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Perspective

Integrating and Exploiting Molecular, Supramolecular, and Time Crystal Synthons in Advanced Synthesis

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Abstract: Molecular reactions occur through functional groups that drive covalent synthesis. These reactions often proceed via catalytic processes, leading to the formation of time crystals, which can be integrated into shared molecules or reactions—a concept referred to as the time crystal synthon. The concept of time crystal synthons, introduced by Sahoo, pushes these ideas into the temporal realm, where molecular assemblies exhibit periodic behavior over time. This temporal aspect allows the creation of materials with unique functionalities, such as enhanced stability and responsiveness to external stimuli. A molecular synthon generates a specifically designed molecule within a catalytic reaction cycle or a time crystal. If this molecule or any associated reaction steps can be transferred or shared with a neighboring time crystal to facilitate their integration, it can be identified as a time crystal synthon. Supramolecular synthons, in contrast, enable the assembly of complex structures through non-covalent interactions among the molecules, playing a crucial role in crystal engineering. This paper further explores the applications of these synthons in various domains, including supramolecular architecture design, the integration of time crystal cycles, and the development of advanced materials. By mastering these interconnected synthons, scientists can gain greater control over molecular and material properties, driving advances in nanotechnology, materials science, and beyond. This paper explores the interconnected paradigms of molecular, supramolecular, and time crystal synthons within their respective engineering fields. Molecular synthons are foundational units within molecules, essential for designing and synthesizing new compounds with targeted properties.

Keywords: time crystal engineering; time crystal synthon; molecular synthon; supramolecular synthon

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1. Introduction

Engineering involves the production of certain designs to solve technical problems better and cost-effectively. In molecular [1], (spatial) crystal [2–5], and time crystal engineering [6–8], corresponding synthons act as tools to generate the desired products with engineering accuracy (Figure 1). In molecular engineering, certain functional groups in the molecules promote their integration in synthesizing new molecules (Figure 1a). The associated functional groups, those that participate in forming the daughter molecule, are called synthons or molecular synthons [1]. As molecular synthesis is driven mainly by the functional groups, we thus can often change the molecular backbone and can design and synthesize new analogous molecules. This is called molecular engineering and can be carried out by the homogeneous or heterogeneous catalytic reaction cycle.

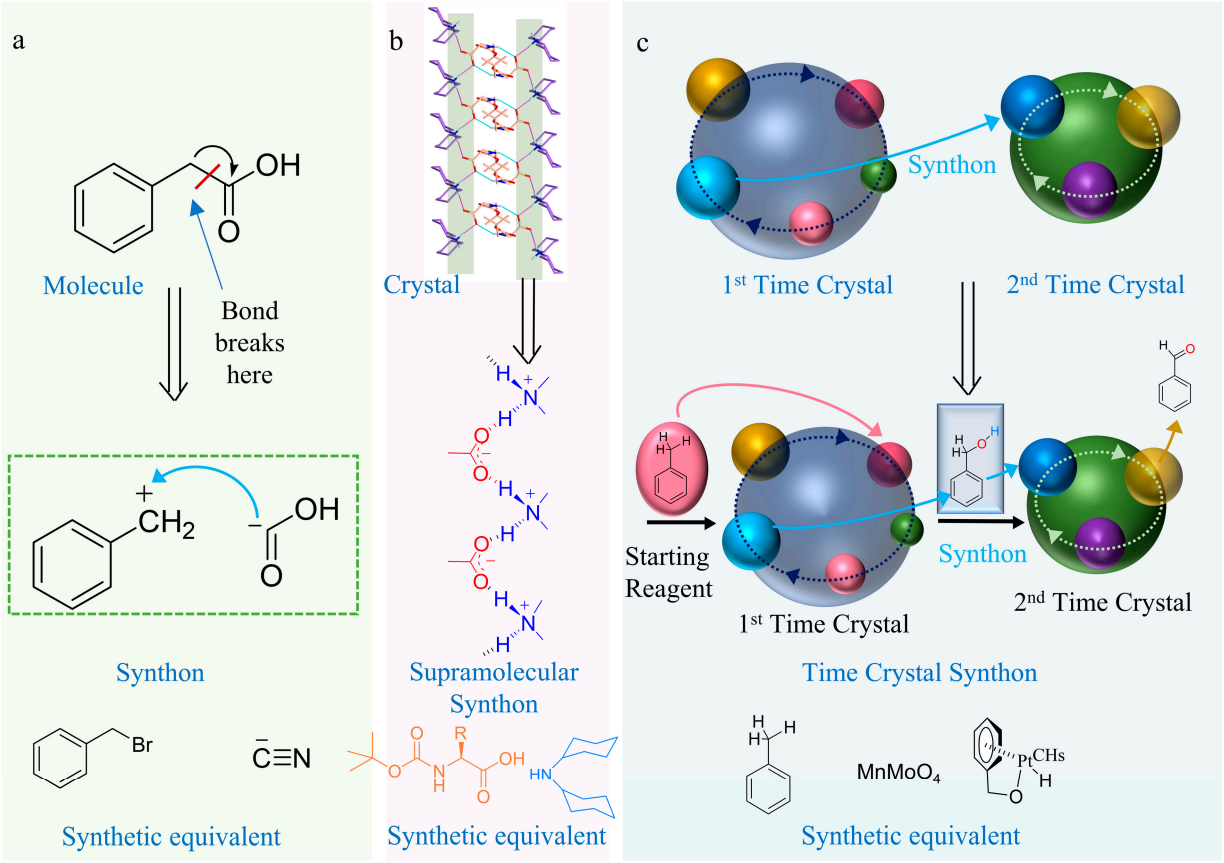

Figure 1. Types of synthons discovered so far: (**a**) molecular synthon, commonly known as a synthon, used for retrosynthesis to design a targeted molecule; (**b**) supramolecular synthon that helps in designing crystal or frustrated crystal in supramolecular chemistry; (**c**) time crystal synthon that integrates two time crystals to exploit multistep flow synthesis.

In crystal engineering [2–5], we can replace certain molecules with those capable of forming the same supramolecular synthon. Supramolecular synthons are specific spatial arrangements of functional groups that play a key role in forming supramolecular architectures (Figure 1b). They are characterized by their robust and directional bonding properties, which can often be predicted in order to facilitate the assembly of complex structures. In the time crystal cycle, we can change the substrate by keeping the event the same. In such cases, the molecular synthons should be the same, so that a similar functionality-based molecule can participate in the catalytic cycle. This happens via the molecular synthon approach.

On the other hand, catalytic reactions are repeated over time and form a clocking topology by breaking the translation symmetry (Figure 1c). All the single reactions in the catalytic cycle work as an event and are repeated over time (Figure 2) in the formation of clocking topology-based time crystals. The method works like a perpetual machine. Catalytic reactions in biological systems [9,10] characterized by fractal pathways [11] naturally integrate multiple catalytic reaction cycles into their synthetic routes. By understanding and exploring the principles behind the integration of these reaction cycles, we can design multistep flow synthesis in the laboratory. Sahoo coined the term "time crystal synthon" to illustrate these integrating principles in executing a multistep flow synthesis. As a time crystal is constructed via a catalytic reaction cycle, we can see the mechanism of covalent synthesis that transforms a molecule to another molecule. Thus, inside every reaction cycle, we can see a (molecular) synthon. In multistep synthesis, the catalytic cycles or time crystals are integrated through forming time crystal synthons.

Time crystals that share similar phases can be integrated [12,13]. Catalytic reactions are a special type of time crystal, where in addition to physical phase similarities seen in other systems, chemical phase similarity must also be maintained [6]. The physical phase similarities are influenced by solvent, pH, and temperature within the proximity range. Chemical phase similarity can be achieved by sharing a compound or a reaction step between consecutive reaction cycles, or by coupling the cycles through the exchange of molecular fractions via a metathesis reaction. A sharing chemical entity that connects two consecutive catalytic reaction cycles is termed a time crystal synthon.

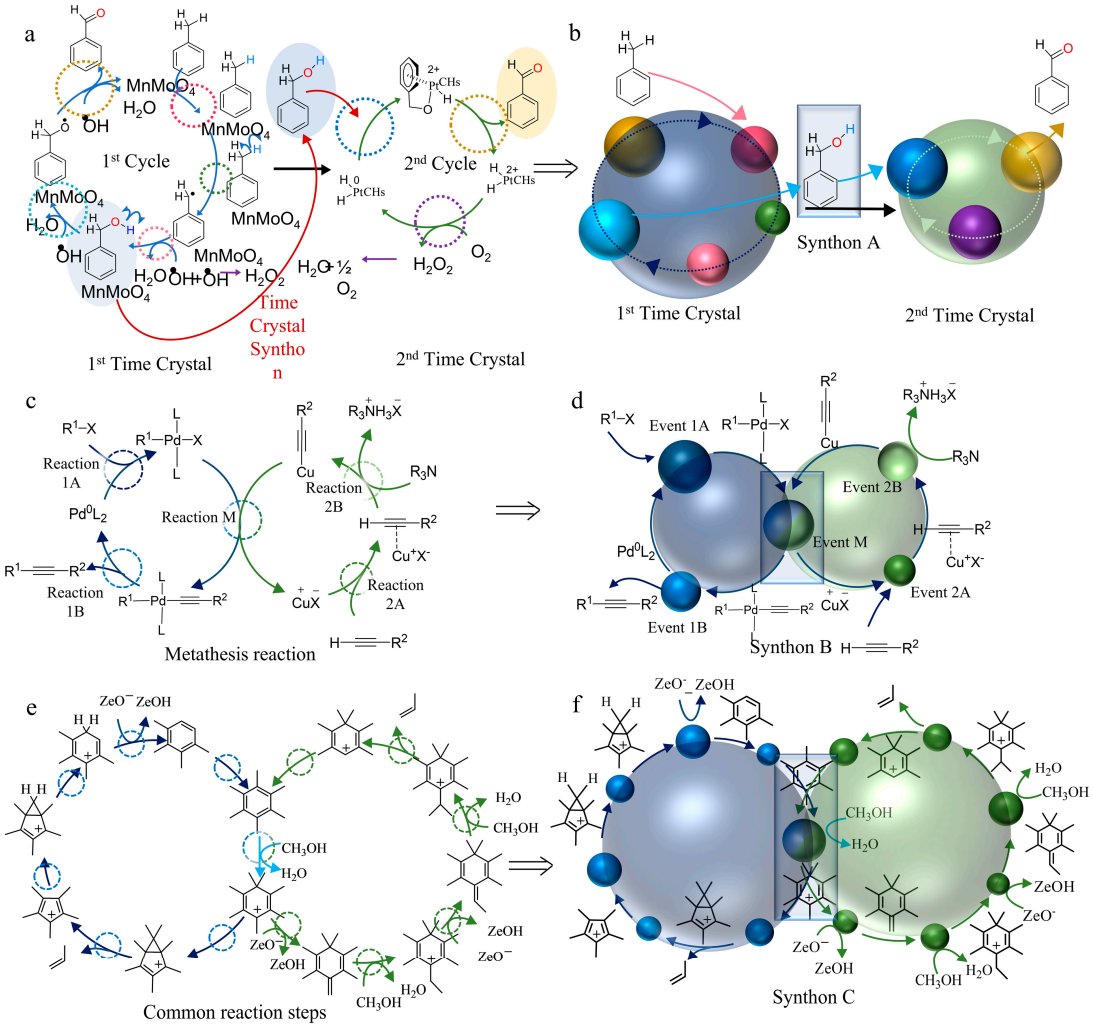

Figure 2. Three types of time crystal synthons: (**a**) among the two different catalytic reaction cycles, the first cycle produces benzyl alcohol [14] and consumed as a reagent by the second cycle [15]; (**b**) the corresponding time crystal of the two catalytic reactions, integrated by synthon A, highlighted by a transparent blue rectangle; (**c**) a metathesis or exchange reaction can be used to couple two catalytic cycles [16]; (**d**) the corresponding time crystal is illustrated and the synthon is highlighted by a transparent blue rectangle; (**e**) when two catalytic reactions have the same physical phases and share one or few common reaction steps [17], this can be exploited as the time crystal synthon C; (**f**) the corresponding synthon C for integrating two time crystals is highlighted by a transparent blue rectangle. Similarly, in (**c**), the two catalytic reactions are transformed into a time crystal in Figure (**d**), where a metathesis reaction is specifically exploited to integrate the two reactions. This metathesis reaction is designated as time crystal synthon B. Sharing a common reaction step, the two catalytic cycles in (**e**) can be integrated to generate a time crystal, as illustrated in (**f**), using time crystal synthon C. In this case, the common reaction step itself is regarded as synthon C.

Figure 2 shows how different types of catalytic reactions can form time crystals and how they can be integrated using the time crystal synthon concept under the same phases. In Figure 2a, a catalytic cycle on the left side produces benzyl alcohol ($PhCH_2OH$), which can then be transferred to the next catalytic cycle to produce benzaldehyde. The left cycle comprises five consecutive catalytic reactions, marked by dotted circles over their corresponding blue arrows. The next catalytic reaction cycle comprises three consecutive reactions, depicted by three dotted circles over the green arrows. These dotted circles represent time-consuming events and can be illustrated using a clocking topology to form their corresponding time crystals, as shown in Figure 2b. When a single product is used to connect two catalytic cycles, it is referred to as a "time crystal synthon", here denoted as synthon A. Synthon A is highlighted as the integrating unit that bridges the two reaction cycles.

2. Molecular Engineering

Molecular engineering is a multidisciplinary field that involves the design, manipulation, and synthesis of molecules to create new materials and technologies with specific functions (Figure 1a). This field integrates principles from organic chemistry to develop innovative solutions in areas such as drug design [18–20], nanotechnology [21], energy storage [22–25], supramolecular gel [26–28], and optical materials [29,30]. By understanding and controlling molecular interactions at the atomic level, molecular engineers can design molecules with tailored properties to address various technological and societal challenges. Applications of molecular engineering include creating more efficient solar cells, developing advanced pharmaceuticals [18,19], and designing self-healing materials.

Molecular Synthon

A molecular synthon is a concept in organic chemistry that refers to a structural unit within a molecule which serves as a building block for synthetic design (Figure 1a). The term was coined by E.J. Corey, the pioneer of retrosynthetic analysis, referring to a strategy used to deconstruct complex molecules into simpler components or synthons [1]. This approach facilitates the planning and execution of chemical syntheses, by providing a clear pathway from simpler starting materials to the target molecule.

Synthons can be functional groups, carbon skeletons, or other molecular fragments that guide chemists in constructing more complex molecules. They are essential in the design and synthesis of pharmaceuticals, agrochemicals, and new materials. The strategic use of molecular synthons enables chemists to efficiently build complex structures with desired properties and functions, advancing the development of innovative solutions in various scientific and industrial fields.

3. (Spatial) Crystal Engineering

A repeated and periodic arrangement of constituents that breaks translational symmetry forms a crystal. When ions or molecules are arranged periodically and break the spatial translational symmetry, they form crystals in space and are called crystals in common practice. After discovering the time crystal, which breaks time translation symmetry to arrange events periodically, in 2012, Wilczek [31] broadened the definition of crystals. To distinguish both types of crystals using proper classification, here, we refer to the conventional 'crystal' as a 'spatial crystal'.

Supramolecular Synthon

A supramolecular synthon is a fundamental concept in supramolecular chemistry, referring to a specific, repeated structural motif within a supramolecular assembly (Figure 1b). The term was coined by Desiraju to describe non-covalent building blocks that guide the organization and assembly of molecules into larger, ordered structures through intermolecular interactions such as hydrogen bonding, van der Waals forces, π–π interactions, and metal coordination [2–4]. The concept of supramolecular synthons is crucial for

the rational design and synthesis of complex molecular architectures and materials with tailored properties.

In supramolecular chemistry, the design of a supramolecular synthon involves understanding the specific interactions and recognition patterns between molecules. This requires a detailed knowledge of molecular geometry, electronic distribution, and the nature of non-covalent interactions. By carefully selecting and designing synthons, chemists can predictably assemble molecules into desired structures, ranging from simple dimers and trimers to complex networks and frameworks.

Supramolecular synthons are particularly valuable in the development of crystalline materials, such as metal–organic frameworks (MOFs) and covalent organic frameworks (COFs), where the precise arrangement of building blocks is essential for achieving specific porosities, stabilities, and functionalities [32–34]. They also play a crucial role in the design of molecular machines [35,36], drug design [37], sensors [38–40], and thermos-responsive materials [41,42], where the dynamic and reversible nature of non-covalent interactions can be harnessed to create systems that respond to external stimuli.

Supramolecular synthons are also extremely important in designing frustrated crystals like supramolecular gels. Supramolecular gels can be formed by deriving 1D self-assembled fibrillar networks (SAFiNs) and can be entangled at their junction jones to form a 3D cage for trapping certain solvents. Several types of gels like heat-set gels [43–53], liquid crystal gels [41,42], antisolvent-induced gels [54–58], and self-healing gels [59–68] can be designed via the supramolecular synthon approach [69–71].

4. Time Crystal Engineering

Time crystal engineering is an emerging and cutting-edge field at the intersection of physics, materials science, and molecular engineering. Time crystals, first proposed by Wilczek in 2012, are a novel phase of matter where the atoms or molecules are arranged in a pattern that repeats over time, defying the traditional concept of equilibrium states. Sahoo exploited this concept in the catalytic reaction cycle to build time crystals (Figures 1c and 2) [6–8]. Time crystal engineering aims to create and control these non-equilibrium phases to harness their unique properties for various applications. Sahoo also described how spatial crystals can be employed as multipurpose catalysts in the time crystal model for exploiting the molecular engineering process [6,7]. When we can connect time crystals by exploiting his time crystal synthon approach, we can develop a multistep flow synthesis process. Time crystal engineering represents a frontier of scientific research, promising to unlock new realms of material properties and technological capabilities.

Time Crystal Synthon

The "time crystal synthon" is an innovative concept coined by Sahoo, representing a significant advancement in the field of crystal engineering and supramolecular chemistry (Figures 1c and 2). Unlike traditional synthons, which are static building blocks used in molecular synthesis, a time crystal synthon encompasses the dynamic aspect of molecular assemblies that exhibit periodic changes over time.

This concept draws inspiration from time crystals, a state of matter where the structure repeats in time rather than in space. In the context of molecular engineering, a time crystal synthon involves designing molecular units that not only assemble into ordered structures but also exhibit periodic temporal behavior. This dynamic periodicity can lead to unique properties, such as enhanced stability, responsiveness to external stimuli, and novel functionalities that are not possible with static materials.

So far, three types of time crystal synthons have been identified [6]. In time crystal synthon A, one product of the previous cycle is used as a reagent in the second catalytic cycle to integrate the corresponding time crystals (Figure 2a). Two catalytic reaction cycles can also be coupled by sharing an exchange reaction, and such a synthon is termed time crystal synthon C (Figure 2b). In cases when two reaction cycles have one or few common

reaction steps, then, the cycles can be integrated and the synthon is termed time crystal synthon C (Figure 2c).

The introduction of the time crystal synthon opens up new avenues for research and applications, particularly in the development of advanced materials for information storage, sensors, and actuators. By harnessing the temporal dimension in molecular design, scientists can create materials with unprecedented capabilities, paving the way for breakthroughs in nanotechnology, materials science, and beyond [12].

5. Interdisciplinary Area of Synthons in Synthesis

In certain syntheses, we employ two or even three synthons as demonstrated in Figure 3.

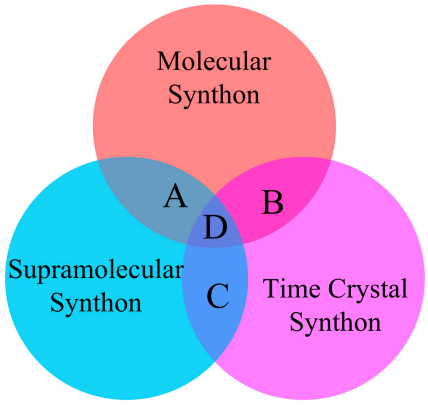

Figure 3. Overlapping zones of the synthons, where advanced synthesis can be pursued. The overlapping jones are denoted by A, B, C and D, which integrate corresponding different synthon for the advanced synthesizes.

5.1. Molecular Synthon in Crystal Engineering (Overlapping Zone A)

A molecular synthon is defined as a structural unit within a molecule that can be used to synthesize larger molecules through a covalent interaction. A covalent bond forms when two atoms share electrons to achieve a stable electron configuration, usually aiming to fill their outermost electron shells. The process involves the overlap of atomic orbitals, mutual attraction for shared electrons, and stabilization through bond formation. Supramolecular bonds do not form through orbital overlapping or electron sharing; instead, they stabilize interactions between molecules via weaker, reversible non-covalent forces such as hydrogen bonding [37,72,73], van der Waals forces [41,42], π–π stacking [74], and halogen bonding [75–78], playing a crucial role in the organization and function of complex chemical and biological systems. Before covalent bond formation, molecules often interact through transient electrostatic attractions or collisions that bring them closer. Overcoming the activation energy barrier is necessary for covalent bonds to form. In contrast, without sufficient activation energy or catalysts, molecules can still associate through reversible, weak supramolecular interactions, allowing them to organize into larger structures without forming new covalent bonds. For example, carboxylic acid and an amine behave as a molecular synthon in a retrosynthesis, forming an amide unit coupling two molecular parts. While forming the supramolecular materials, the carboxylic acid and amine become part of the supramolecular synthon forming the ammonium carboxylate synthon [41,42]. Thus, when developing supramolecular materials like crystal or frustrated crystal [41,79] systems such as supramolecular gel [41], some functional groups become essential for building supramolecular interactions that are robust and predictable. So, based on the situation or reaction type, the same functional groups can participate in building molecular or supramolecular synthons. Among the molecule/s, several supramolecular interactions can operate simultaneously. In such cases, despite having a primary operating synthon,

some different interactions can reform the supramolecular packing into an unknown packing state.

5.1.1. Molecular Engineering before Crystal Engineering

In 2000, Shinkai proposed a new hypothesis suggesting that only one-dimensional (1D) crystals with strong 1D supramolecular interactions can form 1D self-assembled fibrillar networks (SAFiNs, [69]) in suitable solvents [80]. In their work, they demonstrated that among four sugar derivatives, methyl-4,6-O-benzylidyne-a-d-glucopyranoside (G1), methy1-4,6-O-benzylidyne-a-d-allopyranoside (NG2), methyl-4,6-O-benzylidyne-a-d-altropyranoside (NG3) and methyl-4,6-O-benzylidyne-a-d-idopyranoside (NG4), only G1 produced a gel. Both G1 and NG2 exhibited a 1D hydrogen bonding network (HBN), as revealed by single-crystal X-ray diffraction (SXRD) analyses, while NG3 and NG4 exhibited 2D and 0D HBNs, respectively. They concluded that 1D interaction was essential but not a sufficient condition for producing a gel.

Dastidar later expanded and developed the concept of the supramolecular synthon approach in designing supramolecular gels. He categorized gel design principles into two protocols: (1) the molecular engineering approach and (2) the crystal engineering approach.

In the molecular engineering approach, a moiety known for gelation is covalently attached to a desired molecular scaffold to introduce gelling functionality. All covalent gelator molecules fall into this category. On the other hand, in the crystal engineering approach, a supramolecular synthon is used to form a one-dimensional (1D) network, producing a 1D crystal that typically results in gel formation in certain solvents. According to Dastidar, all organic salts precisely fall into this category. He exploited primary ammonium monocarboxylate (PAM) [81], primary ammonium dicarboxylate (PAD) [82], secondary ammonium monocarboxylate (SAM) [83], and secondary ammonium dicarboxylate (SAD) [84] synthons to support the hypothesis.

However, he did not consider how covalent molecules form the 1D SAFiN in supramolecular gel formation. Gelators synthesized via the molecular engineering approach also form supramolecular bonds—such as amide, urea, π–π interactions, and van der Waals interactions—creating their respective supramolecular synthons that contribute to the 1D network. Supramolecular gels are often described as frustrated crystals, and it can be challenging to grow single crystals that allow direct comparison between the crystal structure and the gel. Therefore, predicting the exact crystal structure at the design stage is not always possible. Multiple supramolecular bonds and their synthons collaborate, fine-tuning the final packing arrangement. Nevertheless, in covalent gelators, the primary supramolecular synthon remains decisive in forming the 1D network. In contrast, organic salts relying on strong charge-assisted hydrogen bonding, which produces supramolecular gels with relatively weaker interactions (e.g., van der Waals forces), tend to have more predictable packing patterns. Yet, predicting precise cell parameters and spatial groups remain elusive, leaving some uncertainties in forecasting the exact crystal structures of ionic compounds. While crystal engineering provides a rationale for designing crystals, it does not guarantee a complete prediction of their structures. Similarly, predicting the precise packing of gels designed through molecular engineering can be challenging, but the supramolecular packing plays a decisive role in determining the arrangement of molecules that form the gel.

In practice, we can thus select either covalent molecules or ionic molecules for gelation. In the case of ionic molecules, we can employ molecular engineering through the (molecular) synthon approach to synthesize the corresponding molecules before preparing the salt. However, once an ionic compound (a salt) is synthesized, we have limited options for further molecular synthesis. Thus, after bringing the covalent or ionic molecules to the final step for gelation, we perform supramolecular synthesis through gel formation, where the supramolecular synthon plays a pivotal role in forming the gel. Therefore, whether we perform covalent or ionic synthesis, we are merely preparing the molecules for the gelation test, and the product then undergoes supramolecular synthesis to produce the gel. The

introduction of a supramolecular synthon for the rational design of a gelator falls under crystal engineering and can be applied to both ionic and covalent gelators.

Molecular engineering might be needed to introduce certain properties into gelator molecules, but the supramolecular synthon forming ability must be there, which ultimately produces gel through a 'crystal engineering approach'. For example, a peptide molecule will never exhibit gelation if the amide synthon is not an operative synthon when packing the molecule. Thus, the question arises whether the crystal engineering approach is being implemented here in designing the covalent supramolecular gelator. The subjective closeness and parallel existence of molecular and crystal engineering can complicate their development. Additionally, the series of papers from Dastidar may have inadvertently contributed to this confusion within the community. It is crucial to clarify these concepts to advance our understanding and application of these methodologies. However, in recent years, he has not considered the molecular engineering approach as a parallel tool to crystal engineering in designing gelators. Instead, he has rationally demonstrated the use of crystal engineering in the design of supramolecular gelators [70,71]. Syntheses in such overlapping areas can create ambiguity, and this paper aims to define the boundaries of synthons in advanced synthesis.

5.1.2. Molecular Engineering after Crystal Engineering

Metal–organic frameworks (MOFs) are hybrid materials formed by metal ions or clusters linked by organic ligands to create extended porous networks [85]. These crystalline structures, known for their large surface areas and tunable properties, have become a central area of research in chemistry due to their versatile applications in areas such as gas storage, catalysis, and drug delivery. Over the past two decades, significant strides have been made in understanding their synthesis, crystal engineering, and functionalization. Despite these advances, designing MOFs with precise structures and targeted properties remains a complex challenge that limits their broader industrial use. In recent years, post-synthetic modification (PSM) has emerged as a powerful strategy to fine-tune the properties of MOFs. PSM enables the targeted alteration of linkers, metal nodes, pore sizes, and surface characteristics, enhancing stability and imparting desired functionalities to meet specific application needs.

5.2. Molecular Synthon in Time Crystal Engineering (Overlapping Zone B)

In time crystal engineering, the molecular synthon serves as a pivotal element, enabling the precise designing of a molecule within a time crystal framework. This approach enables the design and exploitation of specialized, yet analogous, molecules that facilitate the integration of time crystals through the time crystal synthon method. By carefully crafting these synthons, researchers can regulate the interactions and phase relationships among molecules, ensuring not only intra-time crystal coherence but also the integration of inter-time crystal connectivity. This coordination is essential for establishing a stable time crystal network within multistep flow synthesis. A molecular synthon generates a designed molecule within a catalytic reaction cycle or within a time crystal unit. In contrast, if the produced molecule can be transferred to the next cycle or if any associated reaction steps can be shared with a neighboring time crystal to facilitate their integration, then the shared molecule or reaction steps can be referred to as a time crystal synthon (Figure 4).

The use of molecular synthons enables the integration of various chemical reactions or processes within a time crystal, linking them in either a sequential or parallel manner. These synthons act as connectors, mediating the transfer of energy, information, or material between different segments of the time crystal. By adjusting chemical properties such as reactivity, solubility, or polarity, molecular synthons can be engineered to facilitate specific interactions at designated times, thereby enabling the dynamic behavior characteristic of time crystals.

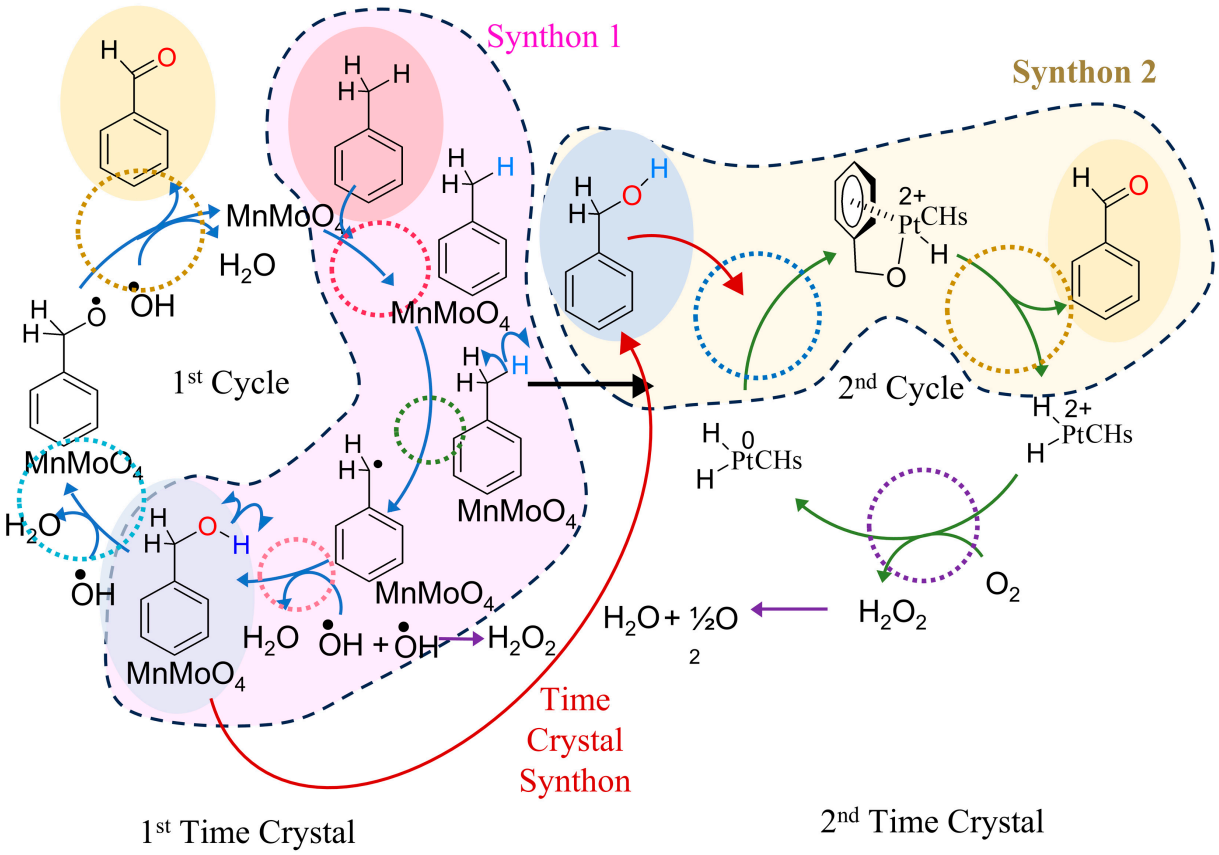

Figure 4. Complementary relation between molecular synthon and time crystal synthon. The first two time crystals from Figure 2a are represented here to demonstrate the contribution of the molecular synthon to the time crystal synthon. Benzyl alcohol is produced in the first catalytic cycle and is used as a reagent at the second reaction cycle. A red arrow depicts the integral path between the two reaction cycles and is designated as time crystal synthon A. The pink background with a dotted boundary shows the conversion of toluene to benzyl alcohol. This is designated as a molecular synthon. Similarly, in the right-hand catalytic cycle, a yellow background with a dotted boundary depicts the conversion of benzyl alcohol to benzaldehyde. This can also be designated as a molecular synthon. The two dashed area with different background color highlights two different (molecular) synthons that participate in forming their corresponding time crystal synthons.

5.3. Crystal Engineering with Time Crystal Engineering (Overlapping Zone C)

By introducing multiple reaction centers with varying band-gap energy levels within a single metal–organic framework (MOF) [32], we can develop a versatile catalyst capable of triggering different photochemical reactions using specific wavelengths of light. This multipurpose photocatalyst can be further enhanced by coating [86] the MOF with different nanoparticles [87–90], optimizing its functionality. Through spatial crystal engineering, this process becomes feasible. Additionally, with time crystal engineering, we can customize the product according to specific needs and facilitate multistep flow synthesis, further expanding the capabilities of the catalyst.

6. Applications of Time Crystal Engineering in Advanced Synthesis

Biological systems showcase remarkable efficiency by seamlessly integrating multiple reactions, often in sequence, to minimize waste and produce final products. These systems can even drive reactions against Gibbs free energy to achieve the desired outcome. By applying principles of time crystal engineering, we can harness this efficiency to develop innovative applications. Our prior research has already demonstrated the potential of chem-

ical reaction-driven time crystals in two key areas. We aim to illustrate the comprehensive range of possibilities that time crystal engineering offers for chemical reactions.

6.1. Multitasking Efficiency by Time Crystal Engineering

Multitasking efficiency is one of the most important parameters in developing a smart device. The demand for versatile catalysts within fixed chemical setups, where their roles can be controlled externally, is increasing significantly. These catalysts allow the production of desired products from a single reaction environment. By utilizing multitasking catalysts or coating various heterogeneous photocatalysts onto an inert grid, it becomes possible to perform multiple reactions within a single vessel [91].

A catalytic cycle involving multiple reaction steps can produce different molecules. By using these molecules as reagents for new catalytic cycles and activating them photochemically with distinct light frequencies, we can stimulate various time crystals within one vessel. This method enables the production of different products, providing the flexibility to selectively collect a specific product as needed. Additionally, the byproducts or intermediates from one catalytic cycle can be employed to initiate subsequent catalytic reactions.

6.2. Multistep Flow Synthesis by Time Crystal Synthon (Overlapping Zone D)

Time crystal engineering provides a novel methodology for sequentially connecting catalytic reaction cycles. By aligning time crystals in the same phase within a controllable distance, we can establish a continuous flow between consecutive reactions [6,92–95]. In this setup, the solvent and product of one reaction cycle automatically become the reagents for the next, effectively linking the entire process in a dynamic chain. Phase similarity can be achieved by maintaining proximity in physical states, such as reaction solvent, pH, and temperature, while ensuring chemical parameters including common reaction steps and adaptable reactants and products (Figure 5). Multistep flow synthesis has recently been exploited for developing pharmaceutical synthesis [93,95]. Rather than synthesizing the drug molecules step-by-step, if we can synthesize the multistep reactions in a single effort through a flow synthesis, we can minimize the synthesis time and cost, which is extremely important for the faster and cheaper development of drug molecules.

This approach, termed a "time crystal synthon", [6] allows the strategic arrangement of reaction vessels, either vertically—where gravity aids in transferring intermediates—or horizontally, creating a streamlined sequence of steps. Such an arrangement offers distinct advantages over traditional multistep synthesis. For instance, external stimuli like microwaves or light can drive the reactions, providing precise control over each step. Additionally, products can be selectively extracted from specific stages, offering flexibility and efficiency that are not typically achievable in conventional setups.

In the first catalytic step, toluene undergoes oxidation to form both benzyl alcohol and benzaldehyde. This reaction is catalyzed by manganese oxide nanoparticles that are combined with molybdenum ($MnMoO_4$) (Figure 5) [14]. The catalyst facilitates the oxidation process by activating the C–H bond of the methyl group in toluene and then converting it to either an alcohol or an aldehyde, using hydrogen peroxide (H_2O_2). The reaction should be carried out at 80 °C for 18 h. After this period, the reaction mixture is transferred to the next stage. The aldehyde produced is stable and does not interfere with the following reaction cycles.

In the second step, a platinum nanocatalyst is supported on active carbon [15], which is then deposited onto an inert grid. This setup ensures that the product can flow through to the third stage without any additional catalytic interaction. The reaction in this step is also conducted at 80 °C but only requires 3 h to complete. A small amount of potassium hydroxide (KOH, 1.5 mmol) and oxygen are necessary to drive this reaction to completion. With minimal substitutions on the benzene ring, the conversion rate approaches nearly 100%. Once the reaction is complete after 3 h, the mixture moves on to the final step.

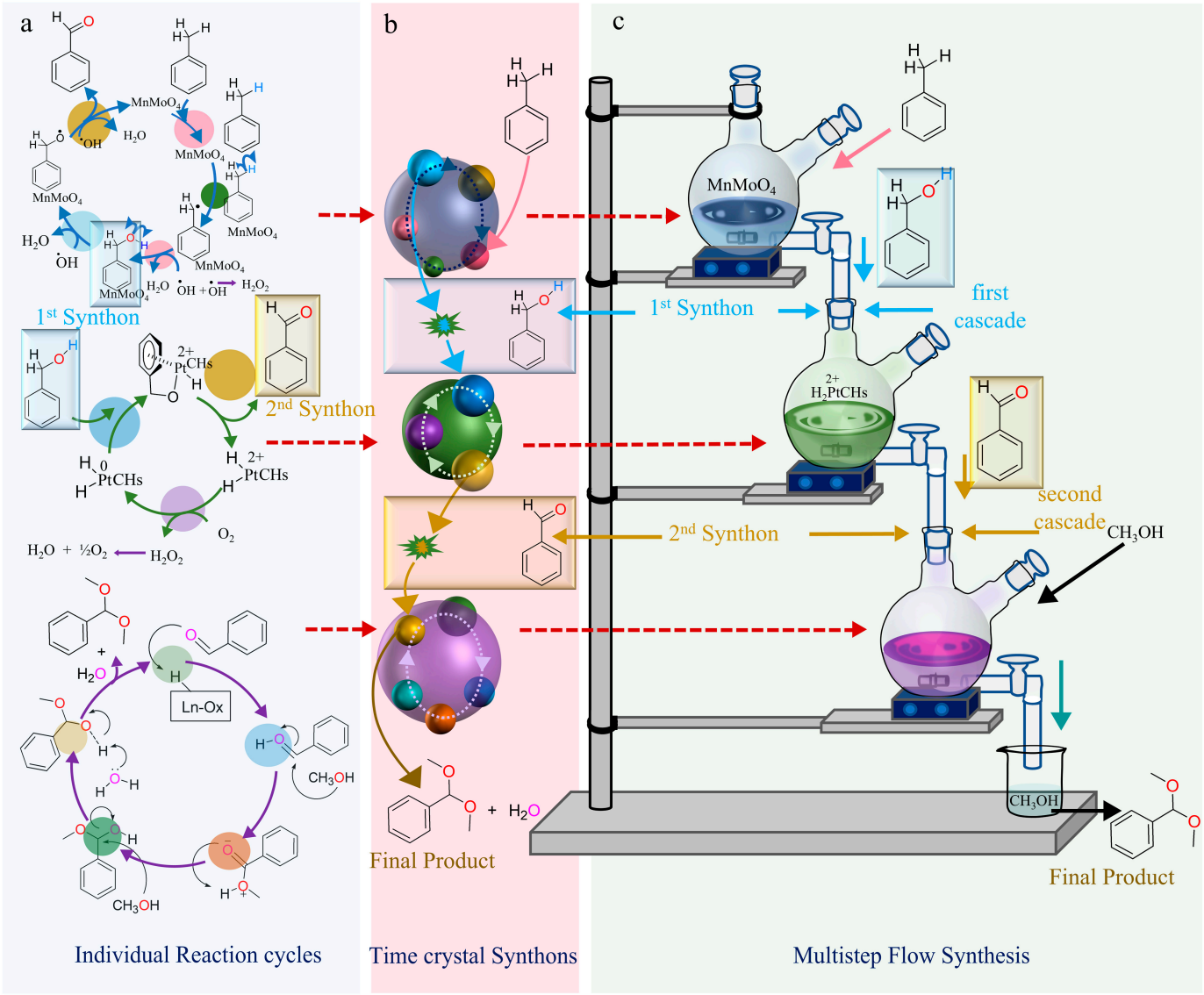

Figure 5. Multistep flow synthesis by time crystal synthon approach: (**a**) The left column shows how the heterogeneous catalytic cycle with same solvent, pH, and temperature can be integrated by exploiting time crystal synthon. All the colored circles depict the events in the corresponding catalytic cycles to demonstrate, how a time crystals forms by integrating those events. (**b**) In the middle column, the time crystals are integrated by time crystal synthons, which appear inbetween the time crystals. (**c**) A multistep reaction, developed from time crystal synthon approach can be driven by exploiting gravitational force. The dotted red arrows integrate the columns by depicting how the catalytic cycles can be converted into the time crystals (middle column), which can be carried out in the reaction pots (at the right-hand column).

Since the first two steps do not require external solvents, there is flexibility in choosing the solvent for the third and final stage. In this stage, methanol is used as the reaction medium [96]. Using this catalyst, crystal engineering was performed to design a new kind of lanthanide-based MOF, presented as Ln-Ox inside the box in the third row of column a, as in the acetalization of benzaldehyde. As the solvent is methanol, thus, the second solution must be cooled for the third reaction vessel (from 80 °C to 50 °C).

6.3. Chemical Computing

Classical computers are limited by the von Neumann bottleneck, which restricts data flow between the processing unit and memory. In contrast, chemical processes offer the

potential to overcome these limitations by merging the processing unit and memory within the same physical space, where computations occur through chemical reactions. However, the challenge of programmability has so far hindered the full realization of chemical computing's potential.

Researchers have made strides by harnessing switchable oscillating chemical reactions, such as the Belousov–Zhabotinsky (BZ) reaction [97,98], to create analogue computers capable of problem solving. In these systems, reactions are conducted in small, closely packed vessels, with each vessel connected to others arranged symmetrically on a horizontal plane. This configuration allows the reaction medium to flow freely, facilitating the observation of reaction patterns that mimic computational processes.

One notable example is the work of Parrilla-Gutierrez et al. [98], who programmed an array of interconnected BZ reactions to create chemically encoded, addressable memory. They also developed a chemical autoencoder for pattern recognition, capable of performing the equivalent of one million operations per second. This demonstrates the potential of analogue computing through a "chemical symphony", where the system can make decisions and solve complex problems.

To advance this field, it is essential to incorporate a variety of chemical reactions into an integrated system using the time crystal synthon approach. Each reaction would contribute its unique reaction order and kinetics, enhancing the analogue computation process. This integrated and more sophisticated reaction mechanism could lead to the development of a self-regulating, computation-based system with the potential to generate a new form of artificial consciousness in the future. However, it is important to clarify that this setup, consisting of four or five reaction vessels, is not being proposed as a system capable of achieving consciousness on par with living organisms. This exploration of the time crystal synthon concept will aid in integrating a complex setup necessary for developing a conscious chemical symphony, similar to that of living systems.

7. Conclusions

In addition to the conventional (molecular) synthon and supramolecular synthon, a newly conceptualized time crystal synthon is introduced here to explore the potential of combined synthons in advanced synthesis. Once the catalytic reaction cycles in the time crystal are converted and integrated through the time crystal synthon, the multistep flow synthesis can be carried out, with potential applications spanning pharmaceutical products to selecting specific products from the reaction set and beyond.

We also explored the intricate relationships and interconnected paradigms of molecular, supramolecular, and time crystal synthons within the context of advanced synthesis. The concept of synthons, traditionally confined to spatial crystal and molecular frameworks, has been expanded to include time crystals, introducing a temporal dimension to synthetic design. By leveraging the principles of molecular engineering, we have demonstrated how molecular synthons can drive the synthesis of complex molecules and materials with desired properties. Similarly, supramolecular synthons have been shown to play a pivotal role in crystal engineering, facilitating the assembly of ordered structures through predictable non-covalent interactions. The work presented here serves as a foundational framework for future research in chemical engineering, where completeness in chemical synthesis can be achieved for the creation of next-generation synthesis and technologies.

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References

1. Corey, E.J. General methods for the construction of complex molecules. *Pure Appl. Chem.* **1967**, *14*, 19–38. [CrossRef]
2. Desiraju, G.R. Supramolecular Synthons in Crystal Engineering—A New Organic Synthesis. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2311–2327. [CrossRef]
3. Desiraju, G.R. Crystal Engineering: A Holistic View. *Angew. Chem. Int. Ed.* **2007**, *46*, 8342–8356. [CrossRef]
4. Desiraju, G.R. Crystal Engineering: From Molecule to Crystal. *J. Am. Chem. Soc.* **2013**, *135*, 9952–9967. [CrossRef]
5. Hall, A.V.; Yufit, D.S.; Apperley, D.C.; Senak, L.; Musa, O.M.; Hood, D.K.; Steed, J.W. The crystal engineering of radiation-sensitive diacetylene cocrystals and salts. *Chem. Sci.* **2020**, *11*, 8025–8035. [CrossRef]
6. Sahoo, P. Time Crystal Synthon: The Way of Integrating Cascade Reactions for Advancing Multistep Flow Synthesis. *ChemEngineering* **2023**, *7*, 88. [CrossRef]
7. Sahoo, P.; Ghosh, S. Space and Time Crystal Engineering in Developing Futuristic Chemical Technology. *ChemEngineering* **2021**, *5*, 67. [CrossRef]
8. Sahoo, P.; Ghosh, S. Time Crystal Engineering in Catalytic Reaction cycles. In *Rhythmic Oscillations in Proteins to Human Cognition*; Bandyopadhyay, A., Ray, K., Eds.; Springer Book Series 'Studies in Rhythm Engineering'; Springer: New York, NY, USA, 2021; Chapter 4; pp. 103–134.
9. Schwarz, P.S.; Laha, S.; Janssen, J.; Huss, T.; Boekhoven, J.; Weber, C.A. Parasitic behavior in competing chemically fueled reaction cycles. *Chem. Sci.* **2021**, *12*, 7554–7560. [CrossRef]
10. Orgel, L.E. Self-organizing biochemical cycles. *Proc. Natl. Acad. Sci. USA* **2000**, *97*, 12503–12507. [CrossRef]
11. Bizzarri, M.; Giuliani, A.; Cucina, A.; Anselmi, F.D.; Soto, A.M.; Sonnenschein, C. Fractal analysis in a Systems Biology approach to cancer. *Semin. Cancer Biol.* **2011**, *21*, 175–182. [CrossRef]
12. Pizzi, A.; Knolle, J.; Nunnenkamp, A. Higher-order and fractional discrete time crystals in clean long-range interacting systems. *Nat. Commun.* **2021**, *12*, 2341. [CrossRef] [PubMed]
13. Solfanelli, A.; Ruffo, S.; Succic, S.; Defenu, N. Logarithmic, fractal and volume-law entanglement in a Kitaev chain with long-range hopping and pairing. *J. High Energy Phys.* **2023**, *2023*, 66. [CrossRef]
14. Shoukat, H.; Altaf, A.A.; Hamayun, M.; Ullah, S.; Kausar, S.; Hamza, M.; Muhammad, S.; Badshah, A.; Rasool, N.; Imran, M. Catalytic Oxidation of Toluene into Benzaldehyde and Benzyl Alcohol Using Molybdenum-Incorporated Manganese Oxide Nanomaterials. *ACS Omega* **2021**, *6*, 19606–19615. [CrossRef] [PubMed]
15. Göksu, H.; Burhan, H.; Mustafov, S.D.; Şen, F. Oxidation of Benzyl Alcohol compounds in the presence of carbon Hybrid Supported platinum nanoparticles (pt@cHs) in oxygen Atmosphere. *Sci. Rep.* **2020**, *10*, 5439. [CrossRef]
16. Chinchilla, R.; Nájera, C. The sonogashira reaction: A booming methodology in synthetic organic chemistry. *Chem. Rev.* **2007**, *107*, 874–922. [CrossRef]
17. Xu, S.; Zheng, A.; Wei, Y.; Chen, J.; Li, J.; Chu, Y.; Zhang, M.; Wang, Q.; Zhou, Y.; Wang, J.; et al. Direct observation of cyclic carbenium ions and their role in the catalytic cycle of the methanol-to-olefin reaction over chabazite zeolites. *Angew. Chem. Int. Ed.* **2013**, *52*, 11564–11568. [CrossRef]
18. Aminpour, M.; Montemagno, C.; Tuszynski, J.A. An Overview of Molecular Modeling for Drug Discovery with Specific Illustrative Examples of Applications. *Molecules* **2019**, *24*, 1693. [CrossRef]
19. Adelusi, T.I.; Oyedele, A.-Q.K.; Boyenle, I.D.; Ogunlana, A.T.; Adeyemi, R.O.; Ukachi, C.D.; Idris, M.O.; Olaoba, O.T.; Adedotun, I.O.; Kolawole, O.E.; et al. Molecular modeling in drug discovery. *Inform. Med. Unlocked* **2022**, *29*, 100880. [CrossRef]
20. Cheng, Y.; Gong, Y.; Liu, Y.; Song, B.; Zou, Q. Molecular design in drug discovery: A comprehensive review of deep generative models. *Brief. Bioinform.* **2021**, *22*, bbab344. [CrossRef]
21. Nagamune, T. Biomolecular engineering for nanobio/bionanotechnology. *Nano Converg.* **2017**, *4*, 9. [CrossRef]
22. Xu, D.; Zhang, C.; Li, Y. Molecular engineering redox-active organic materials for nonaqueous redox flow battery. *Curr. Opin. Chem. Eng.* **2022**, *37*, 100851. [CrossRef]
23. Shakouri, S.; Abouzari-Lotf, E.; Chen, J.; Diemant, T.; Klyatskaya, S.; Pammer, F.D.; Mizuno, A.; Fichtner, M.; Ruben, M. Molecular Engineering of Metalloporphyrins for High-Performance Energy Storage: Central Metal Matters. *ChemSusChem* **2023**, *16*, e202202090. [CrossRef] [PubMed]
24. Zhu, F.; Guo, W.; Fu, Y. Molecular Engineering of Organic Species for Aqueous Redox Flow Batteries. *Chem. Asian J.* **2023**, *18*, e202201098. [CrossRef] [PubMed]
25. Wu, Z.; Liu, Q.; Yang, P.; Chen, H.; Zhang, Q.; Li, S.; Tang, Y.; Zhang, S. Molecular and Morphological Engineering of Organic Electrode Materials for Electrochemical Energy Storage. *Electrochem. Energy Rev.* **2022**, *5*, 26. [CrossRef]
26. Wang, X.; Bao, L.; Zhang, C.; Zhang, J.; Yang, Z.; Yang, W.; Zhou, F.; Liu, W. Supramolecular assembly inspired molecular engineering to dynamically tune non-Newtonian fluid:from quasi-static flowability-free to shear thickening. *J. Colloid Interface Sci.* **2022**, *607*, 1805–1812. [CrossRef]

27. Sahoo, P. Hydrogen-Producing Photocatalyst at Sunscreen for Athletics in Preventing and Healing Muscle-Nerve-Skin Injuries. *Curr. Top. Med. Chem.* **2023**, *23*, 249–256. [CrossRef]
28. Sahoo, P.; Kumar, D.K.; Trivedi, D.R.; Dastidar, P. An easy access to an organometallic low molecular weight gelator: A crystal engineering approach. *Tetrahedron Lett.* **2008**, *49*, 3052–3055. [CrossRef]
29. Ray, S.; Roy, S.; Biswas, S.; Ojha, M.; Singh, N.D.P. A Molecular Engineering Approach to Achieve Wavelength-Selective Photorelease Using a Dynamic Photocage. *Org. Lett.* **2024**, *26*, 6236–6240. [CrossRef]
30. Signorini, R.; Meneghetti, M.; Bozio, R.; Maggini, M.; Scorrano, G.; Prato, M.; Brusatin, G.; Innocenzi, P.; Guglielmi, M. Molecular and Material Engineering for Optical Limiting with Fullerene Based Sol-Gel Materials. In *Multiphoton and Light Driven Multielectron Processes in Organics: New Phenomena, Materials and Applications*; Kajzar, F., Agranovich, M.V., Eds.; NATO Science Series; Springer: Dordrecht, The Netherlands, 2000; Volume 79. [CrossRef]
31. Wilczek, F. Quantum Time Crystals. *Phys. Rev. Lett.* **2012**, *109*, 160401. [CrossRef]
32. Garai, B.; Mallick, A.; Banerjee, R. Photochromic metal–organic frameworks for inkless and erasable printing. *Chem. Sci.* **2016**, *7*, 2195–2200. [CrossRef]
33. Koner, K.; Karak, S.; Ogaeri, Y.; Nishiyama, Y.; Banerjee, R. Structural and Morphological Transformations of Covalent Organic Nanotubes. *Angew. Chem. Int. Ed.* **2023**, *135*, e202300652.
34. Bag, S.; Sasmal, H.S.; Chaudhary, S.P.; Dey, K.; Blätte, D.; Guntermann, R.; Zhang, Y.; Položij, M.; Kuc, A.; Shelke, A.; et al. Covalent Organic Framework Thin-Film Photodetectors from Solution-Processable Porous Nanospheres. *J. Am. Chem. Soc.* **2023**, *145*, 1649–1659. [CrossRef]
35. Garcia-Garibay, M.A. Crystalline molecular machines: Encoding supramolecular dynamics into molecular structure. *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 10771–10776. [CrossRef]
36. Zhang, Q.; Qu, D.-H.; Tian, H.; Feringa, B.L. Bottom-Up: Can Supramolecular Tools Deliver Responsiveness from Molecular Motors to Macroscopic Materials? *Matter* **2020**, *3*, 355–370.
37. Sahoo, P. Complementary Supramolecular Drug Associates in Perfecting the Multidrug Therapy Against Multidrug Resistant Bacteria. *Front. Immunol.* **2024**, *15*, 1352483. [CrossRef]
38. Veits, G.K.; Carter, K.K.; Cox, S.J.; McNeil, A.J. Developing a Gel-Based Sensor Using Crystal Morphology Prediction. *J. Am. Chem. Soc.* **2016**, *138*, 12228–12233. [PubMed]
39. Goyal, H.; Pachisia, S.; Gupta, R. Systematic Design of a Low-Molecular-Weight Gelator and Its Application in the Sensing and Retention of Residual Antibiotics. *Cryst. Growth Des.* **2020**, *20*, 6117–6128. [CrossRef]
40. Ghosh, D.; Deepa; Damodaran, K.K. Metal complexation induced supramolecular gels for the detection of cyanide in water. *Supramol. Chem.* **2019**, *32*, 276–286. [CrossRef]
41. Sahoo, P. Unveiling Discotic Liquid Crystalline Phase Changes through Supramolecular Disc Polymorphism at Their Disc-Driven Gel State. *Cryst. Growth Des.* **2023**, *23*, 6238. [CrossRef]
42. Sahoo, P. Introducing Dihedral Angle Torsion in a Flexible Dicarboxylic Acid: Evolution from Sequential Symmetry Condensing LC Gel to Step-Halting Heat-Set Gel. *Cryst. Growth Des.* **2024**, *24*, 3100–3108. [CrossRef]
43. Zhong, D.-C.; Liao, L.-Q.; Wang, K.-J.; Liu, H.-J.; Luo, X.-Z. Heat-set gels formed from easily accessible gelators of a succinamic acid derivative (SAD) and a primary alkyl amine (R-NH_2). *Soft Matter* **2015**, *11*, 6386–6392. [CrossRef] [PubMed]
44. De Hatten, X.; Bell, N.; Yufa, N.; Christmann, G.; Nitschke, J.R. A Dynamic Covalent, Luminescent Metallopolymer that Undergoes Sol-to-Gel Transition on Temperature Rise. *J. Am. Chem. Soc.* **2011**, *133*, 3158–3164. [CrossRef] [PubMed]
45. Gavrilov, M.; Gilbert, E.P.; Rowan, A.E.; Lauko, J.; Yakubov, G.E. Structural Insights into the Mechanism of Heat-Set Gel Formation of Polyisocyanopeptide Polymers. *Polym. Macromol. Rapid Commun.* **2020**, *41*, 2000304. [CrossRef] [PubMed]
46. Kaspchak, E.; Oliveira, M.A.S.D.; Simas, F.F.; Franco, C.R.C.; Silveira, J.L.M.; Mafra, M.R.; Igarashi-Mafra, L. Determination of heat-set gelation capacity of a quinoa protein isolate (*Chenopodium quinoa*) by dynamic oscillatory rheological analysis. *Food Chem.* **2017**, *232*, 263–271.
47. Park, D.; Wu, W.; Wang, Y. A functionalizable reverse thermal gel based on a polyurethane/PEG block copolymer. *Biomaterials* **2011**, *32*, 777–786.
48. Martin, A.H.; Nieuwland, M.; de Jong, G.A.H. Characterization of heat-set gels from RuBisCO in comparison to those from other proteins. *J. Agric. Food Chem.* **2014**, *62*, 10783–10791. [CrossRef]
49. Liu, Z.; Ren, X.; Cheng, Y.; Zhao, G.; Zhou, Y. Gelation mechanism of alkali induced heat-set konjac glucomannan gel. *Trends Food Sci. Technol.* **2021**, *116*, 244–254. [CrossRef]
50. Bhattacharjee, S.; Maitia, B.; Bhattacharya, S. First report of charge-transfer induced heat-set hydrogel. Structural insights and remarkable properties. *Nanoscale* **2016**, *8*, 11224–11233. [CrossRef]
51. Zhou, J.-L.; Chen, X.-J.; Zheng, Y.-S. Heat-set gels and egg-like vesicles using two component gel system based on chiral calix [4]arenes. *Chem. Commun.* **2007**, *48*, 5200–5202. [CrossRef]
52. Sahoo, P.; Chakraborty, I.; Dastidar, P. Reverse thermal gelation of aromatic solvents by a series of easily accessible organic salt based gelators. *Soft Matter* **2012**, *8*, 2595–2598. [CrossRef]
53. Sahoo, P. Designing Heat-Set Gels for Crystallizing APIs at Different Temperatures: A Crystal Engineering Approach. *Chem. Eng.* **2022**, *6*, 65. [CrossRef]

54. Chevigny, R.; Rahkola, H.; Sitsanidis, E.D.; Korhonen, E.; Hiscock, J.R.; Pettersson, M.; Nissinen, M. Solvent-Induced Transient Self-Assembly of Peptide Gels: Gelator–Solvent Reactions and Material Properties Correlation. *Chem. Mater.* **2024**, *36*, 407–416. [CrossRef]
55. Phaechamud, T.; Mahadlek, J. Solvent exchange-induced in situ forming gel comprising ethyl cellulose-antimicrobial drugs. *Int. J. Pharm.* **2015**, *494*, 381–392. [CrossRef] [PubMed]
56. Jing, P.; Yan, J.; Cai, X.; Liu, J.; Hu, B.L.; Fang, Y. Solvent-induced molecular gel formation at room temperature and the preparation of related gel-emulsions. *Sci. China Chem.* **2013**, *56*, 982–991. [CrossRef]
57. Shi, Z.; Hao, L.; Zhang, M.; Dang, L.; Wei, H. Gel formation and transformation of Moxidectin during the anti-solvent crystallization. *J. Cryst. Growth* **2017**, *469*, 8–12. [CrossRef]
58. Misra, S.; Singh, P.; Das, A.; Brandão, P.; Sahoo, P.; Sepay, N.; Bhattacharjee, G.; Datta, P.; Mahapatra, A.K.; Satpati, B.; et al. Supramolecular assemblies of a 1,8-naphthalimide conjugate and its aggregation-induced emission property. *Mater. Adv.* **2020**, *1*, 3532–3538. [CrossRef]
59. Devi, V.K.A.; Shyam, R.; Palaniappan, A.; Jaiswal, A.K.; Oh, T.-H.; Nathanael, A.J. Self-Healing Hydrogels: Preparation, Mechanism and Advancement in Biomedical Applications. *Polymers* **2021**, *13*, 3782. [CrossRef]
60. Rumon, M.M.H.; Akib, A.A.; Sultana, F.; Moniruzzaman, M.; Niloy, M.S.; Shakil, M.S.; Roy, C.K. Self-Healing Hydrogels: Development, Biomedical Applications, and Challenges. *Polymers* **2022**, *14*, 4539. [CrossRef]
61. Karvinen, J.; Kellomäki, M. Characterization of self-healing hydrogels for biomedical applications. *Eur. Polym. J.* **2022**, *181*, 111641. [CrossRef]
62. Liu, Y.; Hsu, S.-h. Synthesis and Biomedical Applications of Self-healing Hydrogels. *Front. Chem.* **2018**, *6*, 449. [CrossRef]
63. Xu, J.; Hsu, S. Self-healing hydrogel as an injectable implant: Translation in brain diseases. *J. Biomed. Sci.* **2023**, *30*, 43. [CrossRef] [PubMed]
64. Zhu, W.; Zhang, J.; Wei, Z.; Zhang, B.; Weng, X. Advances and Progress in Self-Healing Hydrogel and Its Application in Regenerative Medicine. *Materials* **2023**, *16*, 1215. [CrossRef] [PubMed]
65. Bertsch, P.; Diba, M.; Mooney, D.J.; Leeuwenburgh, S.C.G. Self-Healing Injectable Hydrogels for Tissue Regeneration. *Chem. Rev.* **2023**, *123*, 834–873. [CrossRef]
66. Quan, L.; Xin, Y.; Wu, X.; Ao, Q. Mechanism of Self-Healing Hydrogels and Application in Tissue Engineering. *Polymers* **2022**, *14*, 2184. [CrossRef]
67. Wang, X.; Zhang, H.J.; Yang, Y.; Chen, Y.; Zhu, X.; You, X. Biopolymer-based self-healing hydrogels: A short review. *Giant* **2023**, *16*, 100188. [CrossRef]
68. Cui, H.; Cui, B.; Chen, H.; Geng, X.; Geng, X.; Li, Z.; Cao, S.; Shen, J.; Li, J. A chitosan-based self-healing hydrogel for accelerating infected wound healing. *Biomater. Sci.* **2023**, *11*, 4226–4237. [CrossRef]
69. Dastidar, P. Supramolecular gelling agents: Can they be designed? *Chem. Soc. Rev.* **2008**, *37*, 2699–2715. [CrossRef]
70. Dastidar, P.; Roy, R.; Parveen, R.; Sarkar, K. Supramolecular Synthon Approach in Designing Molecular Gels for Advanced Therapeutics. *Adv. Ther.* **2019**, *2*, 1800061. [CrossRef]
71. Dastidar, P. Designing Supramolecular Gelators: Challenges, Frustrations, and Hopes. *Gels* **2019**, *5*, 15. [CrossRef]
72. Mondal, T.; Chatterjee, A.; Hansda, B.; Mondal, B.; Sen, P.; Banerjee, A. Cationic and amphiphilic Peptide-Based Hydrogels with Dual Activities as Anticancer and Antibacterial Agents. *Soft Matter* **2024**, *20*, 1236–1244. [CrossRef]
73. Nanda, J.; Kuila, S.; Reddy, K.P.; Dasgupta, S.; Bera, A.; Mukherjee, M.; Pramanik, G.; Datta, P. Supramolecular J-and H-aggregation of Napthalimide-conjugated Dipeptide in Mixed-solvent Systems and Its Application in Cell Imaging. *Chem. Asian J.* **2024**, e202400755. [CrossRef] [PubMed]
74. Nichol, G.S.; Clegg, W. The Importance of Weak C–H···O Bonds and π···π Stacking Interactions in the Formation of Organic 1,8-Bis(dimethylamino)naphthalene Complexes with Z′> 1. *Cryst. Growth Des.* **2006**, *6*, 451–460. [CrossRef]
75. Berger, G.; Frangville, P.; Meyer, F. Halogen bonding for molecular recognition: New developments in materials and biological sciences. *Chem. Commun.* **2020**, *56*, 4970–4981. [CrossRef] [PubMed]
76. Saccone, M.; Catalano, L. Halogen Bonding beyond Crystals in Materials Science. *J. Phys. Chem. B* **2019**, *123*, 9281–9290. [CrossRef]
77. Frangville, P.; Tanwar, A.S.; Kumar, S.; Gelbcke, M.; Wauthoz, N.; Basov, S.; Bael, M.J.V.; Hecke, K.V.; Meyer, F. Sensing diversity in halogen-bonded multi-stimuli responsive materials: Light, pH, magnetism, and electron-rich species. *Mater. Today Chem.* **2024**, *40*, 102234. [CrossRef]
78. Kumar, S.; Body, C.; Leyssens, T.; Hecke, K.V.; Berger, G.; Van der Lee, A.; Laurencin, D.; Richeter, S.; Clément, S.; Meyer, F. Halogen-Bonded Thiophene Derivatives Prepared by Solution and/or Mechanochemical Synthesis. Evidence of N···S Chalcogen Bonds in Homo- and Cocrystals. *Cryst. Growth Des.* **2023**, *23*, 2442–2454. [CrossRef]
79. Syme, C.; Mosses, J.; González-Jiménez, M.; Shebanova, O.; Walton, F.; Wynne, K. Frustration of crystallisation by a liquid–crystal phase. *Sci. Rep.* **2017**, *7*, 42439. [CrossRef]
80. Luboradzki, R.; Gronwald, O.; Ikeda, I.; Shinkai, S.; Reinhoudt, D.N. An Attempt to Predict the Gelation Ability of Hydrogen-bond-based Gelators Utilizing a Glycoside Library. *Tetrahedron* **2000**, *56*, 9595–9599. [CrossRef]
81. Das, U.K.; Banerjee, S.; Dastidar, P. Primary Ammonium Monocarboxylate Synthon in Designing Supramolecular Gels: A New Series of Chiral Low-Molecular-Weight Gelators Derived from Simple Organic Salts that are Capable of Generating and Stabilizing Gold Nanoparticles. *Chem. Asian J.* **2013**, *8*, 3022–3031. [CrossRef]

82. Das, U.K.; Dastidar, P. Extending Primary Ammonium Dicarboxylate (PAD) to Diprimary Ammonium Dicarboxylate (DPAD) Synthon and Its Implication in Supramolecular Gelation. *Cryst. Growth Des.* **2013**, *13*, 4559–4570. [CrossRef]
83. Roy, R.; Adalder, T.K.; Dastidar, P. Supramolecular Gels Derived from the Salts of Variously Substituted Phenylacetic Acid and Dicyclohexylamine: Design, Synthesis, Structures, and Dye Adsorption. *Chem. Asian J.* **2018**, *13*, 552–559. [CrossRef] [PubMed]
84. Adalder, T.K.; Dastidar, P. The role of secondary ammonium cations in controlling the conformation of C3-symmetric acid moieties and its implication for the design of supramolecular capsules. *CrystEngComm* **2014**, *16*, 4867–4876. [CrossRef]
85. Yin, Z.; Wan, S.; Yang, J.; Kurmoo, M.; Zeng, M.-H. Recent advances in post-synthetic modification of metal–organic frameworks: New types and tandem reactions. *Coord. Chem. Rev.* **2019**, *378*, 500–512. [CrossRef]
86. Sahoo, P.; Tan, J.; Zhang, Z.-M.; Singh, S.K.; Lu, T.-B. Engineering Surface Structure of Binary/Ternary Ferrite nanoparticles as High Performance Electrocatalysts for Oxygen Evolution Reaction. *ChemCatChem* **2018**, *10*, 1075–1083. [CrossRef]
87. Chakraborty, I.; Guo, Z.; Bandyopadhyay, A.; Sahoo, P. Physical Modifications and Algorithmic Predictions behind Further Advancing Two-dimensional Water Splitting Photocatalyst: An Overview. *Eng. Sci.* **2022**, *20*, 34–46.
88. Wuttke, S.; Braig, S.; Preiß, T.; Zimpel, A.; Sicklinger, J.; Bellomo, C.; Rädlerc, J.O.; Vollmar, A.M.; Bein, T. MOF nanoparticles coated by lipid bilayers and their uptake by cancer cells. *Chem. Commun.* **2015**, *51*, 15752–15755. [CrossRef]
89. Kim, R.; Ryu, U.; Jee, S.; Choi, K.M. Surface coating of MOF layers on the nanocrystals of other MOFs using nanoparticle mediated nucleation for the efficient removal of formaldehyde. *Appl. Surf. Sci.* **2020**, *505*, 144612. [CrossRef]
90. Du, J.; Jia, T.; Li, F.; Li, Y.; Wang, Q.; He, L.; Ågren, H.; Chen, G. MOF-Coated Upconversion Nanoparticle Agents Enable Synergistic Photodynamic Therapy and Immunotherapy. *Adv. Funct. Mater.* **2024**, *34*, 2401272. [CrossRef]
91. Ghosh, S.; Dutta, M.; Ray, K.; Fujita, D.; Bandyopadhyay, A. A simultaneous one pot synthesis of two fractal structures via swapping two fractal reaction kinetic states. *Phys. Chem. Chem. Phys.* **2016**, *18*, 14772–14775. [CrossRef]
92. Hartman, R.L.; McMullen, J.P.; Jensen, K.F. Deciding whether to go with the flow: Evaluating the merits of flow reactors for synthesis. *Angew. Chem. Int. Ed.* **2011**, *50*, 7502–7519. [CrossRef]
93. Sagmeister, P.; Lebl, R.; Castillo, I.; Rehrl, J.; Kruisz, J.; Sipek, M.; Horn, M.; Sacher, S.; Cantillo, D.; Williams, J.D.; et al. Advanced Real-Time Process Analytics for Multistep Synthesis in Continuous Flow. *Angew. Chem. Int. Ed.* **2021**, *60*, 8139–8148. [CrossRef] [PubMed]
94. Britton, J.; Raston, C.L. Multi-step continuous-flow synthesis. *Chem. Soc. Rev.* **2017**, *46*, 1250–1271. [CrossRef] [PubMed]
95. Tsubogo, T.; Oyamada, H.; Kobayashi, S. Multistep continuous-flow synthesis of (R)- and (S)-rolipram using heterogeneous catalysts. *Nature* **2015**, *520*, 329–332. [CrossRef] [PubMed]
96. Alzard, R.H.; Alsaedi, S.; Alseiari, S.; Aljasmi, S.; El-Maghraby, H.F.; Poulose, V.; Hassan, A.; Kamel, M.; Ali, A.; Abdel-Hafiez, M.; et al. Heterogeneous Acetalization of Benzaldehyde over Lanthanide Oxalate Metal–Organic Frameworks. *ACS Omega* **2024**, *9*, 37386–37395. [CrossRef]
97. Dueñas-Díez, M.; Pérez-Mercader, J. Native Chemical Computation. A Generic Application of Oscillating Chemistry Illustrated with the Belousov-Zhabotinsky Reaction. A Review. *Front. Chem.* **2021**, *9*, 611120. [CrossRef]
98. Parrilla-Gutierrez, J.M.; Sharma, A.; Tsuda, S.; Cooper, G.J.T.; Aragon-Camarasa, G.; Donkers, K.; Cronin, L. A programmable chemical computer with memory and pattern recognition. *Nat. Commun.* **2020**, *11*, 1442. [CrossRef]