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Review article

Investigating the function and design of molecular materials through terahertz vibrational spectroscopy

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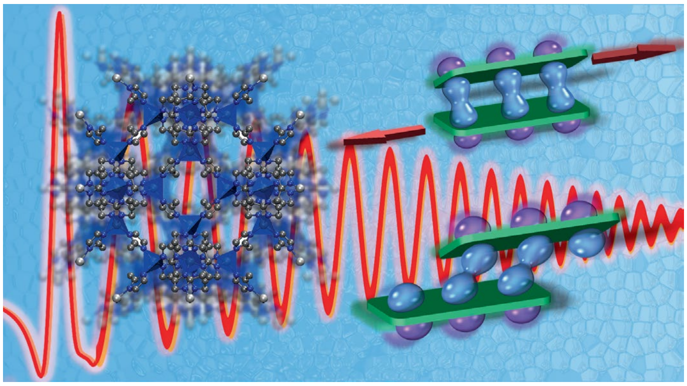
Abstract

Terahertz spectroscopy has proved to be an essential tool for the study of condensed phase materials. Terahertz spectroscopy probes the low-frequency vibrational dynamics of atoms and molecules, usually in the condensed phase. These nuclear dynamics, which typically involve displacements of entire molecules, have been linked to bulk phenomena ranging from phase transformations to semiconducting efficiency. The terahertz region of the electromagnetic spectrum has historically been referred to as the 'terahertz gap', but this is a misnomer, as there exist a multitude of methods for accessing terahertz frequencies, and now there are cost-effective instruments that have made terahertz studies much more user-friendly. This Review highlights some of the most exciting applications of terahertz vibrational spectroscopy so far, and provides an in-depth overview of the methods of this technique and its utility to the study of the chemical sciences.



Sections

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Introduction

Sandwiched between microwave and infrared frequencies lies the terahertz regime, as seen in Fig. 1. With frequencies of approximately 0.1–10 THz (3–333 cm^{-1}) and wavelengths of around 3 mm to 30 μm, the terahertz range has historically been considered a vast region of the electromagnetic spectrum that was next-to-impossible to access, often referred to as the 'terahertz gap'[1]. In reality, the terahertz region has been effectively exploited for much of the twentieth century, and discoveries in the 1980s enabled the development of robust technology that has spurred tremendous growth in the terahertz sciences[2]. Although terahertz spectroscopy originated as a historically exclusive and boutique technique, the experimental method has been in broad use since the mid-1990s, and the thirty years after that served to greatly expand interest in terahertz techniques. In turn, the efforts arising from this focus have recently yielded robust and cost-effective instruments that have made accessing terahertz frequencies easier than ever before, with a number of modern manufacturers offering a variety of commercial spectrometers, designed for a wide array of applications in the chemical sciences.

Difficulties in accessing terahertz frequencies originate from the energy of terahertz radiation, as it is generally too high in frequency to generate or detect using electronic methods and too low in energy to detect with optical techniques. However, the terahertz community has developed numerous approaches to circumvent these challenges, enabling many applications for terahertz radiation across different research communities, including condensed matter physics[3], chemical engineering[4], telecommunications[5] and pharmaceutical researchers[6]. One of the most widely utilized aspects of terahertz radiation is in spectroscopic applications – specifically, condensed phase vibrational spectroscopy.

In this regard, terahertz spectroscopy can be considered an extension of mid-infrared (mid-IR) vibrational spectroscopy to lower frequencies. While mid-IR vibrations primarily involve the dynamics of covalent bonds, the lower energy of terahertz radiation probes weaker interactions, particularly intermolecular forces, although the spectroscopic selection rules of the two techniques are identical, requiring a change in dipole moment as a function of normal mode displacement. Thus, terahertz spectroscopy is uniquely suited to understanding the intermolecular interactions that drive the properties of many condensed phase materials[7]. Additionally, vibrational motions occurring at terahertz frequencies are more complex than their mid-IR counterparts, often involving rigid-body hindered translations and rotations, as well as intramolecular modes associated with displacements of entire functional groups[8]. Furthermore, terahertz vibrations are often highly excited at ambient conditions (thermal energy at 298 K is equivalent to 207 cm^{-1} or 6.2 THz), leading to large-amplitude molecular displacements, often on the Ångstrom scale[9]. As a result, many bulk phase phenomena are directly related to terahertz vibrational modes, such as thermal expansion and entropic effects[10], as well as properties extracted from other techniques, as is the case with thermal ellipsoids obtained from diffraction studies[9].

Since the early 2000s, the terahertz community has continually discovered and leveraged terahertz dynamics to understand the properties of materials[11]. Although terahertz spectroscopy is not inherently a structural probe, the dependence of terahertz vibrations on weak intermolecular forces makes the terahertz response of materials incredibly sensitive to differences in bulk structures. Because of this sensitivity, terahertz spectroscopy has become a powerful tool for the study of polymorphic materials[12,13], and in structure prediction studies, providing an additional layer of confidence alongside more well known diffraction methods[14,15]. Additionally, the complex and large-amplitude intermolecular nature of terahertz phonons has provided great insight into the mechanisms involved in solid-state reactivity, revealing that processes such as phase transformations often proceed along a terahertz vibrational coordinate[16,17]. This has naturally resulted in efforts to drive phase transformations with terahertz radiation alone, which are proving to be fruitful efforts[18].

Finally, terahertz vibrational motions themselves are finding utility in many other areas of the chemical sciences. Terahertz spectroscopy has shown its strength for applications in environmental sensing, including threat detection and reduction[19], identification of illicit substances[20], and monitoring gas adsorption in porous materials, to name a few[21–23]. Additionally, advanced spectroscopic techniques, such as multi-dimensional terahertz spectroscopy, have emerged, capable of revealing non-equilibrium dynamics, such as the interplay of vibrational excitations and bulk electronic properties of molecular crystals[24–26]. For a review of this exciting area of the terahertz sciences, the reader is directed to ref. 27. Further connecting low-frequency vibrational motions and material properties, it has been shown that charge-carrier dynamics in organic semiconductors are strongly affected by terahertz phonons[28,29]. In those works, terahertz spectroscopy is shown to be a valuable tool for the rational design of next-generation organic semiconductors, a research area which is rapidly becoming a form of so-called 'phonon engineering'.

In this Review, recent applications of terahertz spectroscopy to molecular materials are presented. Specifically, we discuss the use of terahertz spectroscopy to understand phase transitions in organic polymorphic solids and its application in crystal structure prediction, highlighting recent efforts into driving solid-state reactivity with terahertz radiation alone. Applications that rely on an understanding of the terahertz mode types themselves are then discussed, such as those utilizing the dynamics and mechanical properties of porous framework materials and electron–phonon coupling in organic semiconductors. Given the rapidly decreasing costs of terahertz instrumentation, it is expected that the field will continue to grow at a steady pace, and it is important that eventual users be aware of the powerful capabilities – as well as difficulties – that are associated with terahertz spectroscopy. For in-depth reviews of the historic development of terahertz time-domain spectroscopy, see refs. 30,31.

Atomic nature of terahertz vibrations

The dynamics of chemical species occurring at terahertz frequencies usually involve high-frequency rotational motions and low-frequency vibrational transitions. The origin for this breadth arises from the location of the terahertz region, falling between the microwave and mid-IR regions of the electromagnetic spectrum. Thus, an understanding of the spectral response of materials can be gained by comparison with better known microwave and infrared techniques. Similar to transitions involved in microwave spectroscopy, rotational transitions are observed in terahertz measurements of gaseous samples, such as water vapour[32], although the vibrations of gaseous samples can be observed, given a suitable sample and experimental apparatus[33].

Chemical origins of terahertz phonons

Terahertz radiation is most widely employed in vibrational spectroscopy of condensed matter, which is conceptually similar to techniques involving mid-IR frequencies. Like vibrations excited by infrared radiation, terahertz vibrational modes arise from the solution of the

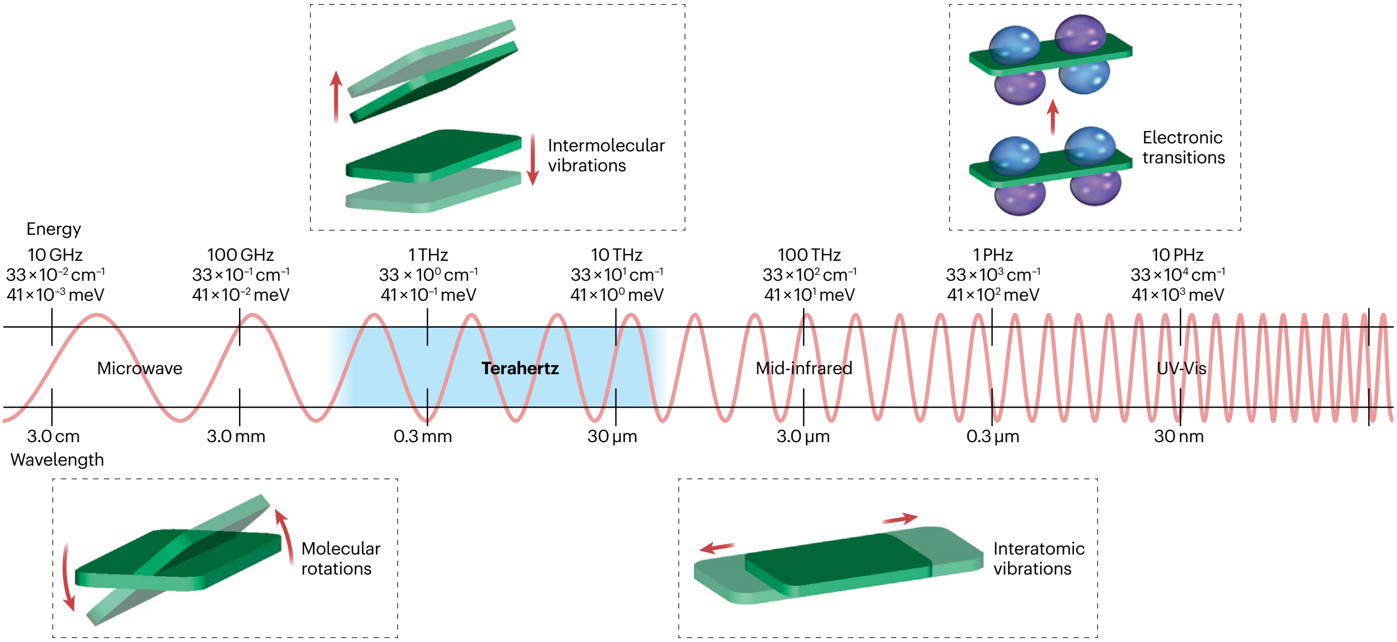

Fig. 1 | Electromagnetic spectrum and corresponding dynamics. Electromagnetic spectrum with images for comparison of different dynamics (rotations, phonons, covalent vibrations and electronic transitions). UV-Vis, ultraviolet-to-visible part of the spectrum.

harmonic oscillator Schrödinger equation, where the energies E_v of quantized vibrational states v are given as:

$$E_v = \hbar\omega\left(v+\frac{1}{2}\right) \tag{1}$$

with the angular frequency ω dependent upon the vibrational force constant k and reduced mass μ:

$$\omega = \left(\frac{k}{\mu}\right)^{1/2} \tag{2}$$

The distinction between infrared and terahertz vibrational modes is derived from the k and μ involved in the oscillations. Rigid covalent bonds in molecular species have strong force constants, giving rise to the intramolecular vibrations excited by mid-IR frequencies. As such, these vibrational modes are often localized to individual bonds, resulting in motion of the few (two to three) associated atoms along their bonding coordinate. As a result, the majority of mid-IR vibrations are described by stretching and bending motions of the component groups of atoms (functional groups) comprising individual molecules. Owing to the nature of covalent bonding, the force constant of a given bond is minimally perturbed by the surrounding chemical environment, and as such, results in similar transition frequencies of specific functional group vibrational modes. For example, the carbonyl stretching modes of ketones, amides, carboxylic acids and esters all fall within a narrow frequency band (about 1,700–1,780 cm^{-1}), with an approximate force constant of 1,150 N m^{-1}.

On the other hand, in condensed matter, the specific positions and orientations of molecules in the solid state produce intermolecular interactions that are often the result of weak forces, such as van der Waals forces, which in turn drive terahertz vibrations. This effect was detailed in an early study of saccharides, wherein terahertz spectra of crystalline samples exhibited discrete absorbance features, while amorphous solids produced broad, featureless spectra[34]. In this study, the sharp features in the spectra of crystalline materials were a result of the ordered nature of crystals, with each crystalline unit cell generating nearly identical vibrational transitions. In crystalline systems, the periodic extension of these interactions gives rise to collective molecular vibrations throughout the lattice (that is, phonons) that can occur at terahertz frequencies. In contrast to covalent bonding, these intermolecular interactions exhibit notably weaker force constants, which often arise from many entangled long-range interactions[35]. As a result, terahertz vibrational dynamics involve molecular motions about their respective intermolecular coordinate. The dynamics of terahertz vibrations are therefore complex, and for most molecular crystals, involve a rich set of intermolecular hindered translational, rotational and intramolecular vibrational motions, which can occur simultaneously over a single vibrational mode[36,37]. In a report regarding sodium peroxodisulfate ($Na_2(SO_4)_2$), the dynamics of low-frequency phonon modes were deconstructed into contributions from its component motions, namely the translational, rotational and vibrational mode types for each predicted vibrational mode, showcasing the complexity of the intertwined motions that constitute terahertz vibrations[38,39]. However, in amorphous solids, the random arrangement of molecules produces a wide range of transitions that are not uniform, ultimately producing a featureless spectrum[34]. However, this is not to say that the spectra of amorphous systems are physically meaningless, and have been the primary focus of a number of studies[40–43]. A review of the terahertz response of amorphous solids can be found in ref. 44.

Owing to the differences in the vibrational dynamics probed by terahertz and mid-IR spectroscopy, and the underlying forces that govern them, the manner in which meaningful conclusions are drawn from the two techniques is incomparable. While functional group specific transitions occurring in the mid-IR enable a relatively straightforward means of analysis and assignment, the assignment of an experimental terahertz spectrum is not as trivial. Because complex, long-range forces govern terahertz vibrations, each distinct three-dimensional structure will exhibit a unique terahertz spectrum. Thus, unlike in the mid-IR, there is no standard set of functional-group-specific transitions at terahertz frequencies. As a result, solids sharing identical molecular components but differing bulk structures (polymorphs) will result in markedly distinct terahertz dynamics, while the higher-frequency (mid-IR) vibrations for the same systems are often very similar, if not indistinguishable[45]. As a result, the general assignment of frequency bands to particular mode types, using experimental data alone, is challenging, and requires additional tools.

Assignment and interpretation of experimental spectra

In this regard, theoretical methods are necessary accompaniments for the assignment of experimentally recorded spectra[46–48]. Alongside experimental developments of terahertz spectroscopy, considerable advances in theoretical methodologies have resulted in robust models that are capable of accurately simulating the full set of vibrational dynamics in crystalline environments, thus producing meaningful captures of terahertz dynamics. Density functional theory (DFT) is one such method, which is a common complement to experimental terahertz measurements, owing to both its set of established pioneering work and historic record of development[35,47,49–53]. However, a pivotal advance for these models stemmed from the inclusion of periodic boundary conditions into the simulation, which is a crucial aspect when modelling crystalline environments[8]. Additionally, certain parameters within the DFT framework, such as density functionals and basis sets, have been expressly developed for solid systems[54,55]. As a result, an overwhelming number of options for these calculations currently exist, but must be carefully selected in order to produce accurate results, while weighing the associated computational cost. A recent report performed and evaluated a large number of calculations for three prototypical molecular crystals, and highlighted the variability of the predicted terahertz spectra as a function of the theoretical methodology. Importantly, this study demonstrated a clear correlation between errors in the predicted structures and errors in the final terahertz spectra, providing a valuable metric for future investigations[53]. Importantly, while periodic DFT is a common method in the prediction of terahertz vibrations, other methods such as ab initio and classical molecular dynamics have also been employed in such applications[56]. An extensive review of modern theoretical methods dedicated to terahertz vibrations can be found in ref. 46.

While many studies have utilized the harmonic approximation to assign terahertz spectra adequately, in reality many terahertz vibrations are highly anharmonic. This is readily apparent in the dramatic temperature-dependence of terahertz spectra, with many absorption features often sharpening and blue-shifting as temperature is decreased – a clear indication of vibrational anharmonicity[57]. There have been attempts over the years to capture vibrational anharmonicity in simulations, but these calculations are often costly to perform. For example, early efforts utilizing molecular dynamics have attempted to extract anharmonic coupling constants for energetic materials[58,59]. Further studies utilizing the quasi-harmonic approximation[60] have been able to accurately capture both anharmonic-driven terahertz frequency shifts as well as the associated temperature-dependent structures, and subsequently the thermomechanical properties of molecular crystals[10,61,62]. Explicit consideration of anharmonic coupling in the solid state has recently been explored, demonstrating the ability to extract this detailed information from quantum mechanical simulations[63]. Also, anharmonic lattice dynamics have been shown to be critical for understanding electron–phonon coupling phenomena in organic semiconductors[64,65], further highlighting the need for additional work in this important area of study, which is active and ongoing.

Recent advances in the terahertz sciences

Although the study of lattice dynamics in ionic crystals with far-IR radiation traces back to the early twentieth century[66], reports in subsequent years involving low-frequency dynamics in crystals often focused on relatively simple solids, owing to difficulties in interpreting the spectra of complex organic solids. Since the development of robust terahertz sources in the late twenty-first century, a wide variety of materials have been investigated using terahertz spectroscopy, ranging from polymorphic crystals to large porous frameworks to organic semiconducting solids, with new classes of materials continually being studied as the field progresses.

Polymorphism in molecular crystals

Towards the turn of the twenty-first century, interest in polymorphism began to grow, with early studies on molecular crystals and, subsequently, crystalline polymorphism. Polymorphic solids are formed from identical components but exhibit different spatial packing arrangements, with direct implications for bulk physical properties. Although any crystalline solid can potentially exhibit polymorphism, the rich conformational flexibility that many molecules possess makes molecular crystals particularly likely to be polymorphic. Because the major structural differences in polymorphic systems often arise from differences in molecular orientation and intermolecular contacts, each unique form will yield a unique spectral fingerprint at terahertz frequencies[45,67], as is highlighted for the α- and β-forms of L-glutamic acid, with the structures shown in[68] Fig. 2a. Although both polymorphic forms crystallize in the orthorhombic $P2_12_12_1$ space group, each exhibits different orientations of the carbon backbone with respect to the C-terminus carboxylate group, with dihedral angles of 59.26 and 8.70 degrees for α-glutamic acid and β-glutamic acid, respectively. As a result, the hydrogen-bonding network of the α-polymorph is stabilized by four hydrogen-bonding contacts, while the more linear skeleton of the β-polymorph exhibits five hydrogen-bonding contacts. The spectral consequences of the changes in intermolecular hydrogen bonding between the α- and β-polymorphs are evident in Fig. 2b, where the two terahertz spectra are clearly distinct, with the most obvious difference being an additional peak around 1.25 THz for the β-form that is absent in the α-form spectrum. It is important to note, however, that while some spectral features of the two systems may appear to be aligned, they are not related, as complementary solid-state simulations has revealed that each peak represents motions that are unique to each polymorph.

Identifying the potential polymorphic forms of molecular crystals is a crucial aspect in pharmaceutical sciences, as each polymorph can have differing associated physical properties, such as stability, solubility and by extension, bioavailability of active pharmaceutical ingredients[69–72]. Without question, there are several other experimental techniques frequently used for structural characterization of crystalline pharmaceuticals, including those based on X-ray diffraction and vibrational spectroscopy[73]. Diffraction methods have been widely used for structural studies of polymorphs, although powder X-ray diffraction (PXRD) patterns can be ambiguous or inconclusive, especially when comparing polymorphs with subtle packing differences that

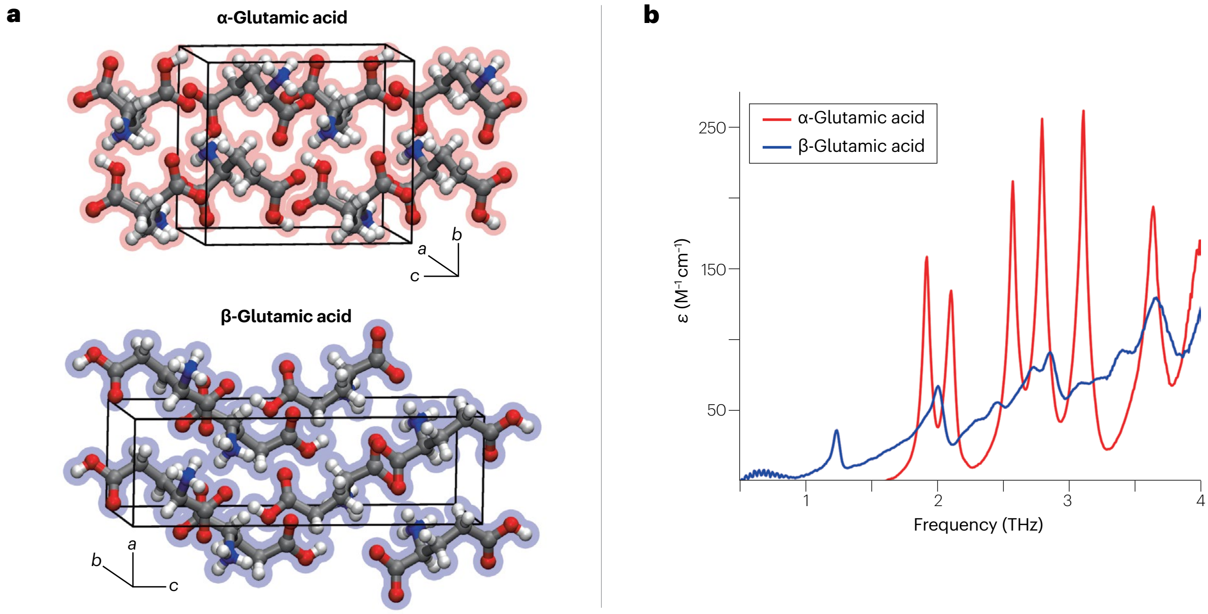

Fig. 2 | Terahertz spectra of crystalline polymorphs. a, α- and β-polymorphs of L-glutamic acid. **b**, Terahertz spectra of α- and β-L-glutamic acid polymorphs, collected at 80 K. ε denotes the molar extinction coefficient. The red and blue colouring in a and b are used to label α- and β- L-glutamic acid, respectively. The data in part **b** were extracted from ref. 68.

may not lead to a sufficient structural change to be differentiated using PXRD. While single-crystal X-ray diffraction (SCXRD) is key to elucidating the precise crystal structure (that is, atomic positions and lattice parameters), measurements require large single crystals, are time-consuming, and provide limited information for polycrystalline or amorphous samples. In many instances, the structural differences between polymorphs do not notably affect the intramolecular covalent forces, making analyses using mid-IR and Raman spectroscopies challenging[12,45]. This was the case for the antibiotic sulfathiazole, where differentiation between its five polymorphic forms proved challenging with traditional characterization methods, as there were small differences in the mid-IR and Raman spectra, and a narrow melting profile for forms II–IV[41]. While the distinct PXRD patterns of each form could potentially be used for identification, the platelike morphologies of forms III–IV are particularly prone to preferred-orientation effects, such that a mixture of these polymorphs may yield a PXRD pattern closely resembling that of a single form, leading to inaccurate conclusions. However, the terahertz spectrum of each form is distinct, allowing definitive compositional analysis to be readily obtained from terahertz time domain spectroscopy (THz-TDS) measurements alone, circumventing the aforementioned issues. Further, the phase-transition processes from forms II–IV to form I could be directly monitored through differences between the spectra obtained from variable temperature measurements.

Additionally, because the terahertz response of molecular crystals is immensely sensitive to bulk structure, terahertz spectroscopy has also been employed in studies of cocrystals, which is of particular importance to the formulation of commercial products in the pharmaceutical sciences[74,75]. For example, using terahertz radiation in both spectroscopic and imaging applications enabled the visualization of the distribution of caffeine–oxalic-acid cocrystals in a pharmaceutical tablet, in addition to the accurate determination of the relative concentration of the component cocrystals with minimal errors[76]. Additionally, terahertz measurements of mechanically ground mesaconic-acid–phenazine powdered mixtures yielded spectra with distinct absorbance features that were absent from the spectra of the individual molecular components, indicating the formation of a new crystalline structure. In this case, terahertz spectra recorded as a function of milling time provided a means of characterizing the composition of the powdered mixture, effectively monitoring and quantifying the formation of the newly formed cocrystal[77].

The pharmaceutical sciences were a particularly fitting setting for this method, but applications of THz-TDS spanned a variety of disciplines during this early period, and the broader chemical community recognized the utility of the experimental technique[3,4,78,79]. However, in their reports, authors often lamented the lack of accurate theoretical tools to accompany the measured experimental spectra, and the ambiguity in assigning the observed transitions on the basis of experiments alone[80]. In this regard, these early publications summoned the attention of theoreticians to the terahertz sciences, and the subsequent development of simulation methods of terahertz dynamics accelerated the expansion of the field.

In an early application of theoretical simulations accompanying experimental terahertz measurements, fully periodic simulations revealed the complex inter- and intramolecular phonon mode types of a few complex organic solids with a strong degree of hydrogen bonding, including crystalline sucrose[81]. The predicted terahertz spectrum of sucrose was reported to closely resemble the experimental one, with respect to both vibrational transition frequency and intensity, and the simulated motions accurately described the low-frequency dynamics of the investigated systems. Experimental spectra could thus be assigned accurately, and the simulations provided detailed insight into the origins of the spectral response. Thus, the combination of THz-TDS and ab initio simulations propelled terahertz spectroscopy to new heights, enabling insight into phenomena such as stability and conformational disorder. In solid systems, thermodynamic parameters largely depend on vibrational motions, where the strongest contributions to the overall entropy arise from low-frequency vibrations, so that agreement between experimental and theoretical terahertz data implies an accurate determination of the vibrational states of a solid, resulting in accurate reproductions of the bulk thermodynamic parameters, such as Gibbs free energies[82]. This suggests that THz-TDS can be used not only to identify polymorphic pharmaceuticals, but it can also further investigate the stability of polymorphs by validating the accuracy of a simulation, whence thermodynamic parameters can be derived. This approach uncovered the energetic origins underlying the stability of two polymorphic forms of irbesartan, a pharmaceutical used to treat hypertension[83], using experimental terahertz measurements to validate solid-state simulations of both polymorphic forms, A and B. Structural differences between the two forms arise from an intermolecular proton transfer on the tetrazole ring, as well as a temperature-dependent conformational disorder about the *n*-butyl hydrocarbon chain found only in form B. Solid-state simulations revealed the underlying competition between internal conformational strain and external cohesive binding that ultimately drives the thermodynamic properties of both polymorphs. Whereas higher aqueous solubility makes form A the desired polymorph for pharmaceutical applications, form B is more thermodynamically stable at ambient conditions, as evidenced by the predicted relative energy difference between forms A and B (more than 12 kJ mol^{-1}) and between the two conformations of form B (less than 3 kJ mol^{-1}). This example highlights how terahertz spectroscopy data can be used beyond its direct utility to provide profound insight into condensed phase phenomena, particularly when coupled to ab initio simulations.

Crystal structure prediction

The starting point for most condensed-phase studies of materials involves analysis of the molecular and bulk structures. Without question, the 'gold standard' methods of structural determination are diffraction methods, including X-ray, neutron and electron diffraction[84]. However, there are scenarios where diffraction methods are unable to provide a clear, atomically resolved, picture of bulk structures[85]. For example, disordered solids do not exhibit the translational symmetry required for Bragg reflections, making structural determination impossible without additional insight. In other cases, physical constraints, such as the inability to grow large enough single crystals, necessitate diffraction experiments on polycrystalline samples (powder diffraction), which complicates the resolution of correct and unambiguous atomic-level structural models. Finally, even optimal single-crystal diffraction experiments can produce ambiguous results, particularly when there are disordered atoms, or when a structure can be solved in multiple different symmetries. Because X-ray data provide a static average of the atomic positions over the entire crystal, the method is unable to discern whether the determined structure is a result of true dynamic disorder or whether, instead, the diffraction response originates from the presence of multiple different ordered domains that, combined, give rise to the apparent disorder. In these cases, complementary data from terahertz measurements and computational studies can help to determine the correct bulk structures, and determine the origin of the ambiguity observed by diffraction methods. This approach was used to resolve ambiguous diffraction data for benzoic acid in order to determine the correct crystal structure[86]. Benzoic acid forms dimeric hydrogen-bonded pairs in its crystal structure, and the X-ray structure indicates that there is disorder present along the hydrogen-bonding coordinate, with two possible configurations. Using computational methods, this study generated distinct (ordered) structural models and simulated the terahertz response of each. Interestingly, subtle differences in the placement of only the hydrogen atoms resulted in markedly different predicted terahertz spectra. By comparing the experimentally observed spectra to those predicted, it was possible to elucidate that the observed disorder arose from different ordered domains rather than from true dynamic disorder.

Because of the extreme sensitivity of terahertz dynamics to even the most subtle structural changes, the accurate prediction of a terahertz spectrum strongly indicates that the utilized structure is in agreement with the experimental one. This was recently demonstrated, where errors in predicted structural parameters such as unit cell volumes were directly correlated with errors in the predicted terahertz dynamics[53]. Not only does this finding have practical implications for computational spectroscopy experiments, but also the connection between the simulated structure and the accuracy of the predicted terahertz spectra can be leveraged to validate computationally generated structural models. Such an analysis was used to uncover the crystal structure of creatine, which was previously unknown[87]. In this work, multiple potential structures of creatine were simulated using dispersion-corrected DFT simulations, and the lowest energy structure was found to yield both a PXRD pattern and simulated terahertz spectra in excellent agreement with the experimentally observed data. Furthermore, constrained-volume structural optimizations and frequency analyses successfully reproduced the temperature-dependent behaviour of the terahertz spectral features – including an anomalous red-shifting of one mode as the temperature is lowered (and the structure is compressed), further validating the proposed structural model. Thus, through the addition of terahertz spectroscopy to crystal structure prediction studies, additional levels of confidence in proposed structures can be found, complementing traditional diffraction studies.

Finally, terahertz spectroscopy can be used to uncover condensed phase materials that are more challenging to study, specifically disordered solids. In a study involving plastic crystals, which are materials where crystalline sites are preserved yet molecules are disordered, the combination of terahertz experiments and simulations enabled an understanding of the molecular structure as well as the origin of the terahertz dynamics – something that was not well understood for disordered systems previously – including plastic crystals, amorphous materials and even liquids[16]. Here, the transition between a low-temperature ordered phase and a high-temperature plastic-crystalline phase in camphor was studied. Using ab initio molecular dynamics simulations, a structural model for the plastic crystal phase was determined, which agreed well with the experimentally observed PXRD pattern. Using the disordered structural model to predict the terahertz dynamics provided insight into the origin of the spectral response, which was only possible after uncovering the structure of the plastic crystalline phase. Such an approach has been extended to the organic molecular crystal diflunisal[88]. In this work, in order to understand the disordered nature of the structure, and the resulting origins of the terahertz response, supercells containing various different structures were created, and the resulting spectra were compiled to obtain a match with the experimental data. This enabled the conclusion that the molecules in the experimental sample were oriented in an alternating packing motif, which would be difficult to discern using diffraction methods alone.

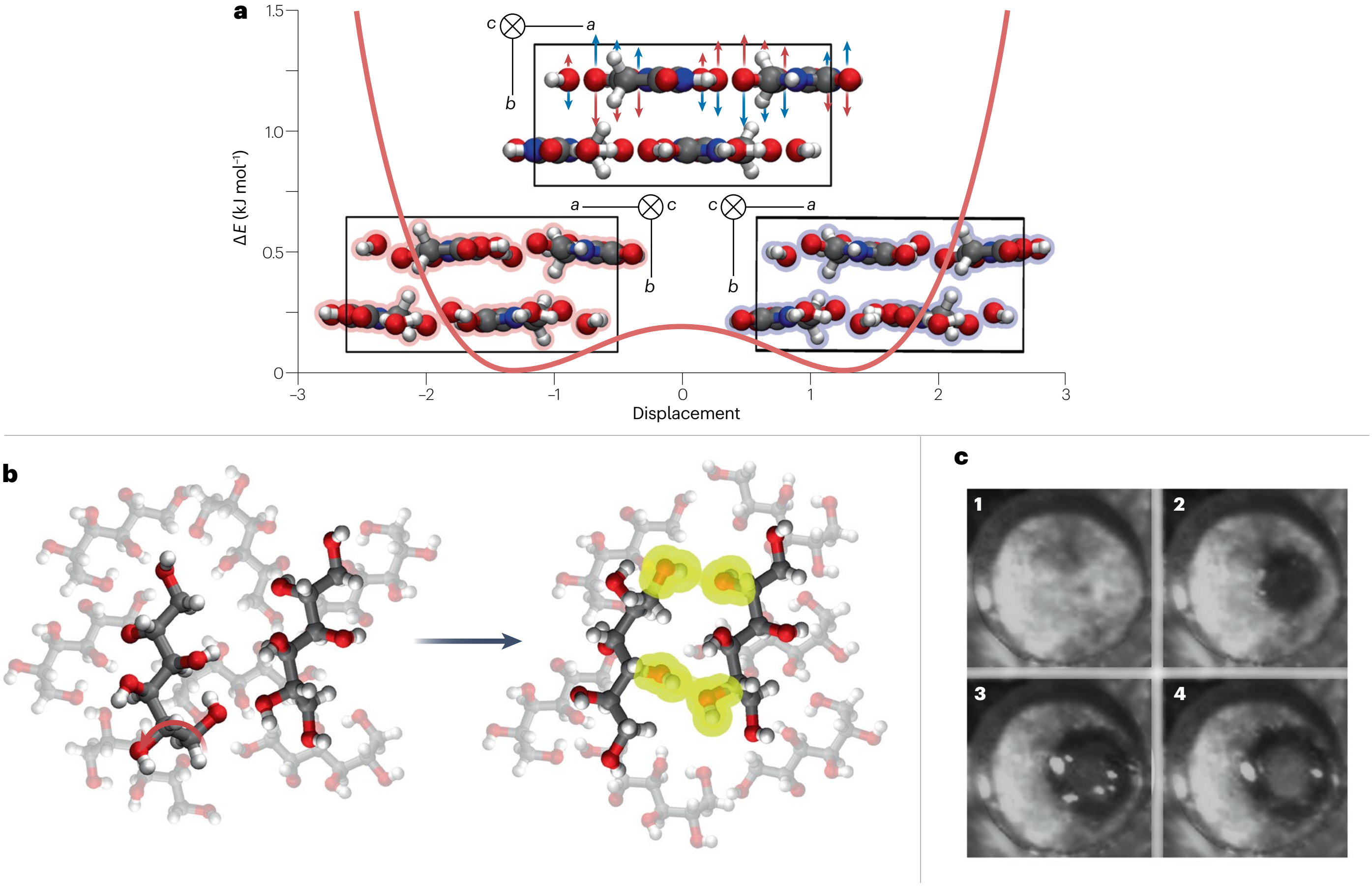

Fig. 3 | Terahertz-driven reactivity. a, Potential energy *E* surface along a terahertz mode in barbituric acid dihydrate where the high-temperature *Pnma* polymorphic structure is located at the maximum and the low-temperature nonmerohedrally twinned $P2_1/n$ polymorphs are found at the minima. Red and blue shading denote the two nonmerohedrally twinned structures. **b**, Example of the unhindered intramolecular torsional motions in amorphous sorbitol that lead to localized molecular order, allowing for crystal nucleation and crystallization throughout the amorphous crystal phase transformation. **c**, Greyscale images of amorphous indomethacin while exposed to high-power terahertz pulses initially (**1**); after 1 minute, 5 minutes and 10 minutes of exposure (**2**, **3** and **4**, respectively). The visibly distinct changes represent crystallization only within the terahertz beam. The data in part **a** were extracted from ref. 93. Part **c** is adapted from ref. 101, CC BY 4.0.

Characterizing and driving phase transformations

The conformational flexibility and rich polymorphism found in molecular crystals are regularly accompanied by the presence of solid-state phase transitions, which are often thermally induced[89]. These phase transformations, including crystal-to-crystal and crystal-to-amorphous transitions, are widely reported for organic materials owing to their profound structural and dynamic flexibility[90,91]. For the majority of phase transformations, the underlying mechanism is often obscured by rapid kinetics and non-intuitive large-scale molecular rearrangements. Thus, the identification of potential transformation pathways represent an important area of research.

Although many phase transformations involve complex rearrangements of entire molecules, one particular class of transformations, known as diffusionless transformations, involves only subtle molecular reorganization in the solid, permitting a more readily obtained depiction of the transition processes[92]. Such phase transformations became the subject of intense study in the mid-2010s by the terahertz community, as they often proceed directly along a terahertz vibrational coordinate[7,15,16]. One recent example of a crystal-to-crystal transition involves a diffusionless transformation in barbituric acid dihydrate[93]. Such crystals were previously reported to undergo a thermally induced phase transformation from a high-temperature ordered structure to a nonmerohedrally twinned structure at low temperatures. Despite the structure of barbituric acid dihydrate being reported by multiple sources over the years, many of those studies noted potential issues with the structure in the *Pnma* space group, with one previous work pointing out the exceptionally large thermal displacements along the stacking axis[94]. Through the use of terahertz spectroscopy and DFT simulations, the low-temperature structure was suggested to be non-merohedrally twinned owing to the presence of double minima along a single terahertz vibrational mode in the stacking coordinate, with the respective minima representing two unique structures that explain the origin of the twinning phenomena, as shown in Fig. 3a. At low temperatures, the crystalline units are forced into one of the two energetic minima. However, at high temperatures, the thermal energy overcomes the potential energy barrier, and the system becomes thermally disordered over the two sites, explaining the large reliability factors (indicating a poor structural model) and thermal ellipsoids, which suggest errors in the high-temperature *Pnma* space group.

Finally, a few reports have suggested a crucial role of terahertz dynamics in crystal-to-amorphous transitions such as spontaneous crystallization of amorphous materials, which is an enduring problem in condensed matter physics, with particular relevance in the pharmaceutical industry[95,96]. Amorphous materials, also known as supercooled liquids, are in a kinetically trapped metastable state where the component molecules do not generate any long-range order[97]. This metastability is desirable in pharmaceutical applications because many drugs currently in development are poorly soluble, which is exacerbated when formulated in the (thermodynamically stable) crystalline form. The metastability of the amorphous state permits a higher solubility than in the crystalline state, yet this metastability also poses risks, as spontaneous phase transformations from the amorphous to crystalline state are frequent and not easily predicted[98]. Although there has been considerable debate over the years surrounding the dynamics of amorphous materials, it is generally accepted that there are two major classes of motion that exhibit distinct relaxation times τ – the α-process with $\tau_\alpha \approx 10^6–10^{-3}$ seconds, and the β-process with $\tau_\beta \approx 10^3–10^{-9}$ seconds. Amorphous dynamics are highly temperature-dependent, and the temperatures at which these relaxation processes become vitrified, or when they are not observable on experimentally accessible timescales, are known as the glass transition temperatures: $T_{g,\alpha}$ and $T_{g,\beta}$, respectively. Generally, it is believed that the α-process involves larger-scale rearrangements of the component molecules, but there has been historical debate over the origin of the β-relaxation, which is considered to originate from more localized dynamics, with some referring to them as ‘cage-rattling’ motions[99,100]. A combined experimental THz-TDS and computational study of the amorphous dynamics in sorbitol suggested that the β-process was coupled to terahertz dynamics, including modes involving intramolecular torsions[101]. The results of this work suggest that the β-relaxation revolves around the (un-hindered) rotation of these torsional angles, and thus that $T_{g,\beta}$ represented the thermal energy required to overcome the rotational energy barriers. Thus, while terahertz dynamics represent hindered rotations, the slower β-dynamics involve an unhindered rotation. Overall, the results of this study conclude that a possible mechanism for the amorphous-to-crystal phase transformation is directly related to these torsional dynamics, as the reorganization of the individual molecular conformations ultimately permit the formation of localized molecular order, acting as the catalyst for crystal nucleation, as shown schematically in Fig. 3b. This conclusion was further validated by storing amorphous pharmaceuticals at temperatures above and below $T_{g,\beta}$, with crystallization observed only in samples stored at temperatures above $T_{g,\beta}$ (ref. 102).

The identification of terahertz vibrational modes that describe solid-state phase-transformation mechanisms has resulted in attempts to drive such phenomena using terahertz radiation alone. Such methods offer potential ways to access specific supramolecular structures selectively, providing a means of controlling final crystal forms. While this is considered a relatively cutting-edge application of terahertz radiation, there is, of course, historical precedence for such studies. For example, in 1989, it was demonstrated that by using high-field strength terahertz pulses from a free-electron laser source, the enzymatic activity of myoglobin could be manipulated[103]. But such studies naturally raise the question of what the fundamental origin of terahertz-induced reactivity is. Do the observed phenomena arise from exciting particular resonant vibrational modes? Or, perhaps these effects are caused by the large electric fields utilized in the experiments? Nevertheless, a number of studies in the mid-2010s have highlighted that terahertz radiation is capable of promoting reactivity in the condensed phase, and efforts are ongoing to uncover the precise physical origins of these phenomena.

As part of the abovementioned study uncovering the link between terahertz dynamics and crystallization, this connection was leveraged to promote crystallization in amorphous pharmaceuticals[101]. There, the amorphous pharmaceutical solids were cooled with liquid nitrogen below the $T_{g,\beta}$ of the material, which is known to inhibit crystallization. The sample (panel **1** in Fig. 3c) was irradiated with terahertz pulses from a free-electron laser, with a power density of 3 MW cm^{-2}, which was hypothesized to excite the torsional dynamics that are responsible for the crystallization process. As a result, a solid-to-solid phase transition was initiated, but only within the spot of the beam, while the surrounding area remained amorphous, as shown in Fig. 3c (structures **2**–**4**). Upon heating, the residual amorphous material underwent a thermally induced transition to the expected polymorphic form. However, the crystalline material within the beam spot was of a different polymorphic form, suggesting that the terahertz-induced crystals accessed a metastable crystalline structure, which cannot typically be accessed thermally.

In a series of related experiments, terahertz radiation was shown to influence the bulk structures of polymers. Solutions of poly(3-hydroxybutylate) in chloroform were irradiated with high-field terahertz pulses (40 mJ cm^{-2}) from a free-electron laser source, which dramatically increased the final crystallinity of the solid samples[104]. In a subsequent report, a similar experimental apparatus was employed, but using terahertz radiation generated by a gyrotron (0.46 THz, 5.7 cm^{-2}, 1 Hz repetition rate) instead of a free-electron laser[105]. In that work, an increase in the polymerization of actin filaments was observed when irradiated with terahertz pulses, with a 350% increase in polymerization when exposed to terahertz radiation compared to the unexposed reaction. The effect of heating on the observed phenomena was considered, and deduced to be minimal, as the experimental conditions never registered a temperature increase greater than 0.1 °C. Furthermore, the influence of sample temperature was explored by performing control experiments under heating, and those experiments did not yield the same results as the samples that were irradiated by terahertz radiation. Thus, the two studies concluded that the terahertz radiation itself ultimately drives the observed phenomena.

Finally, a comprehensive study reported the initiation of a paraelectric-to-ferroelectic phase transition in $SrTiO_3$ crystals[18]. In this work, terahertz pulses were used to excite a phonon resonance, ultimately resulting in a structure corresponding to a ferroelectric phase, with a distorted octahedral coordination environment breaking the initial body-centred cubic symmetry. To elucidate the underlying mechanism, the temperature and incident electric field strength were varied, and the experimental results were coupled to molecular dynamics simulations. This work helped to unambiguously determine the mechanism of this transformation, with the conclusion that this process directly follows a terahertz-induced structural deformation along a single phonon mode.

Finally, it has recently been suggested that terahertz radiation is capable of breaking covalent bonds, which has potential applications in cancer treatment. A study in 2016 claimed to identify a resonance of methylated cytosine in aqueous solutions of DNA, which is an epigenetic modification indicative of carcinogenesis[106]. While there is debate in the literature as to the origin of this resonance, with one report suggesting that the resonance arises from $NaCl \cdot 2H_2O$ crystals[107], while experimental work provides quantifiable evidence of demethylation of cancerous DNA upon application of high-field terahertz pulses[108,109]. Such controversy is expected, given the infancy of this field of research, but these studies emphasize the necessity of continued research in this important area of the terahertz sciences.

Terahertz dynamics in porous materials

Porous solids are a class of supramolecular compounds containing voids of nanometre-to-subnanometre diameter generated by the three-dimensional arrangement of the molecules that form the host complex[110]. These porous materials are readily synthesized, and involve coordination between metal nodes and organic linkers, forming supramolecular coordination networks with highly varied topologies depending on the identity of the metal cations and organic linkers[111–113]. In most cases, small guest molecules can diffuse and become trapped within the voids of the porous framework, which has powerful implications for separation sciences, gas storage and filtering, and drug delivery, among many others[114–117]. It is important to note that there is a distinction between porous crystalline solids, whose pores are generated by the topology of the host atoms and molecules, and more macroscopic porosity arising from the imperfect packing of individual crystalline or amorphous grains on the bulk scale. Understanding the latter phenomenon is required for applications in compaction, and is very valuable in the pharmaceutical industry, where there are well known relationships between macroscopic particle porosity and bulk properties such as dissolution rate. Such porosity has also been studied using terahertz spectroscopy, but instead of relying on individual quantized absorption resonances, relies on the scattering of the terahertz waves owing to the similarities between particle size, pore size and wavelength of the terahertz radiation. For more on this topic the reader is directed elsewhere[4,78,118].

To utilize porous crystals for advanced applications involving adsorption, the structure and dynamics of the pure host material must be understood. Such understanding provides insight into the nature of the intermolecular forces present, suggesting a means of identifying potential adsorption sites and mechanisms, as well as understanding the response of the host material to incorporated guest molecules. In this regard, metal–organic frameworks (MOFs) are a class of supramolecular materials containing porous voids whose guest molecule uptake has been extensively studied. While motions in MOFs occurring at terahertz frequencies can involve deformations of the entire framework, such as breathing- and shearing-type motions, there are other low-frequency vibrational modes that are semi-localized and involve only the linker molecules[119,120]. In particular, hindered rotational motions of the linkers, often occurring at terahertz frequencies, have been shown to be pervasive in MOFs, which can represent the underlying foundation for many larger-scale framework deformations[121–123]. These dynamics have profound implications for the bulk properties of MOFs, including the adsorption (and specificity) of guest molecules, as well as optical phenomena[124,125]. For example, the hindered rotational motion of methyl groups found on the methyl-imidazole linker in ZIF-8 and ZIF-67 (two isomorphic crystals with zinc and cobalt cations, respectively) has been probed using terahertz spectroscopy[126]. As the methyl groups represent possible adsorption sites in these materials, an understanding of their rotational dynamics and coupling to adjacent linkers provides insight into the nature of the interactions within the material – as well as uncovering whether the rotors are hindered or free to rotate. Although the previous example involved intramolecular motions, there have been reports where the entire linker itself is free to rotate. An example of this is found in MOF-5, consisting of ZnO_4 clusters linked by 1,4-benzenedicarboxylate molecules. In a study using inelastic neutron scattering and DFT simulations, the spectral data and associated assignment identified a number of terahertz phonons that involve a hindered rotation of the entire linker about the metal–linker–metal coordinate, as shown in Fig. 4a. In that work, the rotational potential energy was also determined, and the barrier to complete rotation was very high in energy, around 51.8 kJ mol^{-1} or about 130 THz, thus proving that it was indeed hindered, which was later confirmed by experimental ^1H NMR experiments[127]. A review of these particular dynamics can be found in ref. 128.

Such rotational dynamics are hypothesized to play an important part in the ability of MOFs to adsorb guest molecules. This has been extensively studied in the ZIF-8 system, where numerous studies have identified hindered rotational modes of the methylimidazole linkers that act as 'gates' into the pores, and thus have been labeled 'gate-opening' motions[129,130]. This particular system exhibits anomalous gas-adsorption behaviour, with substantial increase in gas loading at high pressures that is attributed to a rotation of the linkers, enabling greater access to the pores (Fig. 4b) – ultimately increasing gas-loading capacity. The gate-opening effect has been attributed to terahertz modes around 1.0 THz and 2.0 THz for the symmetric and anti-symmetric rotation of adjacent linkers, respectively[22,131]. The link between this gate-opening effect and the low-frequency dynamics of the linkers is generating much interest. Consequentially, the controversy surrounding the gate-opening modes in ZIF frameworks has resulted in a generalized model that could theoretically be applied to many MOFs within the ZIF family[132].

The ability of terahertz spectroscopy to probe these crucial dynamics in porous solids provides an alternative way of characterizing the adsorption of guests in these materials. The role of the gate-opening vibration in ZIF-8 was used to monitor the behaviour of the framework while loading the solid with various gases under pressure, using a custom-designed variable temperature and pressure-sample cell for terahertz measurements[133]. In this work, the study highlighted that not only could the gate-opening mode track the adsorption and applied pressure to the framework via the frequency shift observed while pressurized, but also found that a new absorption feature appeared upon loading. With molecular dynamics simulations, this absorption feature was suggested to be a result of the guest molecules effectively causing a reduction in symmetry of the crystal (from its original unloaded structure), which in turn activated a previously IR-inactive mode. In a similar work, gas-loading in ZIF-8 was monitored in a more straightforward manner using terahertz radiation – by simply measuring the transmitted terahertz signal through a ZIF-8 sample under loading[21]. In that work, it was shown that while both of the abovementioned studies[22,131] identified different gate-opening modes at 1.0 and 2.0 THz, respectively, it was the 2.0-THz mode assigned to the anti-symmetric gate-opening motion that proved to be most strongly affected by gas adsorption. By exposing ZIF-8 samples to three different gases – ethane, butane and carbon dioxide – and subsequently monitoring the transmitted terahertz signal at 2.0 THz, the adsorption of gases was clearly observed, cementing the role of the anti-symmetric gate-opening vibration as a crucial aspect of gas adsorption in ZIF-8.

The role of terahertz dynamics in gas loading is not limited to MOFs, and other porous materials exhibit similar phenomena. One recent example involves hydroquinone clathrates, where the crystal structure of hydroquinone exhibits small (subnanometre) voids through the formation of six-membered hydrogen-bonded rings[134–136].

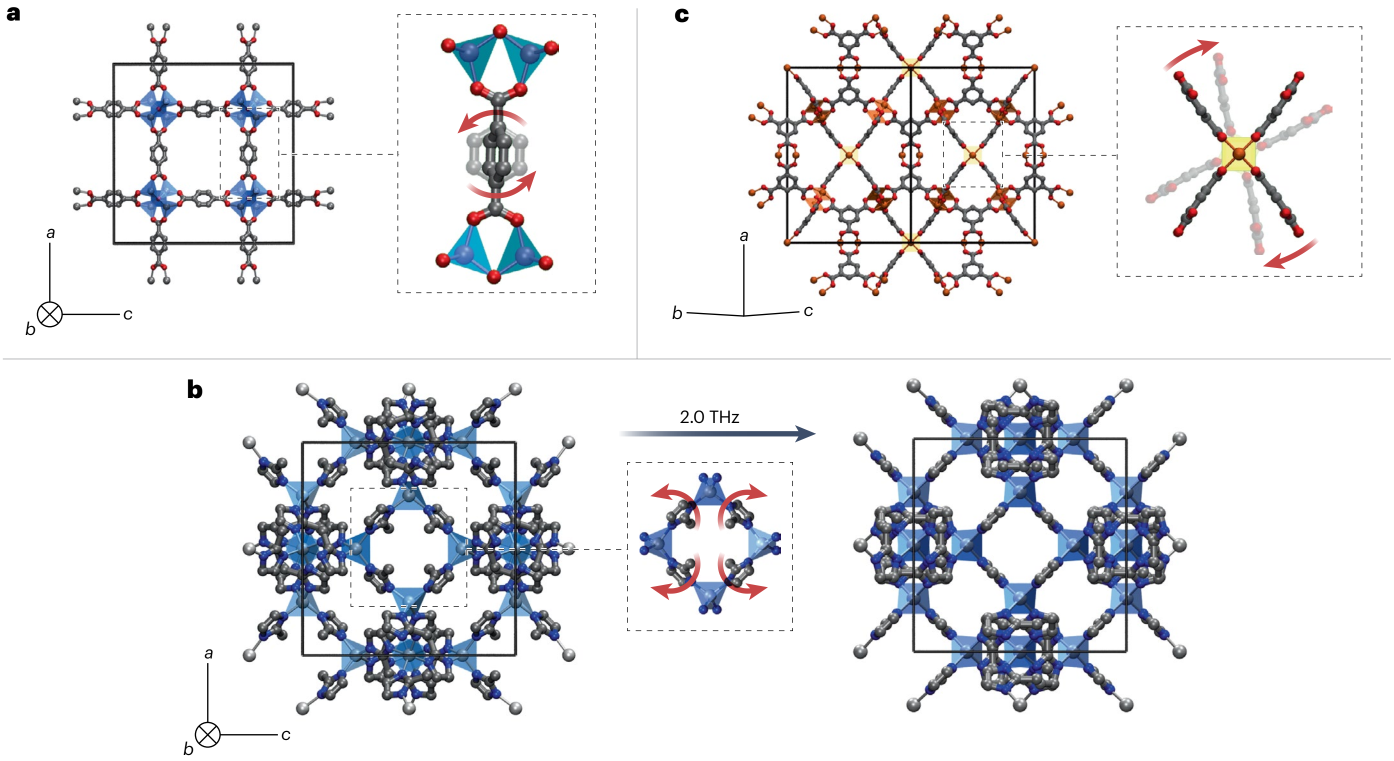

Fig. 4 | Low-frequency dynamics in MOFs. a, Hindered rotation of 1,4-benzenedicarboxylate linker in MOF-5 (ref. 119). **b**, Hindered rotation of the methylimidazole linkers in the 'gate-opening' motion in ZIF-8 (refs. 129,130). **c**, Rotor-like motion of the copper metal nodes in the 'paddlewheel' deformation of HKUST-1 (ref. 120). Blue and orange polyhedra in the crystal structures represent zinc and copper nodes of the MOFs, respectively.

Hydroquinone clathrates can adsorb many different gas molecules, including most of the noble gases, carbon dioxide, nitrogen and methane[137]. Recently, the adsorption of carbon dioxide by hydroquinone crystals was monitored in situ using a custom-designed pressure cell[138]. This adsorption process was particularly interesting, as hydroquinone crystals are polymorphic, with two forms. The α-form is most stable in the unloaded state, while adsorption of guests induces a phase transformation into the β-form. Since the two polymorphs have dramatically different terahertz spectra, gas loading can be readily monitored by the appearance of spectral features corresponding to the β-form, or inversely the disappearance of peaks corresponding to the α-form. Interestingly, in the terahertz spectrum of the carbon dioxide-loaded β-form, there is a vibrational mode that only involves translation of the guest molecule. In this work, the experimental terahertz measurements were coupled to molecular dynamics simulations of the gas-loading process, by simulating a two-dimensional slab of hydroquinone surrounded by gaseous carbon dioxide molecules[138]. The results of the simulations suggest that as the guest becomes adsorbed into the framework, the structure begins to oscillate with a frequency of around 2.0 THz, matching the experimentally observed frequency of the guest oscillation in the bulk sample. Furthermore, these motions were apparently coupled to the first layer of the unincorporated carbon dioxide molecules outside the crystal, prompting speculation that terahertz radiation may be able to drive the gas adsorption/desorption process in these materials.

In addition to adsorption of small gaseous molecules by porous materials, there are many classes of larger compounds that can be incorporated as guests into these solids. One exciting area involves the loading of drug molecules into MOFs, with potential applications in targeted drug delivery. There have been numerous studies concerned with the formation of drug–MOF complexes[139–141], and recently one such system was investigated with vibrational spectroscopy. In this work, the anticancer agent 5-fluorouracil was incorporated in the HKUST-1 MOF via mechanochemical synthesis[142]. The host–guest complex was studied using inelastic neutron scattering over the terahertz region (about 25–500 $\mathrm{cm^{-1}}$), and the spectra were compared to that of the unloaded HKUST-1 spectrum. The spectra exhibited clear differences between the unloaded and loaded materials, and a reduction in the intensity of terahertz spectral features corresponding to hindered rotation dynamics of the copper metal nodes, referred to as 'paddlewheel' motions (see Fig. 4c). This led to the conclusion that the reduction was due to further hindering of the paddlewheel dynamics resulting from the interactions with the guest molecule, providing insight into the adsorption site and interactions between the anticancer drug and the host material.

Additionally, another class of porous materials, covalent organic frameworks (COFs), have garnered substantial attention recently, owing to their applications in chemical sensing and optoelectronics. In contrast to the coordination of organic linker molecules to metal cation nodes, COFs are a class of crystalline polymers, constructed from conjugated monomers that are covalently linked to form two-dimensional polymers. These conjugated polymers then pack in the solid state to afford a porous supramolecular structure, enabling electronic properties that are unique to these systems[143]. For these materials, terahertz spectroscopy serves as a powerful tool in the evaluation of their electronic dynamics. For example, because of the similar ultrafast timescales of terahertz pulses and charge carriers in semiconducting materials, a combined approach employing terahertz spectroscopy and experimental Hall effect measurements revealed the unique mechanism of charge transport and electron conduction behaviours in a class of COFs[144]. Finally, terahertz spectroscopy is often used to evaluate the semiconducting efficiency of COFs, with optical-pump terahertz-probe techniques sampling the photoconductivity of the studied material; with a Drude–Smith model, this can ultimately provide yield intrinsic carrier mobilities in a contactless, non-destructive manner[145]. Whereas advances in applications of terahertz spectroscopy to COFs are primarily focused on probing electronic dynamics in these materials, terahertz studies of nuclear dynamics in COFs are largely unexplored, indicating a promising area of future research.

Studying organic semiconductors

Organic semiconductors have garnered interest for their optoelectronic applications in field-effect transistors, solar cells, and light-emitting diodes, to name a few. These crystalline materials, often composed of closely packed π-conjugated molecules with delocalized frontier orbitals, offer many advantages over traditional silicon-based semiconductors. The component molecules of organic semiconductors can readily be synthesized from solution in high synthetic yields, circumventing the harsh manufacturing process associated with inorganic semiconductors, such as monocrystalline silicon[146]. Additionally, organic semiconductors are readily cast into thin films, permitting mechanically flexible and translucent devices. Terahertz spectroscopy has been used to study organic semiconductors from multiple angles, including the evaluation of electron–phonon coupling on charge carrier dynamics, as well as for the visualization of individual orbitals using terahertz microscopy methods, among others.

Terahertz vibrations and electron–phonon coupling. Organic semiconducting materials are limited by their low performance, which is particularly poor in comparison to monocrystalline silicon. The performance of organic semiconductors is primarily evaluated through charge carrier mobility – a measure of charge carrier velocity through a material under an applied electric field. While monocrystalline silicon exhibits mobilities of the order of 10^3 cm^2 V^{-1} s^{-1}, promising organic semiconductors exhibit charge carrier mobilities on the scale of 10 cm^2 V^{-1} s^{-1}, and methods of improving mobilities are actively being researched[146–149]. However, improving the mobilities of organic semiconductors necessarily requires a comprehension of the unusual transport physics associated with these materials. While debate surrounds the charge transport mechanism in organic semiconductors, it is generally accepted that thermally induced large-amplitude intermolecular motions dramatically hinder the charge transfer process by fluctuating intermolecular electronic couplings throughout the lattice, often referred to by the semiconductor community as 'dynamic disorder'[64,147,149–155]. These low-frequency vibrations have thermally populated excited states at operational temperatures, further affecting these materials because the resulting separation of adjacent molecules strongly diminishes the overlap of their respective molecular orbitals and hence the charge transfer event between them (that is, the transfer integral)[150–152,156,157]. This effect prohibits the necessary delocalization of carrier wavefunctions, diminishing charge transport – a phenomenon observed in molecular crystals that is known as electron–phonon coupling[149]. Unsurprisingly, this class of molecular displacements arise from terahertz vibrations, in which molecules oscillate in the lattice about their weakly bonding van der Waals interactions, and are directly probed through low-frequency vibrational spectroscopy[28].

Although this effect is known, experimentally probing these motions has been difficult historically, with an early connection between the amplitude of molecular motion and mobility demonstrated experimentally only in 2016 (ref. 158). Using variable-temperature electron diffraction experiments, the reported molecular displacement amplitude was defined as the standard deviation of the overall molecular displacement at any given time interval, based on refinement of the simulated diffraction patterns – specifically the streaking in the observed diffraction signals. The reduction of the observed streaking indicated smaller molecular displacements[158]. Although low-frequency, large-amplitude vibrations affect charge transport most, the collected patterns capture only two-dimensional dynamics, because the experiments were performed on thin films. Additionally, these data provided no information related to the energies of the translations, or the specific motion types. Both the energy and nature of the vibrations are crucial aspects of a holistic understanding of low-frequency dynamics and charge transport in organic semiconductors, and their absence in the chemical literature has resulted in potentially unrealized insight into the effects of chemical design upon charge transport.

A depiction of molecular motions occurring in organic semiconductors was required to understand their impact on charge transport. There are techniques capable of providing these details, such as inelastic neutron scattering, which requires the use of international, limited-access facilities. Additionally, even if inelastic neutron scattering spectra were obtained, theoretical models are required to provide the associated mode types and assignment of the experimental spectra. Therefore, the recent advances in low-frequency vibrational spectroscopy ultimately provide an efficient alternative to complex inelastic neutron scattering studies. In tandem, highly accurate computational models of molecular crystals complementing these techniques are equally necessary, and owing to the growing field of terahertz sciences, have been thoroughly developed and are currently implemented in a number of DFT packages[159–163].

A combined THz-TDS and DFT approach has also been used to evaluate a selected series of organic semiconducting materials, including those studied previously[28,158]. Using an array of theoretical and experimental techniques, the low-frequency dynamics of these systems were assigned, providing a mode-resolved picture of electron–phonon coupling as a function of each mode. Specifically, the experimental terahertz and inelastic neutron scattering spectra were assigned using DFT simulations for each material. The resultant vibrational analyses were used to quantify the effect which individual modes had on the charge transfer integral, providing unparalleled insight into the effect that each type of vibrational motion had on charge carrier dynamics in these systems.

A variety of molecular motions were found to contribute to the overall electronic disorder, and the largest influence arose from long-axis antisymmetric translational motion of adjacent molecules, in line with observations from electron diffraction[158]. These dynamics most strongly influenced charge transport owing to the nature of orbital overlap between molecules, as illustrated in Fig. 5a. While the structure is displaced along these vibrations, the charge transfer integral diminishes following a reduced wavefunction overlap of neighbouring molecules, arising from spatial separation as well as the nodal

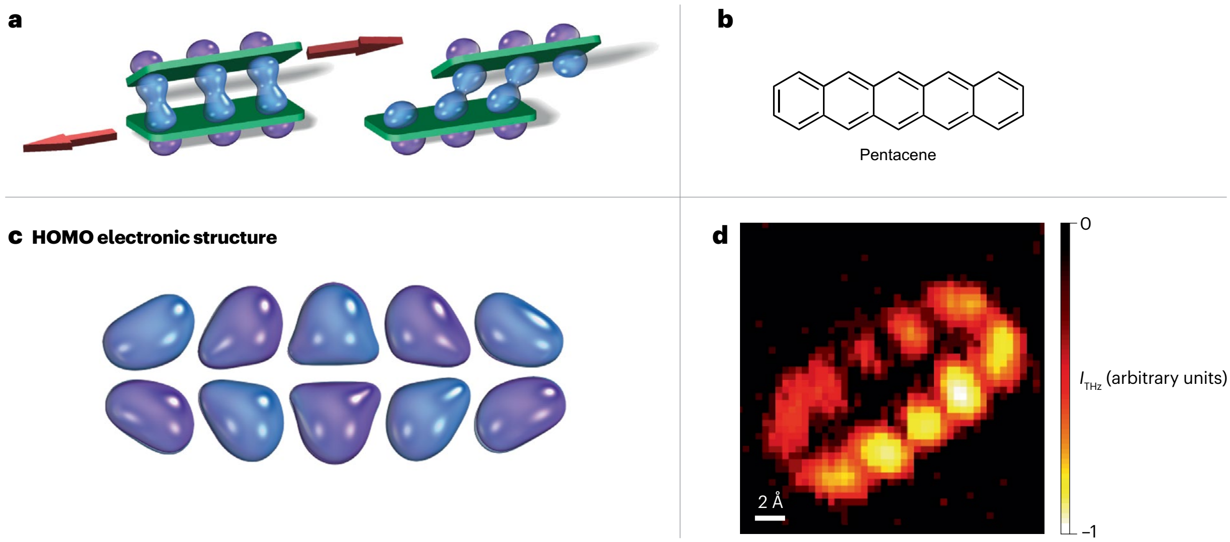

Fig. 5 | Probing organic semiconductors with terahertz radiation. **a**, Illustration of molecular orbital overlap changing over the course of a typical terahertz vibration, with red arrows indicating the direction of displacement. **b**,**c**, Structural formula (**b**) and highest occupied molecular orbital (HOMO) electronic structure (**c**) of pentacene. **d**, Image of pentacene HOMO acquired with terahertz (THz)-scanning tunnelling microscopy. I_{THz}, THz-induced current. Panel **d** reprinted from ref. 167, Springer Nature Limited.

properties of the HOMO (highest occupied molecular orbital) structures. The suggestion that hindering the long-axis sliding would have a pronounced positive effect on charge carrier mobility has opened the door to more rational engineering of these materials.

The results of the previous work highlighted the interplay between chemical structure, vibrational dynamics, electron–phonon coupling and charge transport, and subsequently there have been efforts to design molecules and crystals to mitigate these effects. Attempts to suppress the effects of the intermolecular motions that hinder charge carrier mobility, such as translations, focused on engineering the shape of conjugated molecular cores[146]. The unique V and N shapes of designer molecules such as dinaphtho[1,2-*b*:2′,1-*d*]thiophene (DNT-V), thieno[3,2-*f*:4,5-*f*′]bis[1]benzothiophene (TBBT-V) and dinaphtho[2,3-*d*:2′,3′-*d*′]benzo-[1,2-*b*:4,5-*b*′]dithiophene (DNBDT-N) were specifically synthesized to deviate from linear and quasi-linear molecules (such as pentacene and DNTT)[146], in attempts to increase the transition frequency of these modes, presumably from the increased spatial contacts between adjacent molecules.

While electron–phonon couplings are certainly sensitive to the given mode amplitude, the impact of the mode type upon the intermolecular electronic dynamics is just as influential. Focused upon the latter effects, another class of unusually shaped W-shaped molecules, such as DNT-W and chryseno[2,1-*b*:8,7-*b*′]dithiophene (ChDT), were designed to produce molecular orbitals with intermolecular overlaps that are not affected by long-axis displacement. In this regard, the ‘zig-zag’ shape of the molecular core produces a particular phase-consistent electronic structure traversing the length of the molecule. As a result, much smaller changes in the transfer integral were observed as a function of displacement along this dimension, specifically with respect to the same calculations for linear molecules such as pentacene, with spatially disconnected lobes that alternate in phase along the length of the molecule[148]. Overall, this is a relatively new field of study, and our improved understanding of structure, dynamics and dynamics disorder will continue to enable the production of new materials. In this regard, terahertz studies continue to probe these phenomena, yielding insights with direct implications for chemical design, transport physics and device performance.

Direct imaging of electronic states using terahertz microscopy. While terahertz vibrations have a clear influence upon charge transport, another limiting factor of device performance has been attributed to imperfections at the solid interface[164]. The capture of electronic properties at such junctions can provide insight into semiconducting behaviour that is uncharacteristic of the bulk system. In this regard, scanning tunnelling microscopy (STM) has been used in imaging applications of organic semiconductors to depict electronic states in single molecules[165]. In the THz-STM technique[166], the use of terahertz radiation, in which a terahertz pulse directly modulates the STM junction bias (rather than traditional setups where the bias is applied electronically), provides unique advantages over standard STM experiments. Owing to the ultrafast timescale of the incident terahertz pulses, the applied electric field from terahertz illumination results in subpicosecond lifetimes of the induced STM junction bias, enabling measurements with femtosecond temporal resolution. A study reported previously unobserved electronic phenomena that were revealed by THz-STM. With terahertz pulses tuned with amplitudes (in kV cm^{-1}) in resonance with the HOMO and lowest unoccupied molecular orbital (LUMO) states of an adsorbed pentacene molecule (Fig. 5b), state-selective tunnelling events were observed, producing highly detailed maps of the electronic structures, shown in[167] Fig. 5c,d. Additionally, the femtosecond temporal resolution resulted in the observation of a previously hidden consequence of the STM tunnelling event. Using pump–probe THz-STM measurements, wherein each pulse induces a HOMO tunnelling event, the measured currents oscillated as a function of time delay, with a corresponding frequency of 0.5 THz. This effect was attributed to a vertical vibration of the pentacene molecule, initiated by the sudden changes of Coulombic and van der Waals interactions with the substrate following the tunnelling event of an electron from the pentacene HOMO. As a previously unknown consequence, the positive and negative difference of the current caused by the probe event serve as instantaneous captures of molecular position, as the tunnelling barrier fluctuates with changing distance from the STM tip. Additionally, changes to the underlying gold deposition substrate resulted in an altered van der Waals potential, which in turn produced an oscillation with a frequency of 0.3 THz. With the inclusion of terahertz pulses, this technique provided measurements with sharper contrast in comparison to traditional methods, and captured the induced oscillatory dynamics directly in the time domain.

Conclusion

Terahertz vibrational spectroscopy has proved to be an extremely useful tool for the study of condensed phase materials. From rapidly characterizing polymorphic systems to influencing charge-carrier dynamics, the breadth of applicability of terahertz radiation is unparalleled. As the costs of its instrumentation fall and its ease-of-use increases, an increasing number of researchers are embracing terahertz spectroscopy in their work. This is an exciting time with many opportunities for study in the materials sciences. But although the ability of terahertz spectroscopy to study materials is clearly very useful, new users must balance this utility against the difficulties associated with interpreting terahertz dynamics. However, there exist many opportunities for innovative applications of terahertz spectroscopy, and these are limited only by our imagination and willingness to attempt new studies. This requires collaboration between experts in terahertz spectroscopy and those in more traditional chemical sciences; such a pairing serves a useful dual purpose in helping to expand the terahertz sciences beyond its traditional boundaries while bringing fresh lines of scientific inquiry into the terahertz regime. Such collaborations have caused certain areas of the terahertz sciences to flourish, such as that between pharmaceutical scientists and condensed matter terahertz engineers. The fresh perspectives and enthusiasm of those outside the community trying something new are critical to the continued growth and application of terahertz spectroscopy, from sensing technologies to crystal structure formation to the engineering of next-generation semiconducting materials. It is now time to stop referring to the terahertz region of the electromagnetic spectrum as the 'terahertz gap': this region should instead be recognized for the powerful impact it can have on the materials sciences.

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