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Theoretical studies of interactions in cyprodinil–α-cyclodextrin and cyprodinil–β-cyclodextrin systems

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Abstract: The paper presents the results of theoretical calculations in terms of the G4MP2 composite method for cyprodinil–α-cyclodextrin (C^0@α-CD) and cyprodinil–β-cyclodextrin (C^0@β-CD) systems. Studies also covered analogous systems consisting of the anion (C^-) and the cation (C^+) of cyprodinil. The geometries of the cyprodinil molecule and ions were optimized on the basis of the DFT theory, using hybrid (B3LYP, PBE0), pure (B97-D) and "meta" (M06-2X) GGA functionals for selected Pople basis sets [6-311++G(d,p), 6-311++G(2d,p), 6-311++G(2d,2p)] and Dunning basis set (aug-cc-pVDZ). The research results suggest that the affinity of "guest" molecules for "hosts" is relatively low. Theoretical studies of the "guest-host" systems allow to predict the properties of the designed preparations.

Keywords: α-cyclodextrin, β-cyclodextrin, cyprodinil, hydrogen bonds, inclusion complexes, theoretical calculations

INTRODUCTION

Pesticides are one of the main pillars of modern agriculture, improving quality and increasing yields. However, their use is associated with the risk of adverse ecological effects, the mechanisms and consequences of which are not fully understood. One of the reasons for the negative impact on flora and fauna is the fact that it remains in the environment for a long time, also in its original form, which results in the loss of biodiversity in ecosystems (Richardson *et al.*, 2019).

Cyprodinil is a systemic broad-spectrum fungicide. It is used to protect wheat and rye against brittleness (*Oculimacula yallundae*) (Babij *et al.*, 2000; Leroux *et al.*, 2013; Pieczul and Korbas, 2014), apple trees before scab (*Venturia inaequalis*) (Fiaccadori, 2018; Hirayama, 2022; Köller *et al.*, 2005), as well as in viticulture (*Botrytis*) (Avenot *et al.*, 2018; Fernández-Ortuño, Chen and Schnabel, 2013; Sholberg, Bedford and Stokes, 2003). It is believed to act as an inhibitor of methionine biosynthesis and disrupts the life cycle by inhibiting mycelial growth.

The brittleness of the stalk of cereals is a disease that causes serious economic losses. Protection of winter cereals against this disease is ensured by fungicides classified as derivatives of, inter alia, pyrimidines. However, the problem is the intensive and long-term use of fungicides containing the same active substances, since this leads to the production of resistant strains of fungi. On the basis of the research carried out in Poland on the assessment of the degree of resistance of *O. acuformis* and *O. yallundae* isolates to fungicides used in the protection of cereals against stalk brittleness, it has been shown that the substances that well limit the growth of fungal isolates on the PDA medium (Potato Dextrose Agar) include, next to cyprodinil, also tebuconazole, krezoxym methyl, and fenpropimorph. It should be emphasised that better effectiveness in this regard was proven for boscalid, prochloraz, pyraclostrobin, epoxiconazole, and flusilazole (Pieczul, Korbas, 2014).

Pioneering field research on cyprodinil was carried out, among others, in Great Britain, where pathogens causing brittle cereal stalks (*Tapesia yallundae* and *T. acuformis*) were isolated. Both sites used cyprodinil, prochloraz, and a mixture of these compounds twice a year, with one site exposed to cyprodinil for 3 years and the other for a total of 11 years, including 5 years prior to the start of the experiment. It was found that during the first 3 years of research, the protection efficiency provided by pure substances and their mixture ranged from 43% to 82%. Extending the use for a further 3 years further decreased the number of new cases, but no practical resistance was found. On

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this basis, it can be concluded that factors other than expected are responsible for the lack of complete immunity. In general, field isolates of both strains with reduced susceptibility to cyprodinil were found mainly in plots where it had been applied in the preceding 6-year period for 2 years, and in the last year in the mixed plots population. No clear trends could be identified from these studies, although *in vivo* studies have shown that control of most sensitive isolates can be regained by increasing the dose to one tenth of the recommended field dose. Analysis of sex crosses between a susceptible isolate and a field isolate with an ED50 (median exposure dose) value greater than the baseline range of susceptibility showed that a single gene controlled the reduction in susceptibility to cyprodinil in one *Tapesia yallundae* isolate. This suggests that there is a clear risk of resistance to cyprodinil. The reduction in susceptibility is monogenic in inheritance and to a significant level in some isolates, with any change in sensitivity in field populations so far has been gradual (Babij *et al.*, 2000).

In the studies of Leroux *et al.* (2013), apart from cyprodinil, anti-microtubule fungicides (benzimidazole derivatives), sterol demethylation or succinate dehydrogenase inhibitors, and metrafenone were used. They are in line with the work carried out since the 1980s in France, aimed at monitoring changes in the sensitivity of fungi that make cereal stalks brittle to fungicides. The use of benzimidazole derivatives for this purpose has become ineffective since the nineties due to immunisation. In the case of substances from the triazole group it is generalised, while resistance to prothioconazole has not yet developed. The resistance to prochloraz has gradually evolved in *O. acuformis* and *O. yallundae*, and has been confirmed in the years of the reported research as well-established. Specific resistance to cyprodinil has also been detected, but its frequency remains generally low. Finally, several strains of *O. yallundae* exhibiting multi-drug resistance have been detected since the beginning of the 21st century. These strains show a low level of resistance to, inter alia, prothioconazole and boscalid.

The efficacy of cyprodinil against the sensitivity of *V. inaequalis* isolates was determined for nine populations by measuring the growth of colonies formed from germinating conidia derived from single scab lesions. At the differential dose of pyrimethanil (0.2 $\mu g \cdot cm^{-3}$), the mean relative range of height measured for the eight populations of *V. inaequalis* (n = 39–74) never treated with fungicides ranged from 18.1 to 48.2, which translates into about a six-fold difference in mean basal sensitivity. For all 469 isolates tested, sensitivities to pyrimethanil and myclobutanil were significantly correlated. When isolates were organised into subpopulations based on their sensitivity to a single fungicide, the sensitivity to both fungicides decreased in parallel in very and moderately sensitive subpopulations, but differed for isolates in the subpopulations least sensitive to either fungicide. The result suggested that at least one of the many genes conferring resistance against the pathogen in question also decreased susceptibility to aniline-pyrimidine fungicides. The relative contribution of this group of fungicides to the control of scab was assessed in an experimental orchard from the Great Lakes region in the United States. The prevalence of resistant *V. inaequalis* isolates gave way to practically resistant, and the sensitivity to pyrimethanil was similar to that of several commercial fruit populations that had never been treated with aniline-pyrimidine fungicides. Notably, in the field management programs (1996–2000) of cyprodinil and pyrimethanil, the control of fruit scab and terminal leaf was worse than with non-specific protective measures such as mancozeb or captan. The effectiveness of the aniline-pyrimidine fungicides in controlling scab on grape leaves was equal to that of the non-specific protective agents. This effect can be explained by the lack of prolonged keeping of low temperature, which in previous studies favoured the efficiency of aniline-pyrimidine fungicides in northern Europe, as well as the reduced sensitivity to fungicides of this population group of *V. inaequalis* (Köller, Wilcox and Parker, 2005).

The sensitivity of *V. inaequalis* to aniline-pyrimidine fungicides (pyrimethanil and cyprodinil) was tested on apple populations treated with this group in a variety of ways – from those grown in areas never exposed to fungicides, to fruit from orchards protected with aniline-pyrimidines fungicides to populations derived from the experimental centre. *In vitro* susceptibility tests were performed on monoconidial isolates, while *in vivo* tests with therapeutic or preventive use were performed on populations inoculated on apple seedlings. In the field, apple infestation was assessed as the severity of leaf attack. The results showed that the *in vitro* susceptibility to pyrimethanil and cyprodinil showed a progressive lower reduction from wild-type to well-controlled, ending up in poorly controlled populations. In *in vivo* tests, the same moderate (wide-ranging) decrease in sensitivity and activity was more pronounced with therapeutic and prophylactic applications, as was also seen with difenoconazole. In field studies, populations heavily treated with aniline-pyrimidine compounds showed a decrease in control after several years, which was confirmed in the following years. These decreases in activity were less marked compared to those shown by strobilurins, both in field and *in vitro* tests (Fiaccadori, 2018).

In the control of apple scab caused by *V. inaequalis*, fungicides that inhibit the growth of fungal pathogens in the initial stages of infection are important management tools. In 2019–2021, biological tests assessing the therapeutic effect of fungicides commonly used to control apple scab showed that cyprodinil – along with six other fungicides – had a protective effect against *V. inaequalis*, although it did not show the highest effectiveness (Hirayama, 2022).

Botrytis cinerea causes gray mold disease and can infect the fruit of important crops such as grapes, pistachios, and pomegranates, causing significant crop losses worldwide. In one of the recent studies on protection against the indicated fungi, *in vitro* mycelium growth tests were used to evaluate the sensitivity of 160 individual *B. cinerea* isolates harvested from California-based commercial grape fields (n = 58), pistachios (n = 74), and pomegranates (n = 28) to cyprodinil, fludioxonil, and iprodione. Based on the effective concentration at which mycelium growth was inhibited by 50% (EC_{50}), 100%, 83%, and 38% of the isolates, respectively, were sensitive (EC_{50} < 1 $\mu g \cdot cm^{-3}$) to fludioxonil, cyprodinil, and iprodione. Low, weak or high resistance to cyprodinil was shown by 13%, 3%, and 1% of the isolates, respectively. No cross-resistance was observed between cyprodinil, iprodione, and fludioxonil (Avenot *et al.*, 2018).

Chemical protection of strawberry crops against gray mold caused by *B. cinerea* is essential to prevent fruit spoilage before and after harvest. The cyprodinil and fludioxonil available for many years in the United States are used for this purpose. Both active ingredients are specific inhibitors. In the reported study, 217 single-spore *B. cinerea* isolates from 11 commercial strawberry fields in North and South Carolina were analysed

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for their sensitivity to both fungicides. Isolates that were susceptible (53%), moderately resistant (30%) or resistant (17%) to cyprodinil were identified on the basis of embryo tubular inhibition at different doses of cyprodinil (1 mg·dm^{-3} and 25 mg·dm^{-3}) in 10 out of 11 locations. None of the isolates were resistant to fludioxonil. The phenotypes that were moderately resistant or resistant to cyprodinil were not affected by mycelial growth rate, spore production, or osmotic sensitivity. The detached fruit tests showed cross resistance between cyprodinil and pyrimethanil, and that isolates that were characterised *in vitro* as moderately resistant or resistant were equivalent in pathogenicity on pyrimethanil sprayed fruit. This suggests that the *in vitro* distinction between moderately resistant and resistant isolates is of little or no importance in the field (Fernández-Ortuño, Chen and Schnabel, 2013).

Scab and gray mold in apple trees are the most damaging diseases caused by *B. cinerea*. Despite many years of research into combating them, there is a lack of effective fungicides. Cyprodinil is a potentially good crop protection substance. The mean EC_{50} value of cyprodinil for 32 *Botrytis spp.* isolates was estimated to be 0.02 μg·cm^{-3}, indicating that apple isolates are generally very sensitive. Some of the isolates (19%) were less sensitive and had EC_{50} values greater than 0.03 μg·cm^{-3}, and one isolate from the 'Gala' cultivar was clearly less sensitive (0.095 μg·cm^{-3}). Historically, spraying of cyprodinil alone (1998–1999), possibly in combination with myclobutanil or metiram (1998), reduced the amount of infection of developing fruit by *Botrytis spp.* post-harvest use of cyprodinil (1998) showed that it protected apples against gray mold for 3 months. Cyprodinil applied up to 3 weeks before harvest (1999) reduced the lesion area by 68% and 62% for the cultivars 'Jonagold' and 'Gala', respectively, which were injured and inoculated with *B. cinerea* after storage at 1°C for a period of 6 months. In similar studies on 'Gala' apples (2000–2001), pre-harvest cyprodinil application consistently reduced the occurrence of gray mold and the diameter of lesions on inoculated apples stored for six months (Sholberg, Bedford and Stokes, 2003).

The common feature of most pesticides is their strongly hydrophobic nature, which in the context of counteracting the effects of uncontrolled leakage into the environment translates into the need to select soil reclamation methods based on the formation of inclusion complexes. Despite the profile of the properties of cyclodextrins in terms of the formation of macrocyclic systems, documented by many years of research, the beginning of their wide use to obtain compounds with pesticides dates back to the beginning of this century (Dodziuk, 2002a; Dodziuk, 2006). Molecular systems often used as "hosts" are cyclodextrins, which results from their biological neutrality, specific structure and availability (Dodziuk, 2002a; Dodziuk, 2002b; Verstichel *et al.*, 2004; Dodziuk, 2006), while both native cyclodextrins (Dodziuk, 2002a; Dodziuk, 2006) as well as various derivatives (Lipták *et al.*, 2002), including methyl (Petrović *et al.*, 2013), hydroxypropyl (Galian, Bracamonte and Veglia, 2005; Benfeito *et al.*, 2013; Fernandes *et al.*, 2014; Huang *et al.*, 2014), acetyl (Cassano *et al.*, 2013), amine (Iványi *et al.*, 2004) and sulfobutyl (Yañez, Araya and Bollo, 2010). Successful attempts were made to obtain combinations of them with a wide range of compounds ("guests") – drugs (Redenti, Szente and Szejtli, 2000), cosmetics (Rode *et al.*, 2003), food ingredients (Szente and Szejtli, 2004), odourants (Galian, Bracamonte and Veglia, 2005), dyes (Szejtli, 2003). The interest in creating compounds with these groups of chemical substances is focused on the use of cyclodextrins in the field of chromatography (Juvancz and Szejtli, 2002; Iványi *et al.*, 2004). Cyclodextrins play an important role in environmental protection (Landy *et al.*, 2012) and biotechnology (Singh, Sharma and Banerjee, 2002).

The use of cyclodextrins for the reversible binding of pesticides has been extensively studied, inter alia, for compounds of 2-amino-4-methyl-5-carboxyanilidotriazole (Cserhati *et al.*, 2002), 2-methyl-4-chlorophenoxyacetic acid (MCPA) (Garrido *et al.*, 2012), 2-phenylphenol (Lezcano *et al.*, 2003; Cassano *et al.*, 2013), 2,4-dichlorophenoxyacetic acid (2,4-D) (Pereira *et al.*, 2016), 8-hydroxyquinoline (Lezcano *et al.*, 2003), acetamiprid (Alonso *et al.*, 2014; Liu *et al.*, 2017), acifluorfen (Cserhati *et al.*, 2002), alpha-cypermethrin (Alonso *et al.*, 2014), azoxystrobin (Yang *et al.*, 2015), benalaxyl (Lezcano *et al.*, 2003), bendiocarb (Alonso *et al.*, 2014), benoxacor (Cserhati *et al.*, 2002), bentazone (Yañez, Araya and Bollo, 2010), bioallethrin (Hebeish *et al.*, 2014), bitertanol (Wu, Lee and Li, 2001), bromuconazole (Crini *et al.*, 2017), carbendazim (Lezcano *et al.*, 2002), chlorothalonil (Yang *et al.*, 2015), chlorpropham (Ge *et al.*, 2011; Huang *et al.*, 2014), chlorpyrifos (Coly and Aaron, 1998; Szente, 1998; Báez, Espinoza and Fuentes, 2018), chlorpyriphos-methyl (Vico *et al.*, 2009), ciprofuram (Cserhati *et al.*, 2002), clothianidin (Liu *et al.*, 2017), coumatetralyl (Coly and Aaron, 1998), cyfluthrin (Alonso *et al.*, 2014), cypermethrin (Lu *et al.*, 2015), cyproconazole (Wu, Lee and Li, 2001), cyprodinil (Yang *et al.*, 2015), deltamethrin (Alonso *et al.*, 2014; Coly and Aaron, 1998), diazinone (Báez, Espinoza and Fuentes, 2018), dicamba (Pereira *et al.*, 2016), dichlorvos (DDVP) (Szente, 1998), diclobutrazol (Cserhati *et al.*, 2002), difenoconazole (Wu, Lee and Li, 2001; Crini *et al.*, 2017), dimethoate (Petrović *et al.*, 2013), dimethomorph (Cserhati *et al.*, 2002), diniconazole (Wu, Lee and Li, 2001), dinotefuran (Liu *et al.*, 2017), dodemorph (Cserhati *et al.*, 2002), dodine (Cserhati *et al.*, 2002), epoxiconazole (Crini *et al.*, 2017), esbiothrin (Alonso *et al.*, 2014), fenitrothion (Coscarello *et al.*, 2009), fenvalerate (Coly and Aaron, 1998), flutriafol (Wu, Lee and Li, 2001), fuberidazole (Lezcano *et al.*, 2002), hexachlorocyclohexane (Ferino-Pérez *et al.*, 2019), hexaconazole (Wu, Lee and Li, 2001), imazalil (Cassano *et al.*, 2013), imidacloprid (Alonso *et al.*, 2014; Liu *et al.*, 2017), linuron (Petrović *et al.*, 2013), malathion (Szente, 1998), metconazole (Cserhati *et al.*, 2002), methyl parathion (Coscarello *et al.*, 2009), myclobutanil (Wu, Lee and Li, 2001), *N*-isoxazole-5-yl-*N*-(2,6-xylyl)-DL-alaninate (Cserhati *et al.*, 2002), nitenpyram (Liu *et al.*, 2017), oxadiargyl (Benfeito *et al.*, 2013), paclobutrazole (Wu, Lee and Li, 2001; Cserhati *et al.*, 2002), parathion (Coscarello *et al.*, 2009), penconazole (Wu, Lee and Li, 2001; Cserhati *et al.*, 2002), permethrin (Alonso *et al.*, 2014; Hebeish *et al.*, 2014; Lu *et al.*, 2015), phenothrin (Alonso *et al.*, 2014), pirimiphos-methyl (Coly and Aaron, 1998), pretilachlor (Cserhati *et al.*, 2002), prochloraz (Lezcano *et al.*, 2003), propiconazole (Crini *et al.*, 2017; Fifere *et al.*, 2012; Wu, Lee and Li, 2001), pyrimethanil (Fernandes *et al.*, 2014), pyriproxyfen (Gurarslan *et al.*, 2015), simazine (Petrović *et al.*, 2013), sulprofos (Szente, 1998), sumithion (Szente, 1998), tebuconazole (Wu, Lee and Li, 2001; Alonso *et al.*, 2014; Crini *et al.*, 2017), tetraconazole (Wu, Lee and Li, 2001), tetramethrin (Alonso *et al.*, 2014), thiabendazole (Lezcano *et al.*, 2002; Alexandrino *et al.*, 2013; Cassano *et al.*, 2013), thiacloprid (Alonso *et al.*, 2014; Liu *et al.*, 2017), thiamethoxam (Liu *et al.*,

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2017), thiophanate-methyl (Lezcano *et al.*, 2003), thiram (Cserhati *et al.*, 2002; Petrović *et al.*, 2013), triadimefon (Cserhati *et al.*, 2002; Wu, Lee and Li, 2001), triadimenol (Wu, Lee and Li, 2001; Cserhati *et al.*, 2002), tridemorph (Cserhati *et al.*, 2002), trifloxystrobin (Yang *et al.*, 2015), triflumizole (Köhler, Viernstein and Wolschann, 1996).

The above list of articles published in a wide range of years reflects the high interest in the multifaceted problem of the formation of macromolecular compounds by cyclodextrins. Studies of the physicochemical properties of pesticide inclusion complexes with cyclodextrins are widely carried out with the use of theoretical tools of various degrees of advancement (Dodziuk, 2002b; Coscarello *et al.*, 2009; Ge *et al.*, 2011; Alexandrino *et al.*, 2013; Lu *et al.*, 2015; Fifere *et al.*, 2012; Pereira *et al.*, 2016; Ferino-Pérez *et al.*, 2019), wherein molecular systems based on non-pesticide "guests" were also analysed (Lawtrakul, Inthajak and Toochinda, 2014). The paper of Dodziuk (2002b) discusses the scope of applicability of theoretical methods in the light of the dynamic nature of molecular skeletons of cyclodextrin molecules. The author, paying attention to the existence of numerous and close to each other energy minima for such relatively large systems, points to the inability to describe weak non-covalent interactions by means of calculations based on molecular mechanics and quantum (*ab initio*) calculations. Despite this fact, in older studies in the field of cyclodextrin compounds (also with pesticides) simulations were carried out in terms of molecular mechanics (MM2, MM+) (Coscarello *et al.*, 2009; Ge *et al.*, 2011), while semi-empirical methods (PM3, AM1) were used as a tool for preliminary (Ge *et al.*, 2011; Fifere *et al.*, 2012) or proper (Coscarello *et al.*, 2009; Alexandrino *et al.*, 2013; Ferino-Pérez *et al.*, 2019) optimisation of geometry. Newer and more advanced theoretical research on such systems are based on molecular dynamics simulations (Lu *et al.*, 2015), but its effectiveness cannot be considered universal and depends on the nature of the system under study (Pereira *et al.*, 2016), and DFT calculations (Fifere *et al.*, 2012; Alexandrino *et al.*, 2013; Pereira *et al.*, 2016; Ferino-Pérez *et al.*, 2019), also in the TD variant (Lu *et al.*, 2015), where the calculations that require significant expenditure (also trial calculations) are often performed at the semi-empirical level (PM3) (Fifere *et al.*, 2012; Alexandrino *et al.*, 2013; Ferino-Pérez *et al.*, 2019). Adopting the DFT formalism in combination with the SMD model leads to satisfactory results (Pereira *et al.*, 2016; Ferino-Pérez *et al.*, 2019).

Theoretical studies of the "guest-host" systems, including those composed of pesticides and cyclodextrins, allow to predict the properties of the designed preparations, because the interpretation of their results gives an insight into the mechanisms governing both the binding of components and the processes of disintegration of inclusion compounds, including their kinetics. It should be emphasised not only the fact of a very small amount of documented research on inclusion compounds of cyprodinil and cyclodextrins, but also the lack of studies on the interactions between the components of such potential molecular systems. This is surprising, for example, from the point of view of the multiplicity of applications of preparations based on cyprodinil in its pure form, i.e. not bound in a supramolecular complex.

Density functional theory is a pillar of a number of quantum-mechanical methods for modeling the structure of chemical molecules or crystals. These methods are an alternative to the wave function-based methods. The DFT theory is based on the Hohenberg–Kohn theorems, and its practical implementation is based on the Kohn–Sham method. On its basis, it is assumed that all properties of a quantum system in the stationary state result from the electron density of the ground state (more precisely: all observables are assumed to be unambiguous electron density functionals of the ground state).

B3LYP is an example of one of the most widely used hybrid functional in the DFT theory. Its designation is derived from the name of Becke, the creator of the functional "Becke 88", which was later modified by Lee, Yang and Parr (3 parameters of the generalised gradient approximation) (Hołaj-Krzak, 2021).

In this study, the usefulness of several DFT functionals (Hohenberg and Kohn, 1964; Kohn and Sham, 1965) – B3LYP (Becke, 1993; Becke, 1996; Becke, 1997), PBE0 (Adamo and Barone, 1999), M06-2X (Zhao and Truhlar, 2007), B97-D (Grimme, 2006) was checked – in connection with selected Pople-type basis sets (Ditchfield, Hehre and Pople, 1971; Hariharan and Pople, 1973) – 6-311++G(d,p), 6-311++G(2d,p), 6-311++G(2d,2p) – and Dunning-type basis set (aug-cc-pVDZ) (Dunning, 1989), to optimise the geometry of cyprodinil (C^0) molecules (Fig. 1a), its anion (C^-) – Figure 1b, and cation (C^+) – Figure 1c, as well as α-cyclodextrin (α-CD) molecules (Fig. 2a) and β-cyclodextrin (β-CD) (Fig. 2b). Calculations for model inclusion compounds (C^0@α-CD, C^-@α-CD, C^+@α-CD, C^0@β-CD, C^-@β-CD, C^+@β-CD) were performed using the G4MP2 method (Curtiss, Redfern and Raghavachari, 2007a; Curtiss, Redfern and Raghavachari, 2007b).

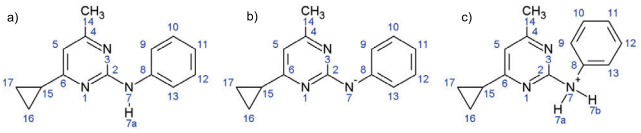

Fig. 1. Formulas of theoretically examined cyprodinil ionic forms (C): a) C^0, b) C^-, c) C^+; source: own elaboration

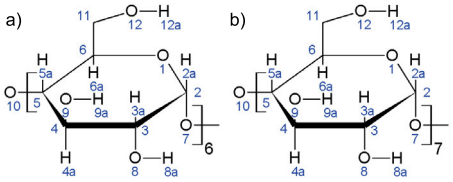

Fig. 2. Formulas of cyclodextrins (CD) used in the research: a) α-cyclodextrin, b) β-cyclodextrin; source: own elaboration

MATERIALS AND METHODS

ORIGIN AND PROCEEDING OF EMPIRICAL DATA OF CYPRODINIL

Initial geometry of the cyprodinil molecule, used for optimisation, was taken from the CCDC database (Fig. 3) (Jeon *et al.*, 2015). Selected empirical structural parameters (bond lengths, *R*; angles, *α*; dihedral angles, *β*) of the isolated cyprodinil molecules are given in Table S1 (available at: https://www.jwld.pl/files/Supplementary-material-Ho-aj-Krzak.pdf). Based on the crystallographic structure of the neutral form of cyprodinil, ionic structures were generated, which were then optimised according to the same scheme.

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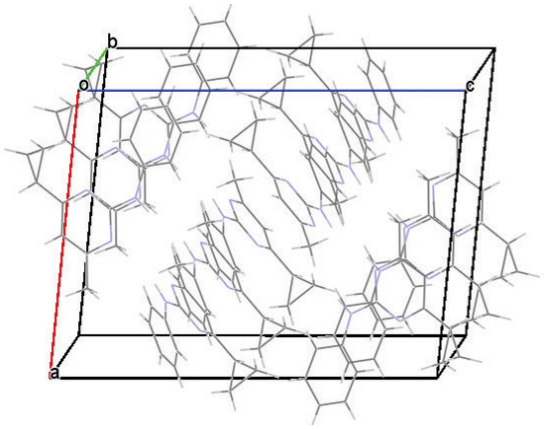

Fig. 3. Projection of the lattice of cyprodinil (C^0) crystals; source: Jeon *et al.* (2015)

ORIGIN AND PROCEEDING OF EMPIRICAL DATA OF CYCLODEXTRINS

Starting from the crystallographic structure of α-cyclodextrin monohydrate (Fig. 4a) and obtained for β-cyclodextrin dodecahydrate (Fig. 4b) theoretical model structures were obtained. Tables S2 and S3 (available at: https://www.jwld.pl/files/Supplementary-material-Ho-aj-Krzak.pdf) present selected empirical structural parameters (bond lengths, *R*; angles, *α*; dihedral angles, *β*) of the isolated α- (Sha *et al.*, 2016) and β-cyclodextrin molecules, respectively (Lindner and Saenger, 1982).

RESULTS

THEORETICAL DATA OF NEUTRAL AND IONIC FORMS OF CYPRODINIL

Theoretical structures of the neutral form of cyprodinil (Fig. 5a), anion (Fig. 5b), and cation (Fig. 5c) were obtained by calculations at the B3LYP/6-311++G(2d,2p) level of theory (the lowest energy criterion). Table 1 is a summary of the energy (Δ*E*) of the molecule and cyprodinil ions, obtained by calculations using the B3LYP, PBE0, M06-2X and B97-D functionals, for the 6-311++G(d,p), 6-311++G(2d,p), 6-311++G(2d,2p) and aug-cc-pVDZ basis sets. Table S4 (available at: https://www.jwld.pl/files/Supplementary-material-Ho-aj-Krzak.pdf) lists selected theoretical structural parameters (bond lengths, *R*; angles, *α*; dihedral angles, *β*) of the isolated molecules and cyprodinil ions [B3LYP/6-311++G(2d,2p)].

THEORETICAL DATA OF CYCLODEXTRINS

Model structures of α- (Fig. 6a) and β-cyclodextrin (Fig. 6b) molecules were obtained in the course of calculations at the B3LYP/6-31++G(d,p) level, meeting the energy minimum criterion. Energy values (Δ*E*) of the α-cyclodextrin molecule obtained by theoretical calculations (DFT/B3LYP) with the use of 6-31G(d), 6-31G(d,p), 6-31G(2d,p), 6-31G(2d,2p) and 6-31++G (d,p) basis sets equals [Ha]: −3664.42397723, −3664.57539559, −3664.69706045, −3664.72550879, and −3664.75381536, respectively. Table S5 (available at: https://www.jwld.pl/files/Supple-

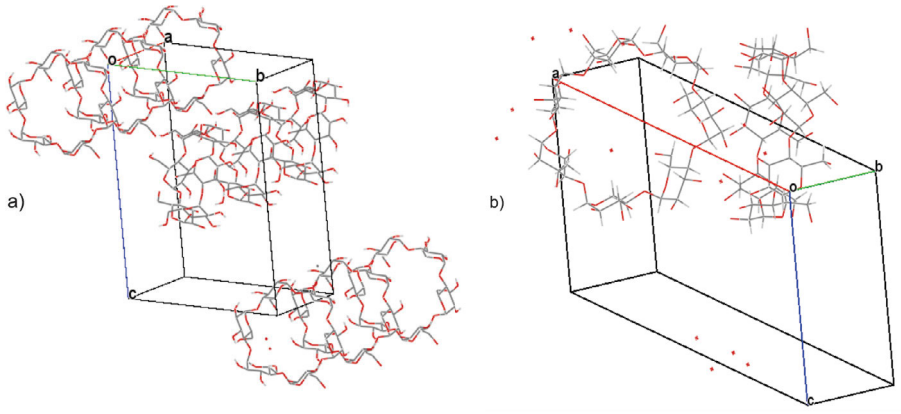

Fig. 4. Projections of crystal lattices of cyclodextrins (CD): a) α-cyclodextrin monohydrate acc. to Sha *et al.* (2016), b) β-cyclodextrin dodecahydrate (bottom) acc. to Lindner and Saenger (1982)

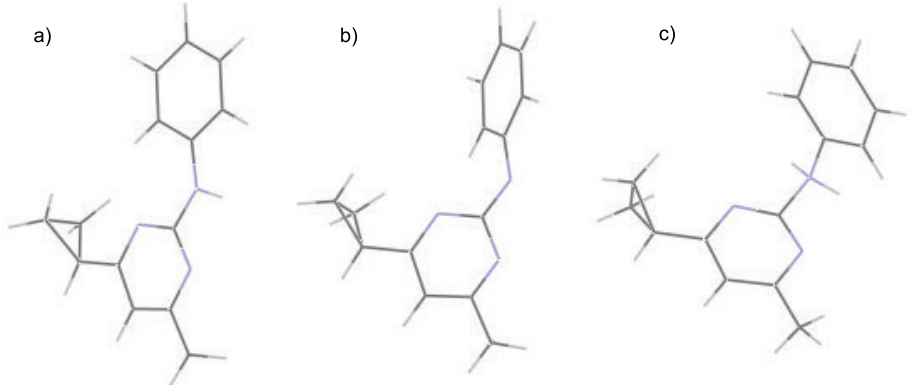

Fig. 5. Optimised [B3LYP/6-311++G(2d,2p)] structures of cyprodinil ionic forms (C): a) C^0, b) C^-, c) C^+; source: own study

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Table 1. Energy (ΔE) of single molecules and cyprodinil ions (C^0, C^-, C^+) obtained by theoretical calculations (DFT)

Functional	ΔE (Ha)			
	6-311++G(d,p)	6-311++G(2d,p)	6-311++G(2d,2p)	aug-cc-pVDZ
C^0				
B3LYP	−706.960928293	−706.978285119	−706.985912841	−706.858687120
PBE0	−706.123774359	−706.141215298	−706.147507853	−706.041119033
M06-2X	−706.663578705	−706.683971878	−706.691828025	−706.589726937
B97-D	−706.439669811	−706.453010334	−706.459827694	−706.350441086
C^-				
B3LYP	−706.385351399	−706.403420855	−706.410340638	−706.284492300
PBE0	−705.546834401	−705.564815335	−705.570464020	−705.465681921
M06-2X	−706.090499788	−706.111226772	−706.118681539	−706.017493029
B97-D	−705.864030081	−705.877700345	−705.883974545	−705.775947194
C^+				
B3LYP	−707.316387899	−707.334510324	−707.342620867	−707.212833702
PBE0	−706.478165183	−706.496599860	−706.503331580	−706.394729878
M06-2X	−707.015754150	−707.037358467	−707.045390991	−706.941673904
B97-D	−706.801031859	−706.815236732	−706.822400318	−706.710563315

Source: own study.

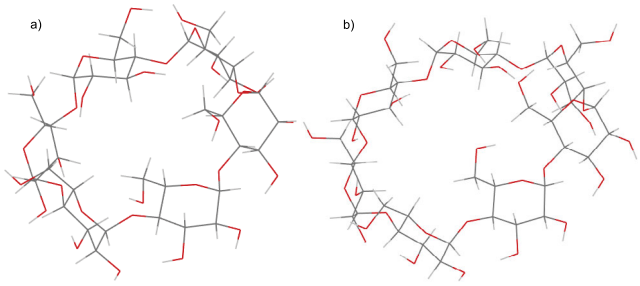

Fig. 6. Model structures [B3LYP/6-31++G(d,p)] of cyclodextrins (CD): a) α-cyclodextrin, b) β-cyclodextrin: source: own study

mentary-material-Ho-aj-Krzak.pdf) is a summary of selected theoretical structural parameters (bond lengths, R; angles, α; dihedral angles, β) of isolated α-cyclodextrin molecules [B3LYP/6-31++G(d,p)]. Energy (ΔE) of single β-cyclodextrin molecules were obtained by theoretical calculations (DFT/B3LYP) for wide range of basis sets [Ha]: 6-31G(d) (−4275.19247987), 6-31G(d,p) (−4275.37382889), 6-31G(2d,p) (−4275.48804411), 6-31G(2d,2p) (−4275.53944150), and 6-31++G(d,p) (−4275.57349174). The corresponding structural data for the β-cyclodextrin model are given in Table S6 (available at: https://www.jwld.pl/files/Supplementary-material-Ho-aj-Krzak.pdf).

THEORETICAL DATA OF SUPRAMOLECULAR STRUCTURES

In the course of calculations at the G4MP2 level, the structures of compounds consisting of the molecule (Fig. 7a), anion (Fig. 7b), and cation (Fig. 7c) of cyprodinil with α-cyclodextrin were optimised. The geometries of the systems based on β-cyclodextrin – for the molecule (Fig. 8a), anion (Fig. 8b), and cation (Fig. 8c) of cyprodinil – were also obtained based on the G4MP2 formalism. Interaction energies [$\Delta(\Delta E)$] (differences in the energy of model complexes and the sums of the energies of the respective components), thermal energies (ΔE_t), isochoric molar specific heat (C_V), and entropy (S) of systems composed of the molecule and cyprodinil ions with α-cyclodextrin are given in Table 2. Selected theoretical structural parameters (bond lengths, R; angles, α; dihedral angles, β) of the systems composed of the molecule and cyprodinil ions with α-cyclodextrin are presented in Table S7 (available at: https://www.jwld.pl/files/Supplementary-material-Ho-aj-Krzak.pdf). The energy characteristics of the appropriate β-cyclodextrin compounds are presented in Table 3.

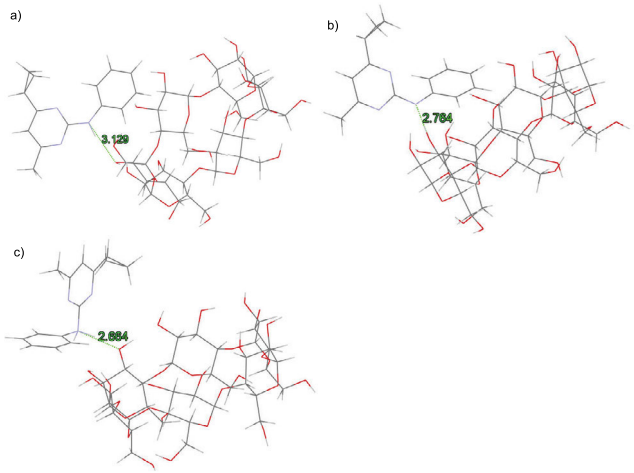

Fig. 7. Theoretical structures (G4MP2) of systems consisting of a molecule and cyprodinil ions (C) with α-cyclodextrin (α-CD): a) C^0@α-CD, b) C^-@α-CD, c) C^+@α-CD; lengths of the distinguished hydrogen bonds are given in angstroms (Å); source: own study

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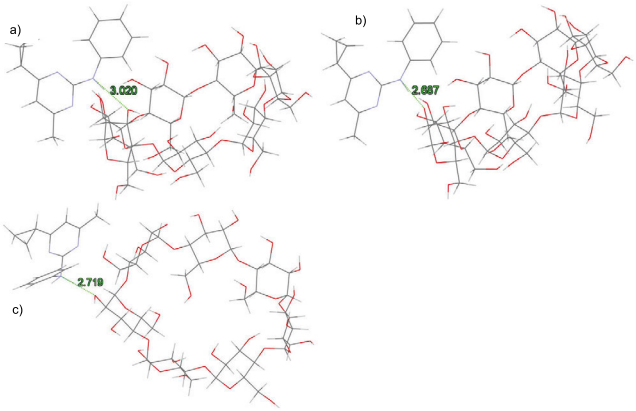

Fig. 8. Optimised (G4MP2) geometries of systems consisting of a molecule and cyprodinil ions (C) with β-cyclodextrin (β-CD): a) C^0@β-CD, b) C^-@β-CD, c) C^+@β-CD; lengths of the distinguished hydrogen bonds are given in angstroms (Å); source: own study

Table 2. Interaction energies [Δ(Δ*E*)], thermal energies (ΔE_t), isochoric molar heat capacities (C_V) and entropies (*S*) of systems consisting of a molecule and cyprodinil ions with α-cyclodextrin (G4MP2)

Δ(Δ*E*) (kJ·mol^{-1})	Contribution	ΔE_t (kJ·mol^{-1})	C_V (J·mol^{-1}·K^{-1})	*S* (J·mol^{-1}·K^{-1})
C^0@α-CD				
303.40	Σ	3641.30	1321.52	1796.63
	e	0.00	0.00	0.00
	t	3.72	12.47	197.15
	r	3.72	12.47	176.44
	v	3633.86	1296.58	1423.05
C^-@α-CD				
191.08	Σ	3601.98	1305.54	1757.54
	e	0.00	0.00	0.00
	t	3.72	12.47	197.13
	r	3.72	12.47	175.23
	v	3594.55	1280.60	1385.18
C^+@α-CD				
190.38	Σ	3675.05	1320.87	1800.63
	e	0.00	0.00	0.00
	t	3.72	12.47	197.15
	r	3.72	12.47	176.79
	v	3667.62	1295.93	1426.67

Explanations: Σ = total, *e* = electronic, *t* = translational, *r* = rotational, *v* = vibrational)
Source: own study.

Structural data on these systems are summarised in Table S8 (available at: https://www.jwld.pl/files/Supplementary-material-Ho-aj-Krzak.pdf). The initial geometries for all modeled inclusion complexes were selected as those whose mutual orientation of the "guest" and "host" molecules resulted from the expected final structure, and thus ensured the convergence procedure the most effective.

Table 3. Interaction energies [Δ(Δ*E*)], thermal energies (ΔE_t), isochoric molar heat capacities (C_V) and entropies (*S*) of systems consisting of a molecule and cyprodinil ions with β-cyclodextrin (G4MP2)

Δ(Δ*E*) (kJ·mol^{-1})	Contribution	ΔE_t (kJ·mol^{-1})	C_V (J·mol^{-1}·K^{-1})	*S* (J·mol^{-1}·K^{-1})
C^0@β-CD				
324.26	Σ	4127.69	1501.32	2038.67
	e	0.00	0.00	0.00
	t	3.72	12.47	198.73
	r	3.72	12.47	180.62
	v	4120.25	1476.37	1659.32
C^-@β-CD				
254.76	Σ	4082.39	1486.61	2031.37
	e	0.00	0.00	0.00
	t	3.72	12.47	198.72
	r	3.72	12.47	180.38
	v	4074.96	1461.67	1652.27
C^+@β-CD				
240.49	Σ	4162.35	1501.15	1997.63
	e	0.00	0.00	0.00
	t	3.72	12.47	198.74
	r	3.72	12.47	180.98
	v	4154.92	1476.21	1617.90

Explanations as in Tab. 2.
Source: own study.

DISCUSSION

GENERAL INFORMATION

The thematic scope of the research presented in this article – the problem of the reversible binding of molecules into supramolecular structures – should be considered in a broader context, combining the theoretical foundations of the phenomena that determine them, as well as discussing the tools for their interpretation. In the first case, therefore, one should focus on the issue of hydrogen bonds as the strongest non-covalent interactions, and on the other hand, understand the foundations of the process of releasing "guest" molecules from inclusion complexes.

The problem of hydrogen bonding in science has been at the centre of many decades. These interactions determine the occurrence of important biological and physicochemical phenomena, and because the consequences resulting from their implementation are still not fully understood, they seem to be the more interesting research object, primarily determining the properties of solutions and molecular crystals.

Particularly difficult, from the point of view of interpretation on the basis of qualitative and quantitative theories, are the problems involving hydrogen bonds that stabilise molecular crystals. The model system is the centrosymmetric cyclic dimer of hydrogen bonds, $(R–COOH)_2$, present mainly in the lattice of monocarboxylic acids (Rekik *et al.*, 2010) and dicarboxylic acids (Hołaj-Krzak, 2021; Hołaj-Krzak *et al.*, 2022).

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A very important concept from the mainstream of qualitative theories is the Fermi resonance (Rekik *et al.*, 2010), in addition to the developed theory of strong anharmonic coupling (Salman *et al.*, 2022). More recent studies in this field include in the mathematical apparatus the formalism of the theory of linear response, the effect of vibration relaxation and the Davydov coupling (Rekik *et al.*, 2019).

THEORETICAL DATA OF NEUTRAL AND IONIC FORMS OF CYPRODINIL

The first phase of theoretical calculations, including structures optimisation of the isolated molecule of cyprodinil (C^0) – Figure 5a, unbound anion (C^-) – Figure 5b, and the cation (C^+) – Figure 5c, as well as α-cyclodextrins (α-CD) – Figure 6a and β-cyclodextrins (β-CD) free molecules (Fig. 6b), starting from the C^0 (Fig. 3) (Jeon *et al.*, 2015), α-CD (Fig. 4a) (Sha *et al.*, 2016), and β-CD (Fig. 4b) (Lindner and Saenger, 1982) crystallographic structures, allowed to obtain a set of model structures necessary for research on supramolecular systems.

In the case of cyprodinil, very slight deviations in the bond lengths between the real (Tab. S1) (Jeon *et al.*, 2015) and theoretical (Tab. S4) structures can be noticed. The N7–H7a bond is an exception, because in the crystal this part of the molecule is involved in the formation of the hydrogen bridge, and model calculations were carried out for the vacuum state. For this reason, slight differences can be found between values of these angles and dihedral angles, for which the atoms that form them are not involved in the formation of hydrogen bonds. Modelling the C^0 molecule in a vacuum state involves the orientation of the phenylene and the heterocyclic rings in a common plane, preventing the implementation of non-covalent interactions.

The presence of a lone pair in the C^- theoretical structure changes the electron density distribution within it, which is reflected in the weakening (N1–C2) or strengthening (C2–N7, C8–N7) of bonds, as well as increasing the degree of rotation of the phenylene ring in relation to the C^0 model structure.

Protonation of the aliphatic N atom, leading to the C^+ structure, changes the particle shape in accordance with the assumed hybridisation. In the case of this structure, the N1–C2 bond is shortened while the C2–N7, C8–N7, and N7–H7a bonds are lengthened.

THEORETICAL DATA OF CYCLODEXTRINS

Analysis of exceptions between the crystallographic and model structures of cyclodextrins generally does not allow to notice the drastic differences resulting from deformation of the molecules. Before starting the optimisation of α- and β-CD structures, H_2O molecules present in the crystal lattices were removed, and the molecular skeletons were supplemented with H atoms.

Comparison of the most important from the point of view of the research, the geometric parameters of the crystallographic (Tab. S2) (Sha *et al.*, 2016) and S7 model (Tab. S5) α-CD structures concerns the description of atoms responsible for reversible bond of the "guest" molecule by hydrogen bonds or hydrophobic interactions, i.e. the O–H bonds and the geometrical parameters of the cavity of the "host" molecule. The transition from the real structure to the model structure is accompanied by the reorientation of the C3–O8 and C4–O9 bonds, which, when extended and averaged their length, indicates the formation of hydrogen bonds between them. This behaviour suggests that when "guest" molecules are included, they can be easily broken off. On the way of optimisation, the spatial structure is practically not modified (the reduction of the cavity width is about 0.17%).

For the β-CD, a similar combination of data from registration of X-ray diffraction patterns (Tab. S3) (Lindner and Saenger, 1982) with those obtained by means of DFT calculations (Tab. S6) does not allow for a reliable assessment of a possible negative impact on the optimisation result by selecting the wrong functional and basis set. This is due to the lack of data for the crystallographic structure of H atoms coordinates, which were supplemented before optimisation. Geometry convergence reduces the width of the cavity by 5.9%.

THEORETICAL DATA OF SUPRAMOLECULAR STRUCTURES

Results of the proper theoretical calculation stage (G4MP2) for the model structures of α-cyclodextrin inclusion complexes with the molecule (C^0@α-CD) – Figure 7a, anion (C^-@α-CD) – Figure 7b, and cation (C^+@α-CD) – Figure 7c of cyprodinil (Tab. 2), indicate that the values of interaction energies of individuals forming the discussed compounds are high and positive, especially in the case of the C^0@α-CD complex. This proves a weak affinity of the components of molecular systems, where the formation of C^-@α-CD (191.08 kJ·mol^{-1}) or C^+@α-CD (190.38 kJ·mol^{-1}) systems is more privileged than the C^0@α-CD (303.40 kJ·mol^{-1}).

Geometries of potential complexes predicted on the basis of theoretical calculations indicate that the "guest" molecules do not undergo significant structural modifications, especially in regions directly involved in non-covalent interactions. The comparison of the structural data collected for the optimised structure of the neutral cyprodinil molecule (Tab. S4) with the data collected in the course of modelling the structure of the C^0@α-CD complex (Tab. S7) shows that in the process of creating a (hypothetical) inclusion complex, the "guest" molecule is only slightly deformed, that is deviations from the coplanar structure (rotation around the C8–N7 bond). The C8–N7 bond is slightly shortened (by 0.79%), while the N7–H7a bond is extended (by 1.1%) due to the presence of the hydrogen bridge. Discussion on influence of cyprodinil inclusion on the structure of α-cyclodextrin (Fig. 6a), in the light of changes in its structural parameters (Tab. S5), may be limited practically only to changing the length of bonds connecting the atoms of those fragments of the "host" molecule that are located in the immediate vicinity of the "guest" molecule, which is accompanied by a slightly marked change in the angles between the respective bonds.

Analysis of the C^0@α-CD complex structure (Fig. 7a) shows preference of the cyprodinil molecule orientation, in which the phenyl ring faces the hydrophobic cavity of the α-cyclodextrin molecule, from the side of the wider edge. This ensures formation of a very weak hydrogen bridge involving the aliphatic N atom of cyprodinil and the O atom of one of the glucose moieties (N7–H7a···O8), 312.9 pm long (Tab. S7).

Comparison of the common spatial parameters of the C^-@α-CD model structure (Tab. S7) with describing the cyprodinil anion theoretical structure (Tab. S4) shows a significant influence related to the process of supramolecular structure formation. Significant shortening of bonds proving the modification of the electron density distribution in the heterocyclic ring

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(N1–C2) and the aliphatic N atom regions (C2–N7) proves that the interaction between the "guest" and "host" molecules is marked more strongly than in the case of C^0@α-CD. As a result of the complex formation process, no drastic change in the angles between the bonds, in particular between the planes in which the aromatic rings lie, is observed.

The C^-@α-CD model structure (Fig. 7b) assumes the orientation of the cyprodinil anion analogously to the C^0@α-CD system, i.e. ensuring the optimal approach of the additional free electron pair of the aliphatic N atom, while directing the hydrophobic pole to the inside of the wider cavity of the "host" molecule. The obtained geometry allows for the formation of a moderately strong hydrogen bond (276.4 pm) with the structure N7···H9a–O9 (Tab. S7).

Interesting in the context of the discussed structures is comparison of data obtained for the isolated cyprodinil cation (Tab. S4) and the C^+@α-CD system (Tab. S7). The energy of the hypothetical C^+@α-CD compound is characterised by the lowest energy among those obtained on the basis of α-CD, which is justified in terms of modification of the bond length (elongation of N1–C2, N7–H7a, and N7–H7b; shortening of C2–N7 and C8–N7) and the angles between them (rotation of the phenylene ring).

The structure of C^+@α-CD (Fig. 7 C) is stabilised by two hydrogen bonds (Tab. S7): N7–H7a···O8 (282.0 pm) and N7–H7b···O9 (266.4 pm), with the hydrophobic pole of the cyprodinil cation not oriented near the edge of the "host" molecule but facing the α-cyclodextrin molecule from the protonated N atom.

Discussion of theoretical calculations (G4MP2) results for the model structures of cyprodinil complexes and its ionic forms with β-cyclodextrin allows to draw conclusions qualitatively consistent with those presented for the corresponding α-CD derivatives (Tab. 3). In the light of collected data, formation of C^0@β-CD (Fig. 8a), C^-@β-CD (Fig. 8b), and C^+@β-CD (Fig. 8c) compounds is thermodynamically unfavourable, as indicated by the corresponding values of $\Delta(\Delta E)$ – 324.26, 254.76, and 240.49 kJ·mol^{-1}.

Structural characteristics of the free cyprodinil molecule (Tab. S4) and bound in the hypothetical model complex C^0@β-CD (Tab. S8) indicate that in qualitative terms, the "guest" molecule behaves in a similar way to that shown as a result of the C^0@α-CD derivative formation. In the currently discussed case, there is a slight deviation from the coplanar structure, with no rotation of the phenyl ring taking place. As a result of the complexation process of cyprodinil, the chemical bonds formed by the N atoms are slightly elongated.

The C^0@β-CD complex model structure (Fig. 8a) reveals the existence (Tab. S8), similarly to the analogous compound with α-CD, of a weak N7–H7a···O9 hydrogen bond (302.0 pm). It should be noted that these structures are distinguished by the orientation of the "guest" molecule – in the currently analysed case the cyprodinil molecule is moved away from the cavity.

Comparison of the C^-@β-CD model complex geometry (Tab. S8) with the structure of the cyprodinil anion (Tab. S4) leads to unexpected conclusions, making it possible to assess the influence of intermolecular interactions in the analysed system. First of all, attention should be paid to the fact that as a result of the inclusion complex formation process, the "host" molecule is deprotonated with the formation of the N7–H7a bond (106.2 pm). This gives a picture of the scale of electrostatic interactions within the model inclusion system, despite the unfavourably high value of $\Delta(\Delta E)$, amounting to 254,76 kJ·mol^{-1} (Tab. 3).

Analysis of the C^-@β-CD model structure (Fig. 8b) indicates such an orientation of the "guest" and "host" molecules that allows for the formation of a moderately strong, 268.7 pm, N7–H7a···O8 hydrogen bond (Tab. S8).

Geometric parameters of the hypothetical C^+@β-CD compound (Tab. S8) combined with the corresponding values collected for the theoretical structure of the cationic form of cyprodinil (Tab. S4) show that the optimal orientation of the "guest" and "host" molecules does not lead to significant modification geometry of the former, in particular for rotation in accordance with the axis of C2–N7 and C8–N7 bonds.

As for the previously discussed C^-@β-CD system, also for the C^+@β-CD structure (Tab. S8) a hydrogen bridge with the constitution N7–H7a···O8 (271.9 pm) is theoretically provided.

In sum, according to the values of the interaction energy [$\Delta(\Delta E)$] obtained by theoretical calculations within the G4MP2 procedure for a series of compounds of cyprodinil and its ions with α-cyclodextrin and β-cyclodextrin, it should be considered that the discussed model structures of inclusion complexes most probably do not form.

The effective interaction between the hydrogen atom and the proton acceptor (proton-acceptor group) takes place when the X and Y poles of the hydrogen bridge are characterised by high electronegativity as compared to the hydrogen atom. The atoms of non-metallic elements having non-bonding electron pairs (O, N, S, F, Cl, Br, I, and their ions), as well as groups composed of them, therefore remain the preferred proton-acceptor centres.

Particularly preferred is the linkage of the atoms and their Lewis soft base moieties via mono- or polycyclic aromatic systems (or unconjugated multiple bonds). The functional groups, containing relatively easily cleavable hydrogen atoms (–OH, –COOH, –SH, –NH, –$CONH_2$, –CH), remain most often involved in the considered interactions. Consequently, strong hydrogen bonds are thus formed by individuals that have excess electron density. The anions constitute this group. The reverse is true for cations. In the case of close proximity to cation and anion, interactions classified as electrostatic may occur. This is a borderline case of non-covalent interactions (Hołaj-Krzak, 2021; Hołaj-Krzak *et al.*, 2022).

CONCLUSIONS

The key argument for initiating the work summarised in this article was, as mentioned in the introduction, a very small number of literature reports on research on cyprodinil-based macromolecular systems, in particular analysed with the use of theoretical methods (as an auxiliary or exclusive tool). In turn, this belief is due to the fact that cyprodinil is a fungicide with a very wide range of applications. Forming it into a combination that increases the solubility and, on the other hand, allows for economical dosing by sustained release, could offer further advantages.

Therefore, the main goal of the study should be to select a potentially new preparation consisting of cyprodinil, the properties of which could be predicted through theoretical research. In the course of theoretical calculations, however, it was found that the affinity of the "guest" and "host" molecules

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may be insufficient. At the same time, laboratory tests were undertaken which partially confirmed this fact. They will be the subject of another publication.

In order to reliably verify above interpretation of carried out theoretical calculations, following steps should be taken, in the indicated order or in parallel: (i) undertaking laboratory tests on the preparation and physicochemical characteristics of compounds, (ii) theoretical calculations for model supramolecular systems based on cyprodinil (and appropriate ions) with γ-cyclodextrin and derivatives of native cyclodextrins, (iii) as well as empirical research on such systems.

Despite continuous development of theoretical methods, empirical research cannot be replaced by computational tools, especially in the field of systems formed by molecules, which can be described by a number of conformational structures, including cyclodextrins. In the case of research on the preparation of (i) the discussed compounds, it is necessary to check the suitability of both the procedure of mixing the substrates by kneading, variants of methods based on co-precipitation of substrates, and methods based on lyophilisation.

Theoretically predicted lack of affinity between the "guests" and "host" molecules must result primarily from the physicochemical properties of macrocyclic systems. Their most important feature, apart from the (variable) internal diameter, is polarity. This fact prompts the use of native cyclodextrin derivatives, including selectively or completely alkylated (methylated). Moreover, theoretical calculations based on other models (SMD) and methods (MD) should be considered.

Finally, especially in the case of obtaining promising results of calculations for model systems based on other cyclodextrins, laboratory tests should (iii) be performed, analogously to those indicated in (i).

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REFERENCES

Adamo, C. and Barone, V. (1999) "Toward reliable density functional methods without adjustable parameters: The PBE0 model," *Journal of Chemical Physics*, 110(13), pp. 6158–6170.

Alexandrino, G.L. *et al.* (2013) "Spectroscopic (fluorescence, 1D-ROESY) and theoretical studies of the thiabendazole and β-cyclodextrin inclusion complex," *Journal of Inclusion Phenomena and Macrocyclic Chemistry*, 75(1–2), pp. 93–99. Available at: https://doi.org/10.1007/s10847-012-0150-8.

Alonso, M.L. *et al.* (2014) "Pesticides microencapsulation. A safe and sustainable industrial process," *Journal of Chemical Technology &Amp; Biotechnology*, 89(7), pp. 1077–1085. Available at: https://doi.org/10.1002/jctb.4204.

Avenot, H.F. *et al.* (2018) "Different levels of resistance to cyprodinil and iprodione and lack of fludioxonil resistance in *Botrytis cinerea* isolates collected from pistachio, grape, and pomegranate fields in California," *Crop Protection*, 112, pp. 274–281. Available at: https://doi.org/10.1016/j.cropro.2018.06.005.

Babij, J. *et al.* (2000) "Resistance risk assessment of cereal eyespot, *Tapesia yallundae* and *Tapesia acuformis*, to the anilinopyrimidine fungicide, cyprodinil," *European Journal of Plant Pathology*, 106(9), pp. 895–905. Available at: https://doi.org/10.1023/a:1008774821945.

Báez, M.E., Espinoza, J. and Fuentes, E. (2018) "Degradation kinetics of chlorpyrifos and diazinon in volcanic and non-volcanic soils: Influence of cyclodextrins," *Environmental Science and Pollution Research*, 25(25), pp. 25020–25035. Available at: https://doi.org/10.1007/s11356-018-2559-0.

Becke, A.D. (1993) "Density-functional thermochemistry. III. The role of exact exchange," *Journal of Chemical Physics*, 98(7), pp. 5648–5652.

Becke, A.D. (1996) "Density-functional thermochemistry. IV. A new dynamical correlation functional and implications for exact-exchange mixing," *Journal of Chemical Physics*, 104(3), pp. 1040–1046.

Becke, A.D. (1997) "Density-functional thermochemistry. V. Systematic optimization of exchangecorrelation functionals," *Journal of Chemical Physics*, 107(20), pp. 8554–8560.

Benfeito, S. *et al.* (2013) "Host-guest interaction between herbicide oxadiargyl and hydroxypropyl-β-cyclodextrin," *The Scientific World Journal*, 2013, pp. 1–6. Available at: https://doi.org/10.1155/2013/825206.

Cassano, A. *et al.* (2013) "PAN hollow fibre membranes with triacetyl-β-cyclodextrin for the removal of pesticides from citrus essential oils," *Separation and Purification Technology*, 116, pp. 124–130. Available at: https://doi.org/10.1016/j.seppur.2013.05.029.

Coly, A. and Aaron, J.J. (1998) "Cyclodextrin-enhanced fluorescence and photochemically-induced fluorescence determination of five aromatic pesticides in water," *Analytica Chimica Acta*, 360, pp. 129–141.

Coscarello, E.N. *et al.* (2009) "Comparative analysis of complexation of pesticides (fenitrothion, methylparathion, parathion) and their carboxylic ester analogues by β-cyclodextrin. Theoretical semi-empirical calculations," *Journal of Structural Chemistry*, 50(4), pp. 671–679. Available at: https://doi.org/10.1007/s10947-009-0103-2.

Crini, G. *et al.* (2017) "Simultaneous removal of five triazole fungicides from synthetic solutions on activated carbons and cyclodextrin-based adsorbents," *Heliyon*, 3(8), e00380. Available at: https://doi.org/10.1016/j.heliyon.2017.e00380.

Cserhati, T. *et al.* (2002) "Interaction of pesticides with a β-cyclodextrin derivative studied by reversed-phase thin-layer chromatography and principal component analysis," *Journal of Inclusion Phenomena and Macrocyclic Chemistry*, 42, pp. 235–240.

Curtiss, L.A., Redfern, P.C. and Raghavachari, K. (2007a) "Gaussian-4 theory," *The Journal of Chemical Physics*, 126(8), 084108. Available at: https://doi.org/10.1063/1.2436888.

Curtiss, L.A., Redfern, P.C. and Raghavachari, K. (2007b) "Gaussian-4 theory using reduced order perturbation theory," *The Journal of Chemical Physics*, 127(12), 124105. Available at: https://doi.org/10.1063/1.2770701.

Ditchfield, R., Hehre, W.J. and Pople, J.A. (1971) "Self-consistent molecular-orbital methods. IX. An extended Gaussian-type basis for molecular-orbital studies of organic molecules," *Journal of Chemical Physics*, 54(2), pp. 724–728.

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Dodziuk, H. (2002a) *Introduction to supramolecular chemistry*. New York, United States: Springer Publishing.

Dodziuk, H. (2002b) "Rigidity versus flexibility. A review of experimental and theoretical studies pertaining to the cyclodextrin nonrigidity," *Journal of Molecular Structure*, 614, pp. 33–45.

Dodziuk, H. (ed.) (2006) *Cyclodextrins and their complexes: Chemistry, analytical methods, applications*. Hoboken, NJ, United States: Wiley.

Dunning, T.H., Jr. (1989) "Gaussian basis sets for use in correlated molecular calculations. I. The atoms boron through neon and hydrogen," *Journal of Chemical Physics*, 90(2), pp. 1007–1023.

Ferino-Pérez, A. *et al* (2019) "Evaluation of the molecular inclusion process of β-hexachlorocyclohexane in cyclodextrins," *RSC Advances*, 9(47), pp. 27484–27499. Available at: https://doi.org/10.1039/c9ra04431k.

Fernandes, C. *et al.* (2014) "Influence of hydroxypropyl-β-cyclodextrin on the photostability of fungicide pyrimethanil," *International Journal of Photoenergy*, 2014, pp. 1–8. Available at: https://doi.org/10.1155/2014/489873.

Fernández-Ortuño, D., Chen, F. and Schnabel, G. (2013) "Resistance to cyprodinil and lack of fludioxonil resistance in *Botrytis cinerea* isolates from strawberry in North and South Carolina," *Plant Disease*, 97(1), pp. 81–85. Available at: https://doi.org/10.1094/pdis-06-12-0539-re.

Fiaccadori, R. (2018) "In vitro, in vivo and in field sensitivity of *Venturia inaequalis* to anilinopyrimidine fungicides with different types of scab management and degree of control," *OALib*, 05 (12), pp. 1–13. Available at: https://doi.org/10.4236/oalib.1105092.

Fifere, A. *et al.* (2012) "Theoretical study on β-cyclodextrin inclusion complexes with propiconazole and protonated propiconazole," *Beilstein Journal of Organic Chemistry*, 8, pp. 2191–2201. Available at: https://doi.org/10.3762/bjoc.8.247.

Galian, R.E., Bracamonte, A.G. and Veglia, A.V. (2005) "Hydroxypropyl-β-cyclodextrin effect on the fluorescence of auxin and skatole and on the simultaneous determination of binary mixtures of indole compounds in urine by first derivative spectrofluorimetry," *Analytica Chimica Acta*, 540(2), pp. 393–401. Available at: https://doi.org/10.1016/j.aca.2005.03.009.

Garrido, E.M. *et al.* (2012) "Host-guest complexes of phenoxy alkyl acid herbicides and cyclodextrins. MCPA and β-cyclodextrin," *Journal of Environmental Science and Health, Part B*, 47(9), pp. 869–875. Available at: https://doi.org/10.1080/03601234.2012.693867.

Ge, X. *et al.* (2011) "Inclusion complexation of chloropropham with β-cyclodextrin: Preparation, characterization and molecular modeling," *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 81(1), pp. 397–403. Available at: https://doi.org/10.1016/j.saa.2011.06.028.

Grimme, S. (2006) "Semiempirical GGA-type density functional constructed with a long-range dispersion correction," *Journal of Computational Chemistry*, 27(15), pp. 1787–1799. Available at: https://doi.org/10.1002/jcc.20495.

Gurarslan, A. *et al.* (2015) "Pyriproxyfen cyclodextrin inclusion compounds," *Journal of Inclusion Phenomena and Macrocyclic Chemistry*, 82(3–4), pp. 489–496. Available at: https://doi.org/10.1007/s10847-015-0526-7.

Hariharan, P.C. and Pople, J.A. (1973) "The influence of polarization functions on molecular orbital hydrogenation energies," *Theoretica Chimica Acta*, 28, pp. 213–222.

Hebeish, A. *et al.* (2014) "New textiles of biocidal activity by introduce insecticide in cotton-poly (GMA) copolymer containing β-Cd," *Carbohydrate Polymers*, 99, pp. 208–217. Available at: https://doi.org/10.1016/j.carbpol.2013.08.002.

Hirayama, K. (2022) "Curative effects of fungicides against *Venturia inaequalis* causing apple scab," *Journal of General Plant Pathology*, 88(4), pp. 264–269. Available at: https://doi.org/10.1007/s10327-022-01071-8.

Hohenberg, P. and Kohn, W. (1964) "Inhomogeneous electron gas," *Physical Review*, 136(3B), pp. B 864-B 871.

Hołaj-Krzak, J.T. (2021) "Lack of the 'long-distance' dynamical cooperative interactions due to low symmetry of hydrogen-bonded malonic acid aggregates in molecular crystals," *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 246, 118993. Available at: https://doi.org/10.1016/j.saa.2020.118993.

Huang, Z. *et al.* (2014) "Complexation of chlorpropham with hydroxypropyl-β-cyclodextrin and its application in potato sprout inhibition," *Carbohydrate Polymers*, 107, pp. 241–246. Available at: https://doi.org/10.1016/j.carbpol.2014.02.072.

Iványi, R. *et al.* (2004) "Influence of (hydroxy)alkylamino substituents on enantioseparation ability of single-isomer amino-β-cyclodextrin derivatives in chiral capillary electrophoresis," *Electrophoresis*, 25(16), pp. 2675–2686. Available at: https://doi.org/10.1002/elps.200406030.

Jeon, Y. *et al.* (2015) "Crystal structure of cyprodinil," *Acta Crystallographica Section E Crystallographic Communications*, 71(1), pp. o5–o5. Available at: https://doi.org/10.1107/S2056989-014025742.

Juvancz, Z. and Szejtli, J. (2002) "The role of cyclodextrins in chiral selective chromatography," *Trends in Analytical Chemistry*, 21(5), pp. 379–388.

Kohn, W. and Sham, L.J. (1965) "Self-consistent equations including exchange and correlation effects," *Physical Review*, 140(4A), pp. A 1133-A 1138.

Köhler, G., Viernstein, H. and Wolschann, P. (1996) "Molecular calculations and thermodynamical considerations on the solubility enhancement of triflumizole by cyclodextrin complexation," *Journal of Inclusion Phenomena and Molecular Recognition in Chemistry*, 25, pp. 237–241.

Köller, W., Wilcox, W.F. and Parker, D.M. (2005) "Sensitivity of *Venturia inaequalis* populations to anilinopyrimidine fungicides and their contribution to scab management in New York," *Plant Disease*, 89(4), pp. 357–365. Available at: https://doi.org/10.1094/pd-89-0357.

Landy, D. *et al.* (2012) "Remediation technologies using cyclodextrins: An overview," *Environmental Chemistry Letters*, 10(3), pp. 225–237. Available at: https://doi.org/10.1007/s10311-011-0351-1.

Lawtrakul, L., Inthajak, K. and Toochinda, P. (2014) "Molecular calculations on β-cyclodextrin inclusion complexes with five essential oil compounds from *Ocimum basilicum* (sweet basil)," *ScienceAsia*, 40(2), 145. Available at: https://doi.org/10.2306/scienceasia1513-1874.2014.40.145.

Leroux, P. *et al.* (2012) "Fungicide resistance status in French populations of the wheat eyespot fungi *Oculimacula acuformis* and *Oculimacula yallundae*," *Pest Management Science*, 69(1), pp. 15–26. Available at: https://doi.org/10.1002/ps.3408.

Lezcano, M. *et al.* (2001) "Complexation of several benzimidazole-type fungicides with α- and β-cyclodextrins," *Journal of Agricultural and Food Chemistry*, 50(1), pp. 108–112. Available at: https://doi.org/10.1021/jf010927y.

Lezcano, M. *et al.* (2003) "Complexation of several fungicides with β-cyclodextrin: Determination of the association constants and isolation of the solid complexes," *Journal of Agricultural and Food Chemistry*, 51(17), pp. 5036–5040. Available at: https://doi.org/10.1021/jf0343682.

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Lindner, K. and Saenger, W. (1982) "Crystal and molecular structure of cyclohepta-amylose dodecahydrate," *Carbohydrate Research*, 99(2), pp. 103–115. Available at: https://doi.org/10.1016/s0008-6215(00)81901-1.

Lipták, A. *et al.* (2002) "Mixed acetals of cyclodextrins. Preparation of hexakis-, heptakis- and octakis[2,6-di-O-(methoxydimethyl) methyl]-α-, β- and γ-cyclodextrins," *Carbohydrate Research*, 337, pp. 93–96.

Liu, G. *et al.* (2017) "Metal–organic framework preparation using magnetic graphene oxide–β-cyclodextrin for neonicotinoid pesticide adsorption and removal," *Carbohydrate Polymers*, 175, pp. 584–591. Available at: https://doi.org/10.1016/j.carbpol.2017.06.074.

Lu, H. *et al.* (2015) "Molecular dynamics simulation and TDDFT study of the structures and UV–vis absorption spectra of MCT-β-CD and its inclusion complexes," *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 149, pp. 564–570. Available at: https://doi.org/10.1016/j.saa.2015.04.102.

Pereira, R.A. *et al.* (2016) "Theoretical inclusion of deprotonated 2,4-D and dicamba pesticides in ß-cyclodextrin," *Journal of Inclusion Phenomena and Macrocyclic Chemistry*, 86(3–4), pp. 343–349. Available at: https://doi.org/10.1007/s10847-016-0665-5.

Petrović, G. *et al.* (2013) "Inclusion complexes of pesticides in aqueous solutions of methylated-β-cyclodextrin," *Chemical Industry*, 67(2), pp. 231–237. Available at: https://doi.org/10.2298/hemind120413068p.

Pieczul, K. and Korbas, M. (2014) "Fungicide resistance level of *Oculimacula acuformis* and *O. yallundae* isolates – the causal agents of eyespot," *Progress in Plant Protection*, 54(3), pp. 339–344. Available at: https://doi.org/10.14199/ppp-2014-055.

Redenti, E., Szente, L. and Szejtli, J. (1999) "Drug/cyclodextrin/hydroxy acid multicomponent systems. Properties and pharmaceutical applications," *Journal of Pharmaceutical Sciences*, 89(1), pp. 1–8.

Rekik, N. *et al.* (2008) "Experimental and theoretical study of the polarized infrared spectra of the hydrogen bond in 3-thiophenic acid crystal," *Journal of Computational Chemistry*, 31(3), pp. 463–375. Available at: https://doi.org/10.1002/jcc.21324.

Rekik, N. *et al.* (2019) "Towards accurate infrared spectral density of weak H-bonds in absence of relaxation mechanisms," *Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy*, 207, pp. 197–208. Available at: https://doi.org/10.1016/j.saa.2018.09.003.

Richardson, J.R. *et al.* (2019) "Neurotoxicity of pesticides," *Acta Neuropathologica*, 138(3), pp. 343–362. Available at: https://doi.org/10.1007/s00401-019-02033-9.

Rode, T. *et al.* (2003) "Complex formation of sericoside with hydrophilic cyclodextrins: improvement of solubility and skin penetration in topical emulsion based formulations," *European Journal of Pharmaceutics and Biopharmaceutics*, 55(2), pp. 191–198. Available at: https://doi.org/10.1016/s0939-6411(02)00194-7.

Salman, S. *et al.* (2022) "Elucidating the theoretical evolution of the IR spectral density and the potential energy surfaces of hydrogen bonded complexes: A quantum dynamical study," *Chemical Physics Letters*, 791, 139380. Available at: https://doi.org/10.1016/j.cplett.2022.139380.

Sha, J.-Q. *et al.* (2016) "Nontoxic and renewable metal–organic framework based on α-cyclodextrin with efficient drug delivery," *RSC Advances*, 6(86), pp. 82977–82983. Available at: https://doi.org/10.1039/c6ra16549d.

Sholberg, P.L., Bedford, K.E. and Stokes, S. (2003) "Effect of preharvest application of cyprodinil on postharvest decay of apples caused by *Botrytis cinerea*," *Plant Disease*, 87(9), pp. 1067–1071. Available at: https://doi.org/10.1094/pdis.2003.87.9.1067.

Singh, M., Sharma, R. and Banerjee, U.C. (2002) "Biotechnological applications of cyclodextrins," *Biotechnology Advances*, 20, pp. 341–359.

Szejtli, J. (2003) "Cyclodextrins in the textile industry," *Starch/Stärke*, 55, pp. 191–196.

Szente, L. (1998) "Stable, controlled-release organophosphorous pesticides entrapped in β-cyclodextrin. I. Solid state characteristics," *Journal of Thermal Analysis*, 51, pp. 957–963.

Szente, L. and Szejtli, J. (2004) "Cyclodextrins as food ingredients," *Trends in Food Science &Amp; Technology*, 15(3–4), pp. 137–142. Available at: https://doi.org/10.1016/j.tifs.2003.09.019.

Verstichel, S. *et al.* (2004) "Investigation of the aerobic biodegradability of several types of cyclodextrins in a laboratory-controlled composting test," *Journal of Polymers and the Environment*, 12 (3), pp. 47–55.

Vico, R.V., De Rossi, R.H. and Buján, E.I. (2009) "Reactivity of the insecticide chlorpyrifos-methyl toward hydroxyl and perhydroxyl ion. Effect of cyclodextrins," *Journal of Physical Organic Chemistry*, 22(7), pp. 691–702. Available at: https://doi.org/10.1002/poc.1502.

Wu, Y.S., Lee, H.K. and Li, S.F.Y. (2001) "High-performance chiral separation of fourteen triazole fungicides by sulfated β-cyclodextrin-mediated capillary electrophoresis," *Journal of Chromatography A.*, 912, pp. 171–179.

Yang, M. *et al.* (2015) "Vortex-assisted magnetic β-cyclodextrin/attapulgite-linked ionic liquid dispersive liquid–liquid microextraction coupled with high-performance liquid chromatography for the fast determination of four fungicides in water samples," *Journal of Chromatography A*, 1381, pp. 37–47. Available at: https://doi.org/10.1016/j.chroma.2015.01.016.

Yañez, C., Araya, M. and Bollo, S. (2010) "Complexation of herbicide bentazon with native and modified β-cyclodextrin," *Journal of Inclusion Phenomena and Macrocyclic Chemistry*, 68(1–2), pp. 237–241. Available at: https://doi.org/10.1007/s10847-010-9750-3.

Zhao, Y. and Truhlar, D.G. (2007) "The M06 suite of density functionals for main group thermochemistry, thermochemical kinetics, noncovalent interactions, excited states, and transition elements: two new functionals and systematic testing of four M06-class functionals and 12 other functionals," *Theoretical Chemistry Accounts*, 120(1–3), pp. 215–241. Available at: https://doi.org/10.1007/s00214-007-0310-x.

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