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Designing Supramolecular Pheromone Containers by Crystal Engineering for Replacing Pesticides

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Abstract

Our experience with supramolecular synthons in the design of functional materials such as supramolecular gel, Metal-organic framework, and pharmaceutical cocrystal categories prompted us to broaden the concept in developing a series of supramolecular sex pheromone containers to attract and trap pests. We proposed some basic criteria for building a series of supramolecular containers based on our earlier research on the supramolecular mechanism, reaction kinetics, and the principles of pheromone container design. If the pKa value was lowered, the proton displacement from acid to amine would be smaller, resulting in a weaker cocrystal system. A higher pKa value will eliminate the lability. The salts can be made labile in presence of moisture with the pKa value difference between a pheromone and its co-former around 3.5. The Pheromone container can be placed inside a physical trap to kill the pest physically. When pheromones will be released from the trap, the brain's olfactory circuits are tricked into believing the presence of their opposite-sex inside the trap and will be captured finally. This study addresses the design principles of both -COOH and -NH2 based pheromones in order to develop a decisive solution to the pesticide replacement dilemma.

Keywords: Supramolecular container; Moisture-catalyzed pheromone release; Supramolecular Synthon; Pest.
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1. Introduction

Is it always necessary to use pesticides to safeguard the greens? Poisonous chemical-based pesticides are classified as insecticides, rodenticides, *etc*., based on their intended use. By murdering insectivorous species, including birds, we jeopardize various fatal diseases such as cancer,[1] neurological disorder,[2] Parkinson's Disease,[3] and infertility.[4] We also jeopardize the food pyramid by killing insectivorous animals, including birds.[5] The presence of chlorinated insecticides in a straw-fed cow is also lethal to several species, including South Asian and African vultures.[6] Genetic engineering of crops to prevent pests may not always be hygienic or safe for human consumption.[7] Slow release of sex pheromone to trap pests could be an alternative method of trapping pests without damaging nature. A pheromone is a chemical signal used in species communication emitted by one organism to modulate the physical or psychological state of a second creature.[8] Several sensory inputs, including hearing, vision, touch, taste, and smell, can regulate the behaviour of animals ranging from insects to rodents. The specialized neuronal circuits of a brain can be engaged and controlled externally via these inputs. External diffusion pheromones can influence the limbic systems of the brain, which coordinate endocrine and behavioural responses by taking over the neuronal olfactory circuits.[9] Hydrogels are extensively employed in the human body for the spatial and temporal release of various pharmacological compounds.[10,11] Similarly, silica gel[12] or supramolecular gel[13,14] aerosol[15] are used to control the release of a pheromone. The main disadvantage of the pheromone released from the gel medium is that complete release of the pheromone from the gel is not achievable since some quantity remains in the gel phase. To avoid such pheromone waste, several weak interactions, such as the *Van-der-Waals* interaction, have lately been investigated to slowly release pheromone.[16] *Tuta absoluta*, male pinworm pests emit (E, Z)-3,8-tetradecadienyl acetate and (E, Z, Z)-3,8,11-tetradecatrienyl acetate to attract female pests. The

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pheromones are gently released into the environment by intercalating them inside graphene oxide and amine-modified graphene oxide. The amine functionality is expected to help the acetate functionality form hydrogen bonds. Long-chain organic compounds are less volatile than short-chain organic compounds; therefore, they can be released from compact devices. The rubber dispensers can trap male phycitid moths, *Ephestia kuehniella*, by releasing (*Z*)-9, (*E*)-12-tetradecadienyl acetate.[17] Codling moth, *Cydia pomonella,* is a pome fruit pest that can be treated using vial-based dispensers releasing *E, E*-8,10-dodecadien-1-ol 6.7–33.4 µg wk^{-1}.[18] However, very volatile tiny pheromone molecules evaporate quickly, thus a slow-release is required to reduce waste. Inadequate *Van-der-Waals* contact might prevent tiny pheromone molecules from being released from graphene-based dispensers.

To address all issues, a crystal engineering technique could be used for gently releasing significant sex pheromone[19] to trap the pest without hurting our surroundings. When the difference in pKa between the acid and amine reaches 3.5, the salt becomes labile. In this instance, the proton over the ammonium ion drifts towards the carboxylic acid, and the salt decomposes into acid and amine.[20,21] Proton drifting is accelerated in the presence of protic solvents. On the other hand, crystallisation energy stabilises the salt state after the crystal structure is formed.[22] An additional molecular length in the carboxylic acid part may be necessary for creating the supramolecular channel for inviting the water molecules inside the crystal structure to make the hydrogen-bonded interaction between carboxylate and the ammonium part available for the protic solvent molecules.[23] The proton from the ammonium component drifts towards carboxylate in the presence of a water molecule, allowing the volatile amine part to release a pheromone. The methylated amino acid esters of valine- (pKa: 7.95), leucine- (pKa: 7.95), isoleucine- (pKa: 7.98) are volatile in nature. Besides the suitable molecular length in cinnamic acid analogues, the pKa value of benzoic acid (4.20), O-methyl Benzoic acid (3.91), m-methyl Benzoic acid (4.27), p-methyl Benzoic acid (4.38) are also lower in comparison to the Cinnamic acid (4.44), O-methyl cinnamic acid (4.50), m-methyl cinnamic acid (4.44) and p-methyl cinnamic acid (4.56), which make the benzoic salts quite stable underwater (ΔpKa> 3.5).

Depending on the pheromone structure, several organic salts produce supramolecular synthons, notably Primary Ammonium Monocarboxylate (PAM),[19] Primary Ammonium Dicarboxylate (PAD),[24-26] Secondary Ammonium Monocarboxylate (SAM),[27] Secondary Ammonium Dicarboxylate (SAD),[28] might be explored. A sequence of similar cinnamic acid can be combined with the volatile amino acid methyl ester (pheromone) to make PAM synthon using such a labile pKa value and the proposed supramolecular channel. The steady release of such amine will attract the corresponding *Phyllophaga* pests without harming the ecosystem. As shown in Fig. 1, after reacting with carboxylic acid, the primary amine group-containing pheromones create Primary Ammonium Monocarboxylate (PAM), which acts as a supramolecular carrier of *Phyllophaga* species sex pheromones.[9] The pheromone container salt is kept inside the physical trap and slowly releases the pheromone in the presence of moisture to capture the phyllophaga male pests.[23]

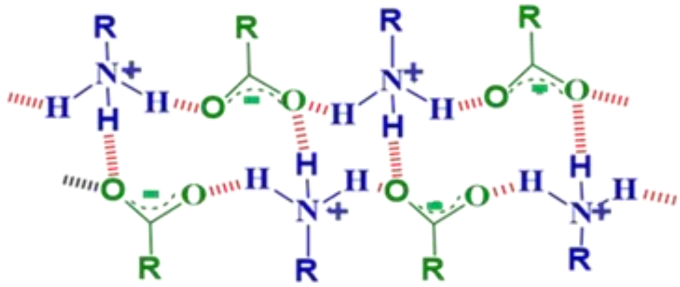

Fig. 1 PAM synthon for designing supramolecular container of pheromone.

2. Pheromone releasing mechanism.

All of the salts prepared in the amino acid ester cinnamate[19] combinatorial library release pheromone; however, only valine methyl ester p-methyl cinnamate was employed to demonstrate the salt breakdown mechanism. The MMFF94 optimization of the proton transfer mechanism revealed that (Fig. 2a), the water molecule first passes to the supramolecular channel, and a proton from ammonium functionality is vibrationally stretched to 1.75Å at step 1. The proton is migrated to the water molecule in the second stage, generating an H_3O^+ ion with an O-H bond (1.75 Å). The amine molecule is liberated from its cinnamate homologue in step 3. The proton linked to the water oxygen is routed linearly to the carboxylate oxygen at step 4 and then extends to 1.20 Å at step 5. Finally, the proton is transferred to the carboxylate in the sixth step to form the carboxylic acid and free up water for the next reaction. Fig. 2b depicts a schematic representation of the entire proton shifting mechanism. To validate the existence and worthiness of the supramolecular channel in the solid form, it was first essential to crystallize some tiny molecules inside it. Unfortunately, the water molecules cannot be crystallized since they will promptly release the amine, preventing crystal formation. The hexane solution's $CHCl_3$ molecules (in green, space fill model) only crystallized after a long trial, demonstrating a supramolecular channel in the crystal structure (Fig. 2c). However, the valine methyl ester cinnamate showed no supramolecular channel once the additional molecular length was reduced.[19] The supramolecular channel has the benefit that once a water molecule is in it, it will constantly breakdown the salt. However, the supramolecular channel is not essential for pheromone release from the pheromone container

3. Study of the kinetics and rate law of release of sex pheromone

The decomposition of PAM salts is said to be 1st order in the presence of moisture and slowly release pheromones into the environment.[19] The release rate of the pheromone is one of the most important parameters as it determines the amount of salt that needs to be ingested for a given period of time to trap the pests. The charge gated H-bonding assisted labile salt slowly releases the volatile amine (pheromone) moiety to the environment. While gravimetric analysis can determine the rate, NMR spectroscopy can be used for more accuracy. During pheromone release, the acid:amine ratio is changed, which can be monitored by ^{1}H NMR spectroscopy. The ratio of the methyl protons of the methylated ester and the methyl groups on the acid moiety determines the rate of release.

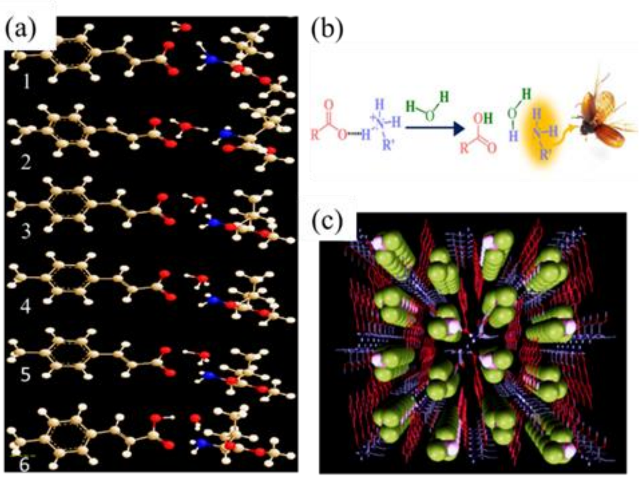

Fig. 2 Molecular mechanism of amine release. (a) MMFF94 optimization showed the proton shifting from ammonium to carboxylate part by the water molecule step by step. In step 1, the water molecule approaches the ammonium carboxylate bonding. In step 2, it takes a proton from the ammonium part to leave amine at the pheromone part and it becomes the hydronium ion. At the 3rd, 4th and 5th part, it carries the proton to carboxylate moiety. Finally, in the 6th step, it provides protons to carboxylate to generate the COOH group and hydronium becomes a water molecule. (b) A schematic presentation of moisture-catalyzed pheromone release to invite the *Phyllophaga* male pests. (c) Supramolecular channel, filled by $CHCl_3$ molecules inside the supramolecular container of the sex pheromone.

When a supramolecular container, valine methyl ester p-methylcinnamate salt, was exposed to air, it released pheromones that could be detected by IR and NMR spectroscopy. When the time-dependent IR (Fig. 3a) was compared, it was discovered that a strong peak at 1746 cm^{-1} was gradually diminished, indicating that the COOMe is slowly leaching from the salt. The shifting of the carboxylate peak from 1640 cm^{-1} to 1680 cm^{-1} suggests that the carboxylate slowly produces carboxylic acid. The NMR experiment (Fig. 3b) was then repeated to assess the rate of release. The p-methyl group of the acid is at δ2.37ppm as a singlet, and the pheromone (valine methyl ester) is at δ3.74ppm as a singlet (Fig. 3c). Following the first-order reaction rate, the amount of protons from the methyl group of valine methyl ester was gradually lowered against the 3 protons of p-methyl cinnamate over time (Fig. 3d). It demonstrates that PAM synthons can be employed to create a pheromone container for future applications when the pheromones have either amine or carboxylic acid functions.

4. Crystal engineering in designing a new pheromone container.

Supramolecular synthons are robust enough to predict the crystal structure of the PAM salts. Thus, by exploiting the PAM synthon, the pheromones with $-NH_2$ and –COOH functionalities will crystallize from the appropriate solvents using functionality-based co-formers.[29] As the primary target is to make the PAM salts labile, the ΔpKa values between the acids and amines should be ~3.5. If the value becomes considerably higher, the resultant salts cannot disintegrate in the protic solvent, and the supramolecular container cannot be designed. However, the lower ΔpKa value would not allow the proton to get shifted from carboxylic acid to amine group completely, and such a situation will promote the co-crystal formation. In such cases, the co-crystal based on weak hydrogen bonds quickly decomposes and does not serve the purpose of designing a well-engineered pheromone container. Besides long chain and functional groups like –OH, aldehyde, epoxy, ester, Me, many pheromones contain $-NH_2$ and –COOH functional groups. The pheromone container can be designed separately according to the acid or amine groups. Importantly, the conformer should be eco-friendly so that it should not leave any environmental hazards in the farming fields.

4.1 Designing of carboxylic acid containing supramolecular container

Carboxylic acid groups are advantageous since they can all be utilised to build PAM synthon-based supramolecular containers. Multiple COOH group-containing pheromones can be processed for the formation of the supramolecular container by selecting some primary non-volatile amines as co-formers with appropriate pKa values. A species of beetle commonly known as cowpea (*Callosobruchus maculatus*) can be treated with the PAM salts of some suitable amines and the synthetic pheromones such as (E)-3-methyl-2-heptenoic acid, (E)-3-methyl - 3-heptanoic acid, (Z)-3-methyl-3-heptanoic acid, (Z)-3-methyl-2-heptanoic acid 3-methyleneheptanoic acid.[30] *Callosobruchus analis* is another beetle that emits (Z)-3-methyl-2-heptenoic acid as a sex pheromone and can be treated with PAM salts.

Other insects, such as the wood-eating termite *Reticulitermes speratus*, produce a variety of pheromones at their nests. The -COOH-based pheromones detected in the bioassays after gas chromatography and mass spectrometry are trans-vaccinic acid and palmitic acid.[31] A key condition in the design of the pheromone container is that the co-forming amines be non-volatile. Small amine molecules emit a strong odour, which interferes with the scent of acid-based pheromones. As a result, the short amine, which emits the

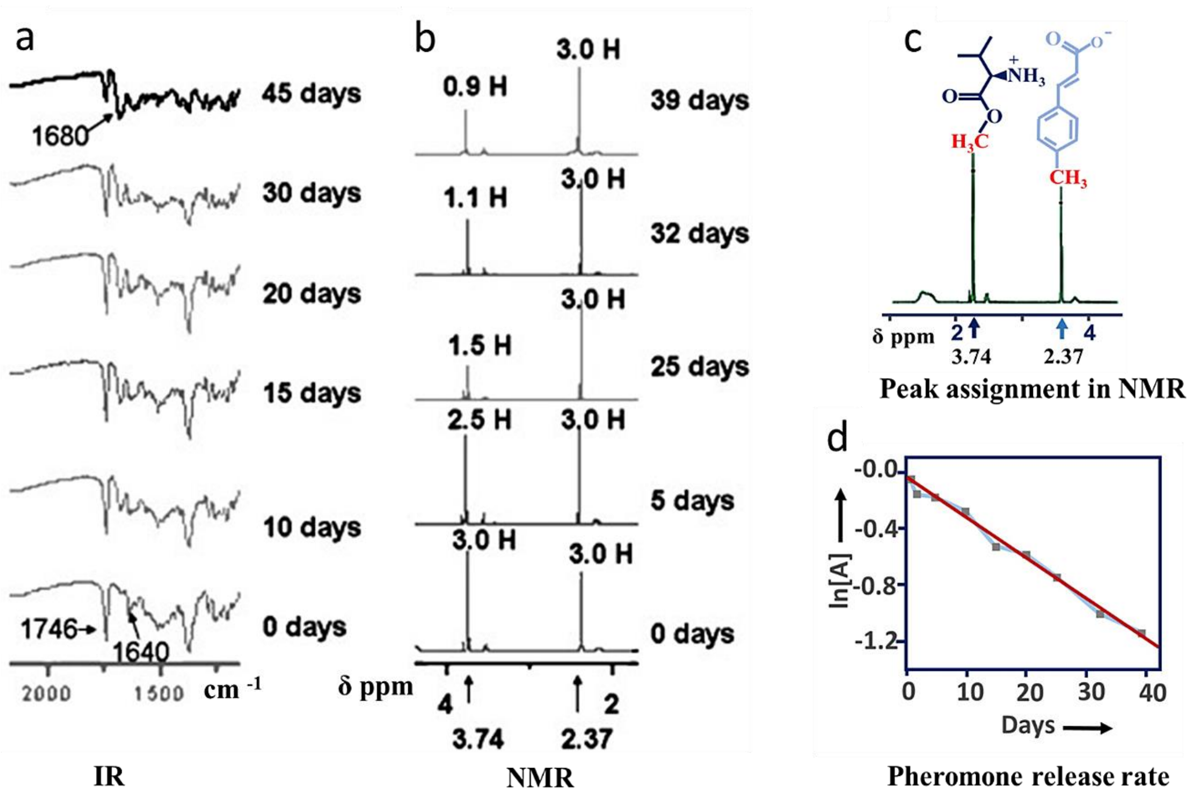

Fig. 3 Moisture Catalyzed pheromone release from supramolecular container. (a) A time depending IR monitoring shows the release of valine methyl ester (1746 cm^{-1}) in the environment and the formation of carboxylic acid (1680 cm^{-1}) from the carboxylate (1640 cm^{-1}). (b) The amount of methyl protons of valine methyl ester slowly goes away with respect to the 3 methyl protons of the p-methyl cinnamic acid. The peaks are assigned in Fig 3(c). (c) The methyl peaks of the ammonium and the carboxylate parts of the newly synthesized salt appeared at $\delta = 3.74$ ppm and 2.37ppm, respectively. (d) 1st order release of a sex pheromone from the supramolecular container.

disagreeable amine odour, should not be employed as a co-former in supramolecular pheromone container building.

4.2 Designing of amine containing supramolecular container

Other $-NH_2$ based pheromones of significant pests can be used to build the supramolecular container of pheromones, in addition to our previously reported amino acid methyl ester pheromones *Phyllophaga* species.[19,23] The german cockroach *Blattella germanica* (L.) can be trapped using 1-dimethylamino-2-methyl-2 propanol. Although it is a tertiary amine, the ΔpKa should be kept at 3.5 to derive a salt.[32] Following the discovery of pheromones as sexual attractants in insect species, it has been found in a variety of creatures ranging from vertebrates to ciliates.[9] Mice are a common bothersome and harmful vertebrate that pheromones can also control. They not only damage the clothes and papers, but the major threat also comes from their transmitted viruses and bacteria to spread fatal diseases. People utilize rodenticides or food-driven physical traps to control such pests. However, a sex pheromone-based trap maybe a preferable option in this scenario.[33]

Urine-derived compounds can activate[9] two G protein-coupled receptors (GPCRs) in olfactory neurons, the odorant receptors (ORs),[34] and trace amine-associated receptors (TAARs).[35] Male mice excrete several chemicals that are particularly appealing to female mice, including trimethylamine, thiol (methylthio)-methylthiol, tetradecen-1-ol, 2-(sec-butyl)-dihydrothiazole, dehydro-exo-brevicomin, farnesene, and darcin.[36-40] In fact, both males and females, release several amine-based pheromones such as amphetamine (primary amine); β-Phenylethylamine (primary amine), cinnamamide (-CO-NH_2), diaminopropane (primary amine); Diethylamine (secondary amine), dimethylamine (secondary amine), isobutyl amine (primary amine), trimethylamine (tertiary amine), which can be used for the pheromone container.[41] All primary amine-containing pheromones can be derived from PAM salts, but the secondary, tertiary amines can be exploited to derive secondary ammonium carboxylate,[27] a synthon-based supramolecular container. In this case, the ΔpKa value should always be kept around 3.5, and for that purpose, the carboxylic acids should be used as co-formers. Electro-negative groups like F, Cl, and OH can be utilized in acid backbones to reduce the pKa value of the acid. Similarly, functional groups with +I effects can be utilized to increase the pKa value.

4.3 Designing other functional groups containing

supramolecular container

As water can disintegrate the salts only around ΔpKa = 3.5, and can not disintegrate other materials, thus, we can not use other synthons for water. However, if we use long-chain based pheromone, then we can use graphene surface for exploiting *Van-der-Waals* interaction to seize the pheromone over the surface. This can be released into the atmosphere slowly, where temperature can accelerate the release rate. The metal-organic frameworks with suitable porosity can also be tried to absorb and release pheromones for trapping the pests.

4.4 Storing the pheromone container

The supramolecular salts with volatile amine/acid can be released easily in the presence of trace amount of moisture. To protect the salts from disentrigation, the compound should be kept in a closed container at -5 °C under nitrogen atmosphere.

4.5 Expected outcomes

The merits of crystal engineering will be investigated here to develop a supramolecular sex pheromone container that will trap pests without damaging nature. The major sex pheromones of various insects such as beetles, cockroaches, and termites (to replace insecticides) and rodents such as mice and rats (to replace rodenticides) can be employed to construct the supramolecular container of sex pheromones to physically confine them. To prevent the animal kingdom from losing its biodiversity, pheromone-releasing devices can be used to substitute the severe usage of toxic substances such as insecticides and rodenticides. The pheromone container's release rate and active periods can be calculated via a kinetic analysis, allowing the correct amount of supramolecular container to be employed for certain pests to be determined. The completion of such an endeavour would aid in the production of green vegetables, promoting human health, and preserving biodiversity.

5. Introducing environment-friendly species

If we prepare a pheromone container for environmentally friendly species, such as bees or other animals, we can use it to invite them to a specific area for inhabitation, pollination or for beautification of the place. They can start living once they like the place. Pollination in apple gardens is a significant issue for apple farmers. They frequently need to add a swarm of bees to the apple trees. Pollination would be easier by keeping the pheromone container of bees in the apple tree. Pheromone containers can also be used for gardening or bringing certain animals to tourist spots.

6. Significance of pheromone container

Though duck, chicken, and geese are used in controlling pests, the major concern in pest management is, that the farmer needs to cultivate a huge number of insectivorous animals.[42,43] It would be a burden for the farmers, and thus they may not get interested in employing birds. Besides, birds may also consume a certain amount of grain. In case the outbreak of certain pests occurs, the limited amount of insectivorous animals can not control the situation and the use of easily available pesticides would be unavoidable.[44] For controlling insects, a wide range of bacteria or viruses might be employed, but once it shows some unpredicted activities would be harmful to health and biodiversity.[45,46] In addition, the toxins are not very selective always for using them as pesticides and as a result, some synergistic insects can be damaged.[47] Often the production cost would be much higher than the pheromone containers. As the insects release very particular pheromones, after synthesizing the pheromones chemically if they can be released slowly from a physical trap to capture the pests. And if we use the crystal engineering approach for developing the pheromone container, a no different insect will be killed as pheromones are target specific. This can be used only in need, like ducks or other insectivorous animals, it won't damage the crops. Pheromone containers are also very environment-friendly chemicals, which can be developed very comfortably with the proposed principles here. It won't need huge investments like producing bio-toxins or massive farms for cultivating ducks. The disadvantage of pheromone containers is that it is difficult to synthesize all types of pheromones in chemical labs, and crystal engineering will not be able to construct pheromone containers for all insects (Fig. 4). These pheromone containers would release corresponding pheromones in presence of naturally abundant moisture (heterogeneous catalyst[48]) and will introduce environment-friendly chemical technology[49] to the farmers. Though the supramolecular container remains in solid state, we never need solid-state NMR[50] for monitoring pheromone release.

7. Conclusion and perspective

Pesticides are extremely harmful to the human body and can create several acute to chronic diseases like cancer, neuro disorders, breathing trouble, and asthma. Thus alternatives to pesticides should be the prime concern for protecting the green. In case pest attack becomes inevitable and alternative remedy is not available to farmers, they will use pesticides. Without proper national policies, awareness could not be generated in farmers. In such cases, the pesticide removal process should be used at the earliest. There are plenty of options for replacing the pesticides from the market and remedies for removing the used pesticides from the environment. Several kinds of bacteria based toxins, genetically modified bacteria, different viruses, spider venoms, insectivorous animals, *etc*., can be explored in replacing pesticides from farmers' hands. All the processes have several advantages and disadvantages as described briefly above. In the case of the crystal engineering approach in developing pheromone containers, the process is cheap, less time consuming, environment friendly, and innocent for non-targeting species, but can not be designed for all the pheromones.

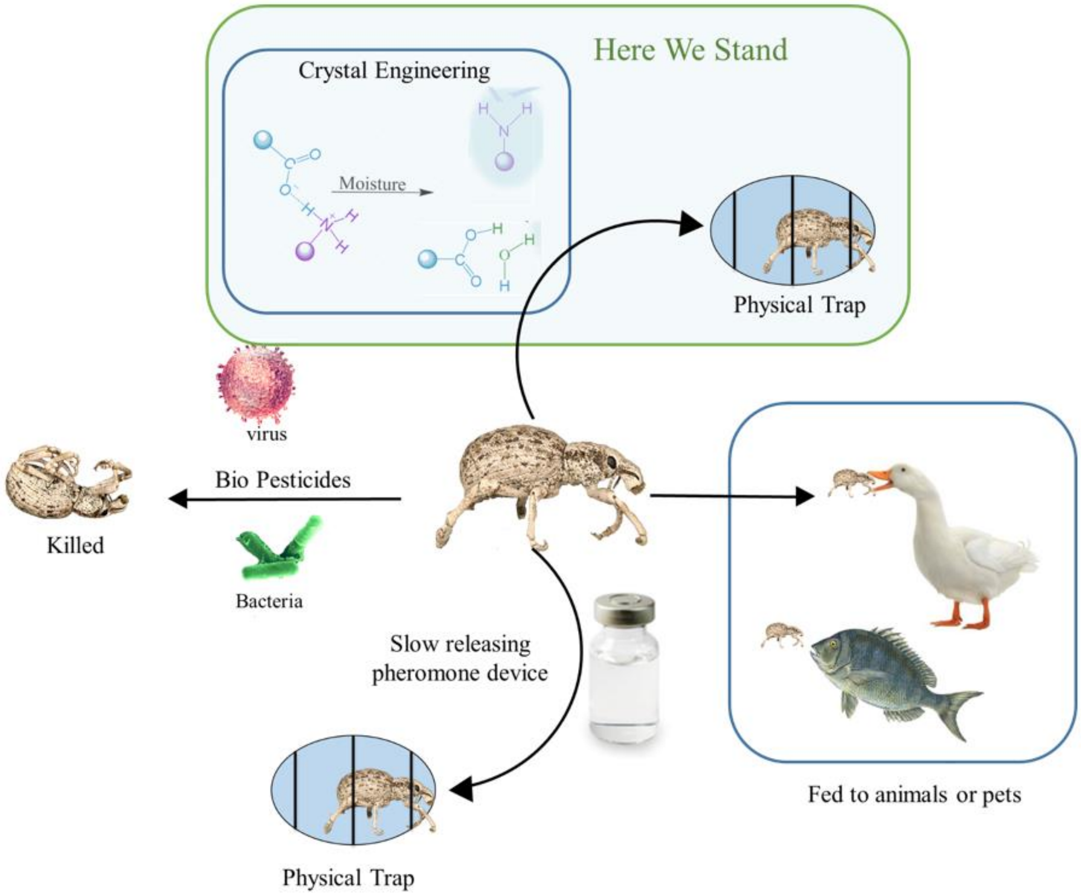

Fig. 4 Killing insects by different bio friendly methods. (Left) Killing pests by bacteria or virus. (Bottom) Attracting pests by slow releasing pheromone through various pheromone container. (Right) Feeding insects to different animals or pets. (Top) We propose pheromone realizing supramolecular device to trap the pest very selectively.

Following the application of crystal engineering knowledge in the design of metal-organic framework[51] supramolecular gel,[22,28] pharmaceutical cocrystals,[29] piezoelectric materials,[52] the application of crystal engineering in the replacement of pesticides and rodenticides is proposed for the first time here. According to the fundamental concepts proposed here, carboxylic acid and amine-based pheromones can be kept in the supramolecular container by building the pheromone container. Primary Ammonium Monocarboxylate (PAM) salts have already been shown to be potentially appropriate for creating supramolecular pheromone containers. Secondary and tertiary amine-based pheromones, on the other hand, can be created for Secondary Ammonium Monocarboxylate or Tertiary Ammonium Monocarboxylate synthons. In all circumstances, the pKa value should be kept around 3.5 to make the supramolecular salts labile for disintegration under moisture. Furthermore, the supramolecular channel for inviting the moisture molecules can be established by intruding on the minor structural variation of the co-formers. Beetles and mice, like many other pests, can be physically trapped by externally providing chemical signals to manipulate their olfactory signals while envisioning their opposite sex. The adverse use of pesticides and rodenticides can be controlled. Using this simple crystal engineering approach, we may substitute insecticides (for beetles, cockroaches, termites, and other insects) and rodenticides (for mice, rats, and other rodents) with supramolecular sex pheromone containers placed in physical traps. Such a simple strategy will protect biodiversity and human health from toxic pesticides.

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Conflict of Interest
The authors declare no conflict of interest.

Supporting information
Not applicable.

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