{n\Delta P_{zz}} \right), \quad (\text{A3})$$

$$\frac{\Delta\rho}{\Delta P_{zz}} = \frac{n^2}{V(V+\Delta V)} \left( \frac{-\Delta\bar{V}}{\Delta P_{zz}} \right), \quad (\text{A4})$$

$$\lim_{\Delta P_{zz} \rightarrow 0} \left( \frac{\Delta\rho}{\Delta P_{zz}} \right)_T = \frac{n^2}{V^2} \left( \frac{-\partial\bar{V}}{\partial P_{zz}} \right)_T, \quad (\text{A5})$$

$$\zeta = \rho^2 \left( \frac{-\partial\bar{V}}{\partial P_{zz}} \right)_T, \quad (\text{A6})$$

$$\zeta = \rho\kappa_T. \quad (\text{A7})$$

In Eqs. (A1)–(A7),  $n$  denotes the amount, in moles, of structural units (molecules, in the case of the molecular liquids studied here) composing the system. We note that when taking the limit in Eq. (A3),  $\Delta V$  also becomes zero as a consequence of its interdependence with  $\Delta P_{zz}$ . Finally, it is visible from Eq. (A5) that  $\zeta$  is related to the isothermal compressibility  $\kappa_T$  for a hydrostatic medium as  $P_{xx} = P_{yy} = P_{zz} = P$ .

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