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Inverse Correlation between Lethality and Thermodynamic Stability of Contact Insecticide Polymorphs

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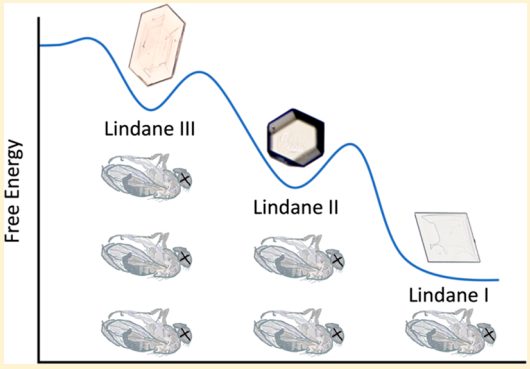
Supporting Information

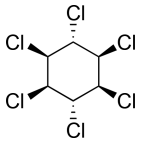
ABSTRACT: Contact insecticides often involve the interaction of whole organisms and toxicant crystal surfaces. The crystalline phase of these compounds has not, however, been considered for the optimization of insecticide performance. Lindane (1*R*,2*r*,3*S*,4*R*,5*r*,6*S*-hexachlorocyclohexane) has been one of the most widely used insecticides, but other (inactive) stereoisomers accompanying its manufacture have led to massive chemical waste remediation problems. Crystalline polymorphs are also isomers in the broadest sense, yet only one crystal structure of lindane has been reported. Herein, we report the discovery and characterization of two new polymorphs, Forms II and III. The efficacy of Forms I, II, and III against *Drosophila melanogaster* revealed an inverse correlation between lethality and thermodynamic stability; the least stable kills fastest. This understanding provides a crystal engineering opportunity wherein formulations containing the most active contact insecticide polymorph can achieve infectious disease prophylaxis while reducing environmental exposure and associated chemical waste.



INTRODUCTION

DDT, among other organochlorine compounds, ushered in the heyday of synthetic chemical insecticides in the 1940s. Many of these compounds work when whole organisms contact toxicant crystal surfaces through their body or feet. Consequently, the activity of these so-called contact insecticides will depend upon the crystallographic interface, which in turn is determined by the crystalline phase, yet research into the crystallography of contact insecticides was nonexistent until our recent work on DDT (1,1′-(2,2,2-trichloroethane-1,1-diyl)bis(4-chlorobenzene) CAS #50−29−3), a notorious compound of the last century.[1] A new metastable polymorph of DDT was found to be more lethal to *Drosophila melanogaster* (also known as fruit flies) than the well-known stable form, suggesting polymorph-dependent lethality. The observation that the least stable polymorph killed fastest is perhaps intuitive, but a claim to generality requires evidence of generality. If this observation can be generalized, then controlling bioavailability through the use of more active polymorphs would represent a strategy for increasing the effectiveness of a given insecticide, enabling reduced amounts for protection against a disease-carrying organism while minimizing environmental impact.[2] The lethality difference of DDT polymorphs, however, was limited to two forms of a single compound, mitigating any claim of causality. Herein, we demonstrate an inverse relationship between lethality and thermodynamic stability of three crystalline polymorphs of the insecticide lindane (Scheme 1, 1*R*,2*r*,3*S*,4*R*,5*r*,6*S*-hexachlorocyclohexane; γ-hexachlorocyclohexane; CAS #58−89−9), thereby generalizing our earlier observation.

Scheme 1. Lindane (1*R*,2*r*,3*S*,4*R*,5*r*,6*S*-Hexachlorocyclohexane)



There are particular issues of remediation of chlorocarbons associated with the manufacture of lindane. Hexachlorocyclohexanes (HCHs) were first produced by chlorination of benzene in sunlight by Faraday in 1825.[3,4] Lindane, first isolated from HCH in 1912,[5] typically constitutes 12% of the stereoisomer mixture, but it is the only insecticide among eight separable stereoisomers, whereas the α- and β-isomers (1*R*,2*R*,3*R*,4*R*,5*S*,6*S*-hexachlorocyclohexane, CAS# 319−84−6, and 1*r*,2*r*,3*r*,4*r*,5*r*,6*r*-hexachlorocyclohexane, CAS# 319−85−7, respectively) are more toxic to mammals.[6−8] As much as 700 000 tons of lindane were used worldwide as a broad spectrum pesticide between 1950 and 2000.[9,10] This was

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accompanied by at least 5 million tons of waste hexachlorocyclohexane isomers now scattered in mountainous dumps throughout the world.[11] Therefore, lindane has been banned for agricultural use under the 2009 Stockholm Convention on Persistent Organic Pollutants.[12] The International HCH and Pesticides Association was formed to remediate the hexachlorocyclohexane waste. While we would not advocate for the reinstatement of lindane, it seems reasonable to suggest that a more active form of lindane would have reduced the amount manufactured, with the associated reduction of waste and environmental impact. As such, lindane illustrates potential benefits of using metastable forms of contact insecticides[13] for public health applications.

RESULTS AND DISCUSSION

Crystal Structures. Despite the widespread study of lindane, only one crystal structure was reported in the Cambridge Structural Database, which we designate as Form I (CSD refcode: HCCYHG).[14,15] As revealed by Raman microscopy and single crystal X-ray diffraction, only lindane Form I crystals were grown by slow evaporation in 20 mL glass vials from a variety of solvents, including hexane, chloroform, acetone, ethanol, acetic acid, ethyl acetate, dichloromethane, and methyl propionate. The crystal structure was redetermined at 100 K (Table S1; $P2_1/n$, $Z = 4$, $Z' = 1$, $a = 8.4517(7)$ Å, $b = 10.1057(9)$ Å, $c = 11.8297(10)$ Å, $\beta = 96.0256(11)°$, $V = 1004.80(15)$ Å^3, V_{mol} =251.2 Å^3) (Figure 1D).

In contrast, a rapidly evaporating droplet of ethanol supersaturated with lindane afforded three distinct crystal morphologies on glass surfaces (Figures 1A–C and S1), each with a unique Raman spectrum (Figure S2). The crystal habit of Form I is rhombic. Forms II and III crystallized as prisms and six-sided plates, respectively. Form II crystallized in the $Pca2_1$ space group, with $Z = 4$, $Z' = 1$, $a = 11.6535(10)$ Å, $b = 11.6657(10)$ Å, $c = 7.3579(6)$ Å, $V = 1000.28(15)$ Å^3, and $V_{mol} = 250.7$ Å^3 (Figure 1E). Form III crystallized in the $Pbca$ space group, with $Z = 8$, $Z' = 1$, $a = 11.217(3)$ Å, $b = 7.248(2)$ Å, $c = 24.978(7)$ Å, $V = 2030.8(10)$ Å^3, and $V_{mol} = 253.9$ Å^3 (Figure 1F). The density of the three forms decreases in the order Form II > Form I > Form III. In 1951, Kofler characterized the melt crystallization of lindane by hot stage microscopy, claiming three polymorphs, two monoclinic and one orthorhombic.[17] We observed two orthorhombic and one monoclinic. Our nomenclature associates forms with specific crystal structures to eliminate ambiguity. We are able to identify two additional forms of lindane (IV and V) with hot stage microscopy (Video S1). Kofler's assignments are correlated with our own in the Supporting Information.

Phase Behavior. Thermodynamic stability of polymorphs can be evaluated by phase transformation behaviors and respective melting points. Single crystals of Form II melt at 112.5–112.8 °C, essentially identical to that of Form I (112.7–113.0 °C). The similarity of melting points suggests a small free energy difference between Forms II and I at elevated temperatures. Single crystals of Form II transformed to Form I, which was identified by Raman spectroscopy. For example, at 75 °C a small crystal of Form I generated at the tip of a Form II prism consumed a 200 μm long crystal within five seconds (2400 μm/min) (Figure 2A and Video S2). Crystalline films of Form II, prepared by cooling a lindane melt between glass slides, also transformed to Form I. The rate was dependent on temperature; for example, at 40 °C, the transformation rate was ca. 2 μm/min (Video S3). At room temperature, the transformation was even slower (0.044 μm/min) as observed by atomic force microscopy (Video S4).

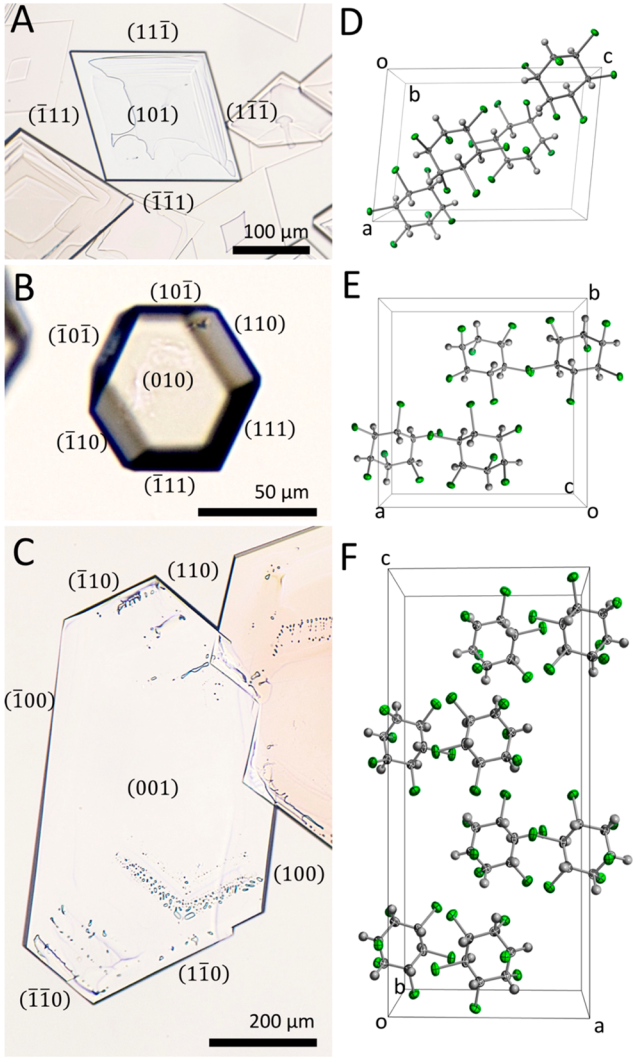

Figure 1. Lindane single crystals of Forms (A) I, (B) II, and (C) III grown concomitantly by rapid evaporation of 5 wt % ethanol solution, and single crystal structures of Forms (D) I, (E) II, and (F) III.[16]

Form III crystals transformed to Form I at ambient temperature when brought into contact with crystals of Form I. The optical transmittance, observed with a wave plate accessory, diminishes at the contacting interfaces, eventually spreading throughout the single crystals of III, clear evidence of changing refractivity and a phase transformation (Figure 2B, Video S5). The optical contrast revealed that the orientation of each new Form I domain was aligned with that of the contacting Form I crystal. The transformation rate at room temperature (53 μm/min) was 3 orders of magnitude faster than that of Form II to Form I (0.044 μm/min) at room temperature, suggesting that Form III may have a higher free energy than Form II.

The relative stability of Forms II and III were corroborated using single crystals sealed in UV curing epoxy to prevent seeding from adventitious Form I and to prevent sublimation. Such crystals remained in their original forms after storage for 13 months under ambient conditions (Figure S4). Apparently, Forms II and III were reasonably stable in an ambient environment in the absence of Form I. At 100 °C, however, a

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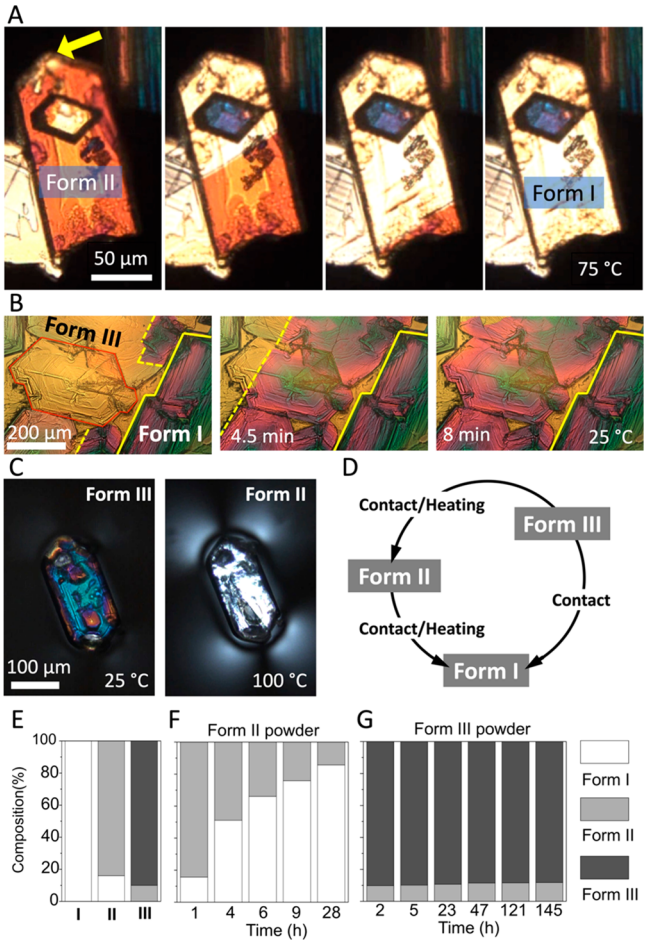

Figure 2. Phase transitions among lindane polymorphs. (A) Transformation of a crystal of Form II to Form I at 75 °C. Yellow arrow shows the small crystal of Form I generated at the tip of Form II crystal. (B) Transformation of a crystal of Form III to Form I at room temperature. (C) Transformation of a crystal of Form III to Form II at 100 °C. (D) Summary of phase transformations among lindane polymorphs. (E) Initial polymorph composition of lindane powders. (F) Time-dependent polymorph composition of Form II powder, which contains ca. 15% Form I. (G) Time-dependent polymorph composition of Form III powder, which contains ca. 10% Form II.

single crystal of Form III sealed in epoxy rapidly transformed to Form II (Figure 2C). These observations are consistent with a room temperature stability ranking I > II > III. Phase transformations among lindane polymorphs are summarized in Figure 2D.

Given that lindane was usually applied in powder form as an insecticide[18] and that particle size has been reported to affect contact insecticide toxicity,[19] it is important to evaluate the polymorph stability as powders with a comparable particle size (Figure S5). Commercial lindane is available as pure Form I powder. The powder sample of Form II, prepared by grinding a cooled melt of lindane, afforded 84% Form II and 16% Form I based on the quantitative X-ray analysis using the TOPAS software[20] (Figures 2E and S6). While standing at ambient conditions for 5 h, the XRD analysis revealed that the amount of Form II dropped from 84 to 35% as it transformed to I (Figures 2F and S7). The powder of Form III, prepared by adding water to an acetic acid solution of lindane (see the Supporting Information for more details), contains 90% Form III and 10% Form II (Figure 2E). Standing in air for 1 week, 2−3% Form III sample transformed to Form II (Figure 2G, S7). Transformation of Form III to Form II was observed in powders dominated by Form II at room temperature (Figure S8). These observations corroborated the relative room temperature stability ranking of the three phases, I > II > III.

Crystal Structure Prediction. Relative energies of Forms I−III at 0 K were evaluated using crystal structure prediction methods (CSP) based on an evolutionary algorithm, USPEX.[21,22] Searches were performed for the most frequent space groups (see the Supporting Information for more details). CHARMM[23] and DFTB+[24] codes were used for structure relaxations within USPEX.[22] The geometries of the 100 lowest energy structures were collected from successive runs and then reoptimized using the VASP code at the optB88 level,[25] as we had done previously for DDT.[1] According to the optB88 ranking, as illustrated in Figure 3 and Table S4, our

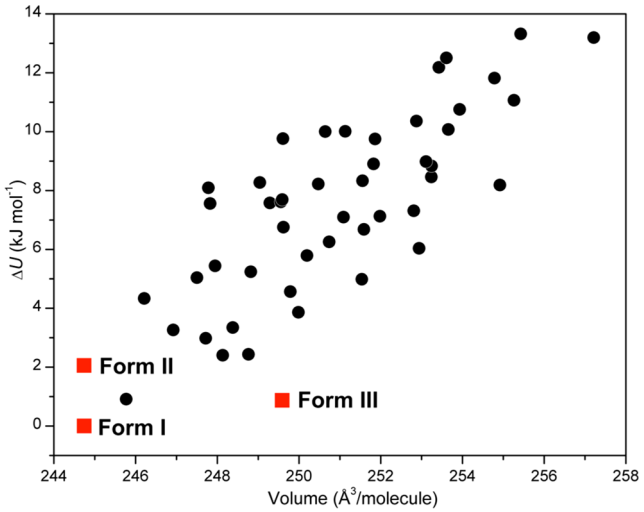

Figure 3. Lattice energy vs molecular volume for the 50 lowest energy crystal structures calculated for lindane at the optB88 level.[24] Red squares denote Forms I, II, and III.

CSP search found all three crystallographically characterized forms together with many other low-energy polymorphs within 10 kJ·mol^{-1} of the ground state (the CIF files of 50 lowest energy structures are provided in the Supporting Information). The predicted ground state of all structures computed has an RMSD = 0.173 Å for a 20-molecule supercell relative to a single crystal structure of Form I collected here at 100 K. Form II is ranked fourth, with a $RMSD_{20}$ = 0.077 Å. Structure 2 matches Form III with a $RMSD_{20}$ = 0.048 Å. Structures ranked 1 through 4 span only 2.1 kJ·mol^{-1}, less than kT at room temperature. Crystal structure prediction often yields more low-energy polymorphs than observed experimentally.[26] The predicted stability ranking (I > III > II) differs from the experimental observation (I > II> III) possibly a result of the finite temperature effect, as the DFT calculations were performed at 0 K. The choice of functional, basis set and dispersion correction model may also affect the energy ranking, as demonstrated recently for coumarin[27] and ROY.[28]

Polymorph Lethality. The lethality of all three forms of lindane were compared by exposing fruit flies (*Drosophila melanogaster*), good models for pesticide development,[29] to equal quantities of their respective powders dispersed evenly in 90 mm-diameter plastic Petri dishes (Video S6). The motions

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of each individual fly were monitored by a video camera. Lethality was deduced by the standard measurement of knockdown time,[30] defined as time required to immobilize a fly in a supine or sideways position for at least ten seconds. Paralyzed flies never recover. The median knockdown time (KT_{50}) for each polymorph was determined from multiple trials using 20 female flies each. KT_{50} is defined as the time required to render 50% of the insects motionless.[31,32]

The average knockdown times for 35 μg of Forms I, II, and III were 127, 82, and 42 min, respectively (Figure 4). The

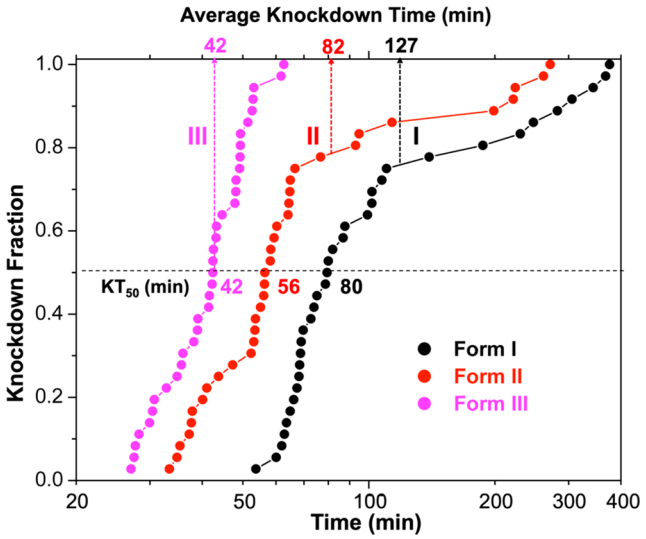

Figure 4. Comparison of *Drosophila melanogaster* knockdown times in 35 μg of Form I, II, and III powders. The corresponding average knockdown times and median knockdown times (KT_{50}) are denoted.

KT_{50} values were 80, 56, and 42 min, respectively (Figure 4). The onset of hyperactivity and the first death occurred earliest for flies exposed to Form III, followed by Form II and finally Form I (Video S6). A second trial, performed with the same protocol but more (100 μg) of Forms I, II, and III, afforded average knockdown times of 89, 47, and 34 min, KT_{50} of 46, 43, and 31 min, respectively (Figure S9).

These results demonstrated the lethality ranking of three ambient polymorphs of lindane, III > II > I. This ranking is the inverse of the thermodynamic stability ranking at room temperature. Given that some powders are contaminated by a less effective polymorph, i.e., Form III contains a small amount of Form II, and Form II contains some Form I, the disparity in knockdown times would only be larger if the powdered forms were pure.

Despite the extremely small energy differences among the three polymorphs (2.1 $kJ \cdot mol^{-1}$, Figure 3) and the metastability of Form III, the lethality of Form III powder, as measured by the average knockdown times and KT_{50} values, was clearly superior to that of Forms I and II. In both trials, while exposed to Form III, almost no fruit flies survive after 1 h; in contrast, with Form I, some live >5 h. Moreover, even 35 μg of Form III (KT_{50} = 42 min) is more effective than 100 μg of Form I (KT_{50} = 46 min, Figure S9), indicating that Form III is at least 3-fold more lethal than Form I.

Although the World Health Organization classifies lindane as a contact insecticide,[13] it is possible that insects also can be poisoned by the non-negligible vapor of lindane. Flies separated from the lindane particles by porous paper (Kimwipes) did indeed die, but much more slowly (Figure S10).

In our previous study of the polymorphism of DDT, we found that the metastable phase was more lethal than the one used in the field, which was thought previously to be the only crystal form.[1] The inverse correlation of the lethality of three forms of lindane with thermodynamic stability has a probability of 1 in 6. In the aggregate, the results for DDT and lindane have an 8% chance of being random (probability of lethality ranking of lindane III > II > I by chance × probability of lethality ranking of DDT II > I by chance), arguing for a general principle wherein the lethality of phases is inversely related to their thermodynamic stability. This rule can guide the crystal engineering of contact insecticides to improve lethality while minimizing environmental exposure by employing the most metastable crystals in the control of disease-carrying insect vectors.

CONCLUSION

The observations above have revealed two metastable polymorphs of lindane characterized by single crystal diffraction in addition to the previously reported Form I. The phase behavior and insect lethality assays for the three crystallographically characterized forms revealed an inverse relationship between the room temperature thermodynamic stability ranking and fruit fly lethality. Combined with prior observations for the two polymorphs of DDT, this supports our earlier conjecture that the lethality of contact insecticide polymorphs depends inversely on the order of their thermodynamic stability. Form III is the least thermodynamically stable form, but the most lethal.

Our results support the notion that lindane Form III would have provided greater protection against pests for a given application. Between 1950 and 2009, 700 000 tons of lindane were manufactured, but inefficiently: For each ton of lindane, 8−12 tons of ineffective HCH stereoisomers were produced that are more toxic to mammals than lindane and threaten the environment and human health. At least five million tons of waste HCH isomers have been stockpiled in nonsecure heaps throughout the world.[11] Imagine that in the last century, lindane had always been crystallized as the metastable Form III from acetic acid and water. Further imagine that Form III was not only long-lasting at ambient temperature but formulated in such a way that it remains indefinitely kinetically stable. Then, on the basis of the ratio of lethality for Forms I and III, lindane manufacture might have been reduced by at least two-thirds, with a corresponding reduction of HCH stereoisomer waste, as many as three million tons.

Unfortunately, the history of lindane cannot be rewritten, but chemical insecticides for infectious disease prophylaxis are here to stay for some time. Newer infectious diseases such as Zika continue to threaten and are likely to become more problematic with a warming climate. The development of pesticides with high efficacy and minimal health or environmental risks is a public health imperative,[33] but the development of new pesticides requires sustained efforts and resource mobilization.[34] Parasitologists focused on disease-carrying insect vectors emphasize that improvement of existing tools are needed, specifically, smarter ways to use existing insecticides.[35,36]

It now seems likely that the thermochemistry of polymorphs can contribute substantially in this regard. The results described herein suggest that engineering, discovering, and

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formulating new polymorphs of well-studied insecticides that are the least stable and most lethal may be an efficient and cost-effective way to achieve public health objectives with a smaller environmental footprint.

EXPERIMENTAL SECTION

Materials and Methods. Lindane was obtained from Sigma-Aldrich and used as supplied. ***Caution:*** *Lindane should be treated as a hazardous compound, may be toxic if swallowed or brought in contact with skin, is suspected of causing cancer, and may cause damage to organs through prolonged or repeated exposure if swallowed.*[37] *All safety conditions should be read and understood before handling.*

Raman spectra were recorded using a Raman microscope (DXR, Thermo Fisher Scientific, Waltham, MA) using a 532 nm excitation laser operating at 2 mW, with a 2 cm^{-1} resolution and slit width of 50 μm; hot stage was applied when temperature control is needed.

X-ray Powder Diffraction. X-ray microdiffraction (μ-XRD) was performed on a Bruker D8 Discover GADDS Microdiffractometer equipped with a VÅNTEC-2000 two-dimensional (2D) detector and a sealed Cu X-ray tube. Further details are given in the Supporting Information.

Single-Crystal Structure Determination. The X-ray intensity data of Forms I, II and III were recorded on a Bruker D8 APEX-II CCD system using graphite-monochromated and 0.5 mm MonoCap-collimated Mo Kα radiation (λ = 0.71073 Å) with the ω scan method at 100 K. The crystallographic information files (CIFs) including the HKL and RES data are deposited in the Cambridge Crystallographic Data Centre with Nos. 1874157 (I), 1874158 (II), and 1874159 (III). Further details are given in Supporting Information.

Preparation of Lindane Powders. Powdered Form I was produced by grinding the commercial lindane crystals (Sigma-Aldrich) with a mortar and pestle. Form II predominated when grown from the melt in a glass tube (NMR tube). Powdered Form II was prepared by grinding this material. Powdered Form III powder was obtained by rapidly injecting 1 mL of water in 3 mL of acetic acid solution containing 10% w/w lindane.

Lethality Assays. The effect of lindane polymorphs was determined by the residual exposure method.[38] Lethality assays were performed for each powder sample as well as control. Female fruit flies (*Drosophila melanogaster*) were temporarily anesthetized by CO_2 exposure, then transferred to the 90 mm diameter Petri dishes with lindane powder. The dishes were covered, and the motion of the fruit flies was recorded to establish knockdown time (that time after which there was no further translation). Further details are given in the Supporting Information.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.cgd.8b01800.

Photographs of crystals, crystal data, thermal displacement parameters, Raman spectra, particle sizes, polymorphic composition data, PXRD patterns, lowest energy structures, transformation of crystals, atomic force microscopy, effect of lindane powders on fruit flies, experimental details (PDF)

Video S1: reversible transformation between lindane II and lindane IV during one heating/cooling cycle (MPG)

Video S2: transformation of lindane II single crystal to lindane I after heating (MPG)

Video S3: transformation of lindane II crystalline film to lindane I after heating at 40 °C (MPG)

Video S4. atomic force microscopy video of the Form II to Form I phase transition measured at 25 °C (MPG)

Video S5: transformation of lindane III single crystal to lindane I at room temperature (MPG)

Video S6: fruit fly exposure to lindane polymorphs (forms I, II, and III) (MPG)

Accession Codes

CCDC 1874157−1874159 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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ABBREVIATIONS

DDT, Dichlorodiphenyltrichloroethane; HCH, hexachlorocyclohexane; CSD, Cambridge Structural Database

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