

Article

The Inability of Metal Coordination to Control the Regioselectivity of Dimerization of *Trans*-Cinnamic Acid Derivatives

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Abstract: Upon exposure to irradiation, *trans*-cinnamic acid can dimerize, producing truxinic and truxillic acids, regioisomers distinguished by the relative arrangement of acid and phenyl groups on the formed cyclobutane ring. Solid-state dimerization, governed by Schmidt's specified conditions, hinges on the initial molecular setup. This study endeavors to manipulate the reaction's outcome in the solid state. To achieve this, the target molecule was paired with metals (Ag, Cu) to modify molecular orientation in the solid. Investigated derivatives included *para*-hydroxy-*trans*-cinnamic acid, *ortho*-methoxy-*trans*-cinnamic acid, *ortho*-ethoxy-*trans*-cinnamic acid, and *ortho*-chloro-*trans*-cinnamic acid. Despite easy synthesis of all complexes, only the complex between Ag and *ortho*-chloro-*trans*-cinnamic acid exhibits photoreactivity, mirroring the outcome of the metal-free derivative. Thus, while this approach has the potential to alter the photobehavior of cinnamic acid derivatives, obtaining the desired structure will require extensive screening to identify an appropriate metal complex.

Keywords: *trans*-cinnamic acid; photodimerization; regioselectivity; complexes

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1. Introduction

Solvent-free reactions align with the principles of green chemistry, aiming for more sustainable chemical processes in response to today's environmental challenges. The [2 + 2] photocycloadditions are representative of reactions that can be performed without the requirement for a solvent [1,2]. Cohen and Schmidt extensively studied these reactions and postulated that the "reaction in the solid state occurs with a minimum amount of atomic or molecular movement" with the resulting product structure, therefore, depending on the initial crystal structure of the reactant species [3,4]. Furthermore, performing these reactions in the solid state allowed for better control of regioselectivity/stereospecificity in comparison to solution-phase reactions [5]. Schmidt established two conditions required for solid-state [2 + 2] reactions to occur: the double bonds must align parallel to each other, and the distance between these bonds should be shorter than 4.2 Å [6].

Trans-cinnamic acid (TCA) and its derivatives form an example of compounds that can dimerize following a [2 + 2] cycloaddition to yield truxinic or truxillic acids. These latter are regioisomers, differing only by the relative position of the phenyl and carboxylic acid functional groups. For the former, the phenyl groups are linked to two adjacent cyclobutane carbon atoms, while in the latter, these phenyl groups are linked to opposite carbon atoms [7]. Linking Schmidt's rules with molecular orientation, *trans*-cinnamic acid, and its derivative's solid forms, can be classified into three types (Figure 1). The α -type and β -type respect Schmidt's rules and, respectively, show a "head-to-tail" (HTT) and "head-to-head" (HTH) packing arrangement. After irradiation, the HTT packing leads to the HTT dimer or α -truxillic acid, and the HTH packing leads to the HTH dimer or β -

truxinic acid. The third type of packing, the γ -type, does not fulfill Schmidt's rules and those crystal structures are, therefore, photostable [7,8].

Two crystalline forms of TCA exist, the α - and the β -types. These forms are, respectively, named in the literature the α - and β -polymorphs, and irradiation of these forms leads, respectively, to α -truxillic acid and β -truxinic acid. Both polymorphs are monotropically related, with the α -polymorph the more stable polymorph. The β -polymorph spontaneously transforms into the α -form over time. Consequently, when irradiating the former, the obtained product is almost always a mixture of α -truxillic and β -truxinic acids. *para*-hydroxy-TCA (p-OH-TCA), *ortho*-methoxy-TCA (o-OMe-TCA) and *ortho*-chloro-TCA (o-Cl-TCA) have only one known polymorph, belonging, respectively, to the α -type for the first two and the β -type for the latter. *ortho*-ethoxy-TCA (o-OEt-TCA) shows three polymorphic forms: two packing in the α -type, one of which is only accessible at high temperatures (named α - and α -HT-polymorphs) and one packing in the γ -type (the γ -polymorph) (Figure 2) [8–11].

In addition to α -, β -, and γ -types, packing δ - and ϵ -types are theoretically also possible, leading, respectively, to δ -truxinic [12] and ϵ -truxillic acids [13]. However, these solid arrangements have not yet been observed experimentally.

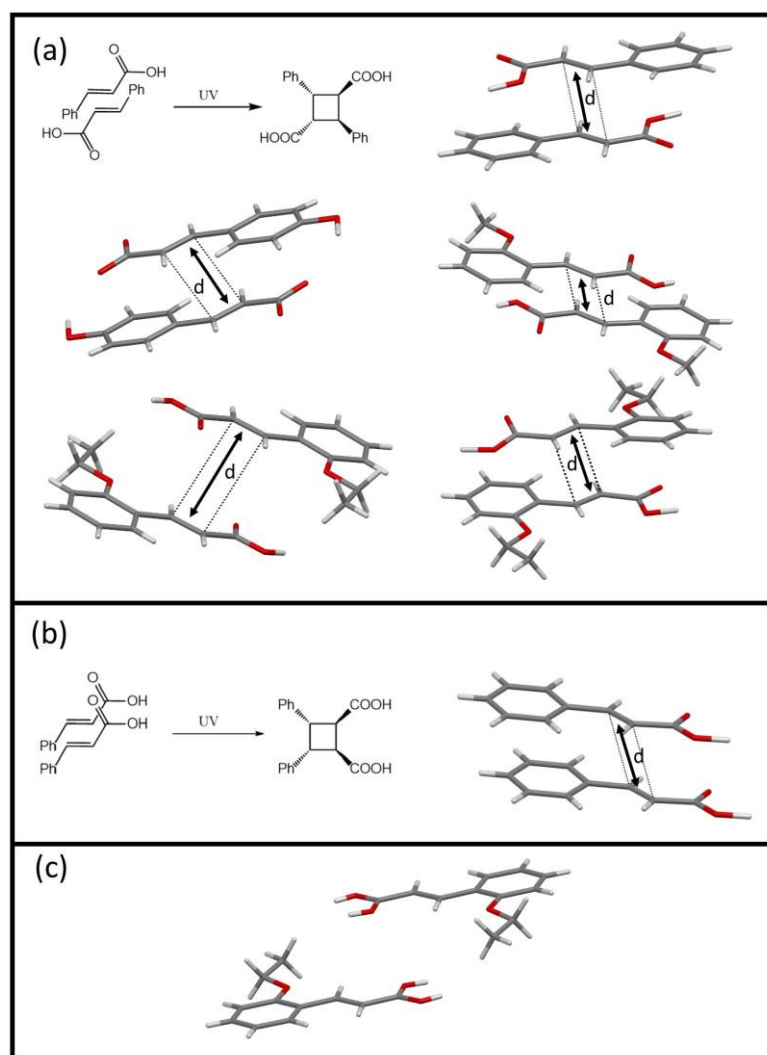


Figure 1. (a) α -type (HTT orientation): Scheme representing the photobehavior of TCA in the α -type, the crystal structure of the α -polymorph of TCA (top right, $d = 3.7 \text{ \AA}$) [14], of p-OH-TCA (**center left**, $d = 3.8 \text{ \AA}$) [15], of o-OMe-TCA (**center right**, $d = 4.1 \text{ \AA}$) [16], of the α -polymorph of o-OEt-TCA (**bottom left**, $d = 4.5 \text{ \AA}$) [11] and of α -polymorph-HT (**bottom right**, $d = 3.7 \text{ \AA}$) [10]; (b) β -type (HTH orientation): Scheme representing the photobehavior of TCA in the β -type and the crystal

structure of the β -polymorph of TCA ($d = 4.0 \text{ \AA}$) [17]; (c) γ -type (No reaction): Crystal structure of ($d = 5.3 \text{ \AA}$) [11]. The dotted lines represent the bonds formed after irradiation.

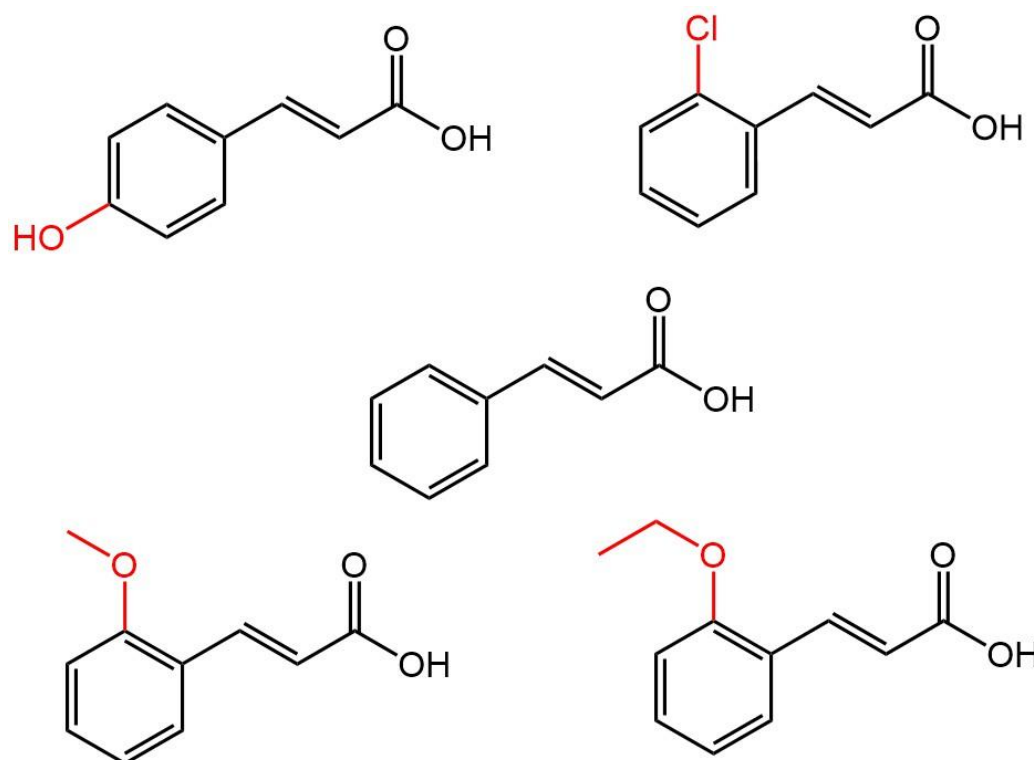


Figure 2. Scheme representing TCA (**center**) and the different derivatives studied in this work: p-OH-TCA (**top left**), o-Cl-TCA (**top right**), o-OMe-TCA (**bottom left**), o-OEt-TCA (**bottom right**).

Theoretically, for a given compound, if its packing type can be altered, control over the achieved photoproduct can be obtained. Crystal engineering offers the tools that allow for changing the packing of a given target compound. In 1989, Desiraju defined crystal engineering as “the understanding of intermolecular interactions in the context of crystal packing and in the utilization of such understanding in the design of new solids with desired physical and chemical properties” [18]. In previous work, we used a cocrystal engineering approach to successfully alter the packing type and associated reactivity of TCA and two of its derivatives [19]. The main disadvantage of this approach is associated with the low success rate of cocrystallization, with only a limited amount of coformers successfully yielding a cocrystal. Furthermore, if a target cocrystallizes with a given coformer, this does not imply a second target will also successfully cocrystallize with this coformer (e.g., 4,6-dichlororesorcinol allows the formation of a β -type cocrystal for TCA but 4,6-dichlororesorcinol does not cocrystallize with p-OH-TCA).

In this contribution, we investigate a different crystal engineering approach using metal complexation. As TCA and its derivatives have a carboxylic acid function, we aimed at creating $R\text{-COO}^-\text{M}^+$ bonds. Considering these bonds are stronger than the hydrogen bonds used in our previous cocrystal approach, we hypothesized that a given metal should theoretically couple to all TCA derivatives, removing the limitation of the cocrystal approach mentioned above. In their work, Li et al. already synthesized the $\text{Ag}(\text{o-Cl-TCA})(\text{H}_2\text{O})$ complex, which fulfills Schmidt’s conditions (Figure 3) [20]. This structure packs according to the β -type, but the reactivity of this complex has not yet been studied. Besides silver, copper can be a cheap and easily accessible alternative. Multiple examples exist where copper-carboxylate complexes show parallel ligands packed at a distance inferior to $4.2 \text{ \AA}$ (Figure 4) (e.g., 2,4,6-trifluorobenzoate [21], 2-carbamoylphenoxyacetate [22], 2-carboxyphenoxyacetate [23], benzene-1,3,5-tricarboxylate [24], or isophthalate [25]).

Here, we investigate whether metal complexation can be used to alter the stacking type of TCA and derivatives with the ultimate goal of controlling the regiochemistry of the product resulting from irradiation. To conduct this, we investigated carboxylate complexes of Ag^{+1} and Cu^{+2} .

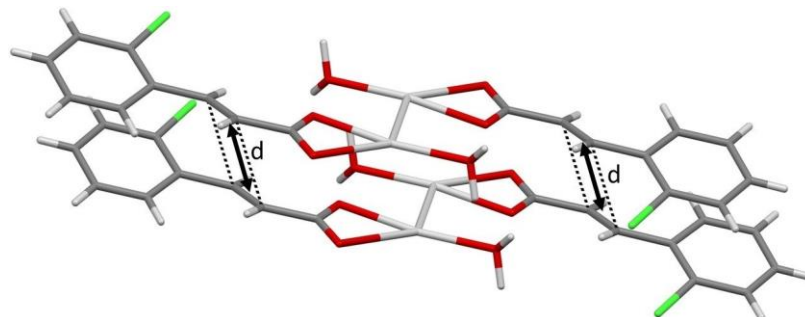


Figure 3. Crystal structure of $\text{Ag}(\text{o-Cl-TCA})(\text{H}_2\text{O})$ ($d = 3.9 \text{ \AA}$) [20]. The dotted lines represent the bonds that can potentially form upon irradiation.

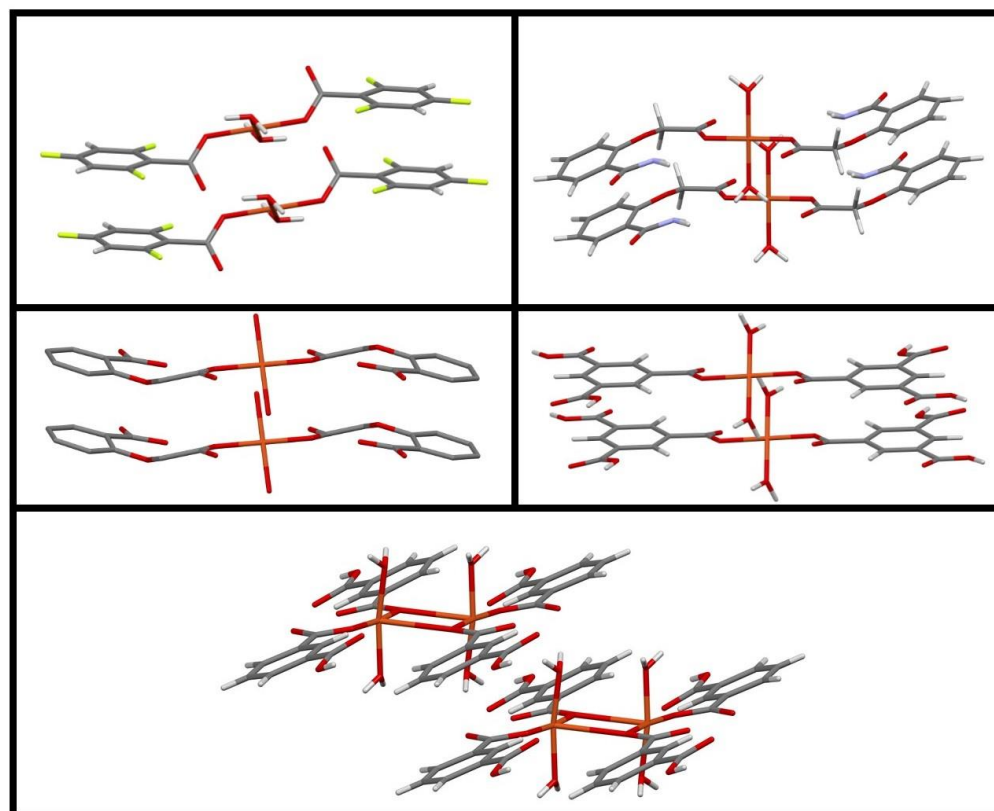


Figure 4. Crystal packing of the complexes between copper and 2,4,6-trifluorobenzoate (**top left**, $d = 3.6 \text{ \AA}$) [21], 2-carbamoylphenoxyacetate (**top right**, $d = 4.1 \text{ \AA}$) [22], 2-carboxyphenoxyacetate (**center left**, $d = 4.1 \text{ \AA}$) [23], benzene-1,3,5-tricarboxylate (**center right**, $d = 3.7 \text{ \AA}$) [24] and isophthalate (**bottom**, $d = 3.7 \text{ \AA}$) [25]. The distances reported are calculated between the center of the phenyl groups.

2. Materials and Methods

2.1. Materials

All solvents used in this study were commercially sourced from VWR. These solvents were employed without any further purification. Trans-cinnamic acid (TCA) (97%) was procured from Sigma-Aldrich. The two derivatives, o-Cl-TCA (98%) and p-OH-TCA (98%) were acquired from TCI. o-OEt-TCA was supplied by ABCR and o-OMe-TCA (97%) was obtained from Acros. Strem Chemicals provided Ag₂O (99.99%), while CarlRoth supplied AgNO₃ (99%). Anhydrous CuCl₂ (99%) was sourced from ThermoScientific. All these substances were used in their original state without additional purification.

2.2. Methods

Single-Crystal Growth of o-Cl-TCA: 1 mmol (183 mg) of o-Cl-TCA was dissolved in acetone (polymorph I) or methanol (polymorph II). The solution was allowed to undergo slow evaporation at room temperature until colorless crystals were obtained.

Synthesis and Single-Crystal Growth of Complexes: The synthesis and single-crystal growth were accomplished via three different evaporative crystallizations. These methods are adapted from reported procedures and are detailed below [20–22,25,26].

Method 1: Compound of interest (COI) (1 mmol) is dissolved in 5 mL of a water-miscible organic solvent and a metal salt (MX) (1 eq of the metal) is dissolved in 5 mL of water. The solutions are subsequently combined. In the event of a precipitate formation, the supernatant is carefully removed. The precipitate is analyzed using XRPD, while the supernatant is left to evaporate to grow single crystals.

Method 2: First, the COI salt is prepared by stirring an equimolar mixture of COI and NaOH. After complete dissolution is achieved, water is removed using a rotary evaporator. Second, COI salt (1 mmol) and MX (1 eq of the metal) are dissolved in 10 mL of water. The solution is stirred for 1 day. In the event of a precipitate formation, the supernatant is carefully removed. The precipitate is analyzed using XRPD, while the supernatant is left to evaporate to grow single crystals.

Method 3: COI (1 mmol) and the metal oxide (1 eq of the metal) are dissolved in 10 mL of 28% aqueous ammonia solutions. The solution is stirred for 30 min. The solution is left to evaporate to yield single crystals.

Silver Complexes: The silver salt employed is AgNO₃, and the oxide used is Ag₂O.

When COI is o-Cl-TCA, only Method 3 was used. Through rapid evaporation, a combination of both the hydrate and anhydrate forms was obtained. However, when the evaporation process was slowed down, only the hydrate form was obtained.

For the anhydrate structure of o-Cl, a solution of ammonia in isopropyl alcohol was used. Crystals of the anhydrate form were formed on the wall above the solution. Crystals submerged into the solution were found to be in the hydrate form.

With the four other COIs, Method 3 was also applied using slow evaporation. With p-OH-TCA, the solution became black during the evaporation and no complexes could be formed. With TCA and o-OEt-TCA, single crystals of the complexes were obtained, while with o-OMe-TCA only the powder of this complex could be synthesized.

Method 1 (with acetone, acetonitrile, ethanol, methanol, iso-propanol, and tetrahydrofuran) and Method 2 were also tried but no new crystal structure was obtained. For these methods, evaporation occurs at 5 °C.

Note that slurring these complexes in water at 5 °C for 1 week does not impact the crystal structure.

All synthesized complexes are white.

Copper Complexes: The copper salt employed is CuCl₂, while no copper oxide was used.

Only Method 1 (with acetone, ethanol, methanol, iso-propanol, and tetrahydrofuran) and Method 2 were tried with the 5 COIs. With Method 1, no complexes were formed

contrary to Method 2 where new crystal structures appeared. Slow evaporation leads to a single crystal with COI's p-OH-TCA and o-OMe-TCA.

All synthesized complexes are blue.

Powder X-ray Diffraction (XRPD): X-ray powder diffraction patterns of the samples were obtained using a Bruker D8 Advance powder X-ray diffractometer, which was equipped with a Cu-K α X-ray source (wavelength, $\lambda = 1.5406 \text{ \AA}$) operating at 40 kV and 30 mA. The data were collected over 2θ values ranging from 5 to 35°, with a step size of 0.02° and a total scan time of 10 min.

Single-Crystal X-ray Diffraction (SCXRD): Single-crystal X-ray diffraction analysis was conducted on an appropriate single crystal and examined using an MAR345 image plate with MoK α radiation generated by an Incoatec I μ S microfocus source equipped with Montel mirrors. The data were processed using the CrysAlis^{PRO} software package [27]. Resolution and refinement by full-matrix least-squares were accomplished using SHELXT [28] and SHELX-2018/3 [29], respectively. Anisotropic refinement was applied to non-hydrogen atoms, while hydrogen atoms were positioned through calculations and allowed to ride on their parent atoms. Isotropic displacement factors were set to 1.2 Ueq of the parent atoms (Uiso(H) = 1.5 Ueq(C) for methyl and OH hydrogens). Methyl group hydrogen atoms were permitted free rotation about the local 3-fold axis. For Ag(o-Cl-TCA), the high residual density peaks/holes (3.094, −2.231) are ascribed to the combination of the high absorption coefficient of the crystal (2.580 mm^{−1}) and the observed twinning, leading to errors in the absorption model. Symmetry analysis and validation were conducted using PLATON [30]. Molecular visualization figures were generated using Mercury 2022.3.0 [31]. Crystallographic and refinement details are provided in Tables S1–S7 (Supporting Information). The supplementary crystallographic data for CCDC 2342097–2342103 can be freely accessed and downloaded from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/structures.

Irradiation + ¹H-NMR: The powder was placed between two glass plates, which were subsequently sealed together. The compound underwent photoactivation using a UV lamp, specifically the “Oriel instrument: Universal Arc Lamp Housing” (model: 66921; source: Hg(Xe)), at 500 W for 4 h and flipped every 30 min to avoid overheating and maximize exposure of both sides. The resulting irradiation products were analyzed using ¹H-NMR spectroscopy using a Bruker-300 spectrometer operating at 300 MHz. NMR spectra were recorded in DMSO-d₆, internally referenced to residual solvent (¹H) resonances, and reported relative to tetramethylsilane. Chemical shifts are expressed in ppm with tetramethylsilane as the reference. To avoid magnetic interference with copper, this metal was first removed by dissolution in aqueous HCl. As silver does not interfere with ¹H-NMR, this treatment was not applied to the silver complexes. As only the surface of crystals is irradiated, only partial transformation occurs, with full transformation requiring cycles of irradiation followed by grinding to expose a new layer of compound.

3. Results and Discussion

3.1. Single Crystal Structures of o-Cl-TCA

As mentioned above, the TCA derivative, o-Cl-TCA crystallizes as a β -type. This observation is based on the outcome of an irradiation experiment, but no structural confirmation has been available thus far. We were successful in obtaining and analyzing two polymorphic structures of o-Cl-TCA, both of the β -type. As shown in Figure 5, the molecules show an HTH packing and respect Schmidt's conditions, with the parallel double bonds separated by 3.8 Å in both cases. In Figure S11, both polymorphs are superposed, showing the packing similarities and differences between both forms.

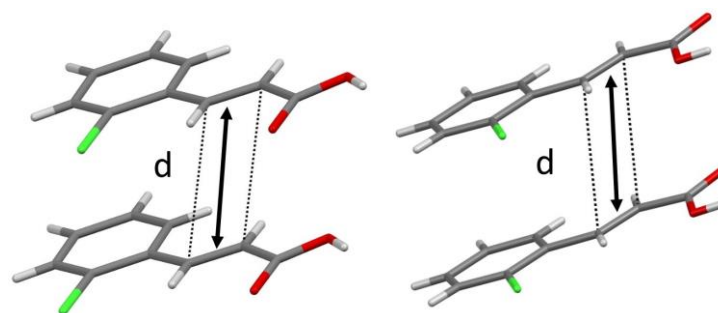


Figure 5. Structural arrangement of polymorph I (**left**) and polymorph II (**right**) of o-Cl-TCA (β -type) ($d = 3.8 \text{ \AA}$). The dotted lines represent the bonds that will form upon irradiation.

3.2. Metallic Complexes

Our goal was to identify and study the metal complexes of TCA and derivatives. To conduct this, synthesized powders were analyzed by XRPD, to confirm the phase (Figures S2–S10), after which they were irradiated. The irradiated product is analyzed by $^1\text{H-NMR}$, to verify whether cycloaddition occurred. To understand the reaction outcome, the structure was determined through single crystal analysis.

3.2.1. Silver

As mentioned above, the complex $\text{Ag}(\text{o-Cl-TCA})(\text{H}_2\text{O})$ (Figure 3) should lead to the formation of β -truxinic acid. We indeed confirmed this to be the case. As shown by the $^1\text{H-NMR}$ data (Figure S1), when irradiating the hydrated complex (Figure 3), β -truxinic acid is obtained. As mentioned above, no full transformation occurs, as only molecules close to the crystal surface react. Importantly, the metal center does not hinder the $[2 + 2]$ photoreaction. However, upon synthesizing this complex, we unexpectedly encountered the anhydrate form $\text{Ag}(\text{o-Cl-TCA})$, as shown in Figure 6. Interestingly, this anhydrate is photostable (γ -type), with non-parallel double bonds separated by $5.3 \text{ \AA}$, showing how small compositional changes can have a substantial impact on the overall structure and, hence, the photoreactivity.

We then extended silver complexation to the remaining four model compounds. However, none of the obtained complexes was photoactive. The anhydrate complexes $\text{Ag}(\text{TCA})$ and $\text{Ag}(\text{o-OEt-TCA})$ show non-parallel double bonds separated by $5.1 \text{ \AA}$ and $4.5 \text{ \AA}$, respectively (Figure 6), explaining the observed photostability. For the p-OH-TCA and o-OMe-TCA complexes, no single crystals were obtained, but both complexes were found to be photostable.

Different attempts were made to obtain hydrated forms of these four complexes, but all attempts resulted in the formation of anhydrate phases.

From the crystal structure itself, it is hard to predict why these hydrates do not form for the other compounds. What can be said is that the addition of water coordinating to the metal leads to a rearrangement of the organic compounds in the crystal structure. As shown in our previous work, slight changes can be sufficient to lead to an alignment of TCA derivatives respecting Schmidt's rules. However, these subtle changes are due to a combination of intermolecular interactions, and constructing guiding lines based on the limited amount of structures is not feasible. We suspect that the strong metal–ligand coordination explains first of all why hydrates are not easily obtained. In the case of the $\text{Ag}(\text{o-Cl-TCA})(\text{H}_2\text{O})$ complex, the π - π stacking interaction is expected to be more important, aligning TCA molecules, and allowing it to free up a coordination possibility for water. To confirm this hypothesis, crystal structure prediction studies would be required, which go beyond the scope of this work.

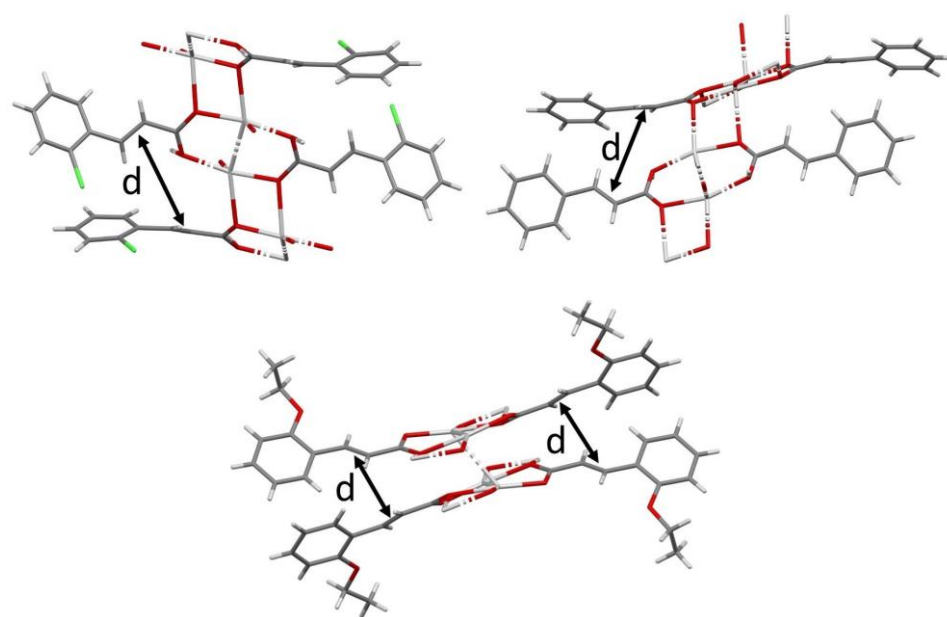


Figure 6. Crystal packing of Ag(o-Cl-TCA) (**top left**, $d = 5.3 \text{ \AA}$), Ag(TCA) (**top right**, $d = 5.1 \text{ \AA}$) and Ag(o-OEt-TCA) (**bottom**, $d = 4.5 \text{ \AA}$).

3.2.2. Copper

We then switched to bivalent copper complexes. Contrary to the silver complexes, no copper complex of TCA or its derivatives are reported in the literature. Copper, chosen as carboxylate hydrated complexes, is described in the literature showing parallel molecules distanced by less than $4.2 \text{ \AA}$ (Figure 4).

With the exception of o-Cl-TCA, we successfully synthesized complexes (see Supplementary Materials Section 1) of the type $\text{Cu}(\text{TCA})_x(\text{H}_2\text{O})_y$ (TCA or one of its derivatives) with all compounds (although the presence of water is not confirmed for the complexes with TCA and o-OEt-TCA due to the absence of crystal structure).

All obtained powders crystallized as hydrates and turned out to be photostable. The structure of complexes $\text{Cu}(\text{p-OH-TCA})_2(\text{H}_2\text{O})_4$ and $\text{Cu}_3(\text{o-OMe-TCA})_6(\text{H}_2\text{O})_2$ (Figure 7) illustrate that, indeed, double bonds are not aligned in a parallel manner and separated, respectively, by $4.7 \text{ \AA}$ and $5.3 \text{ \AA}$. In both cases, the simulated and experimental XRPD align (SI).

Attempts to synthesize anhydrate forms were unsuccessful.

In this case, we assume the main driving force for the structural orientation is a metal–ligand bond, instead of π - π stacking between organic compounds. This interaction guides the orientation of the molecules rather than the stacking interactions, explaining why the likelihood of aligning the double bonds according to Schmidt’s rules is less likely.

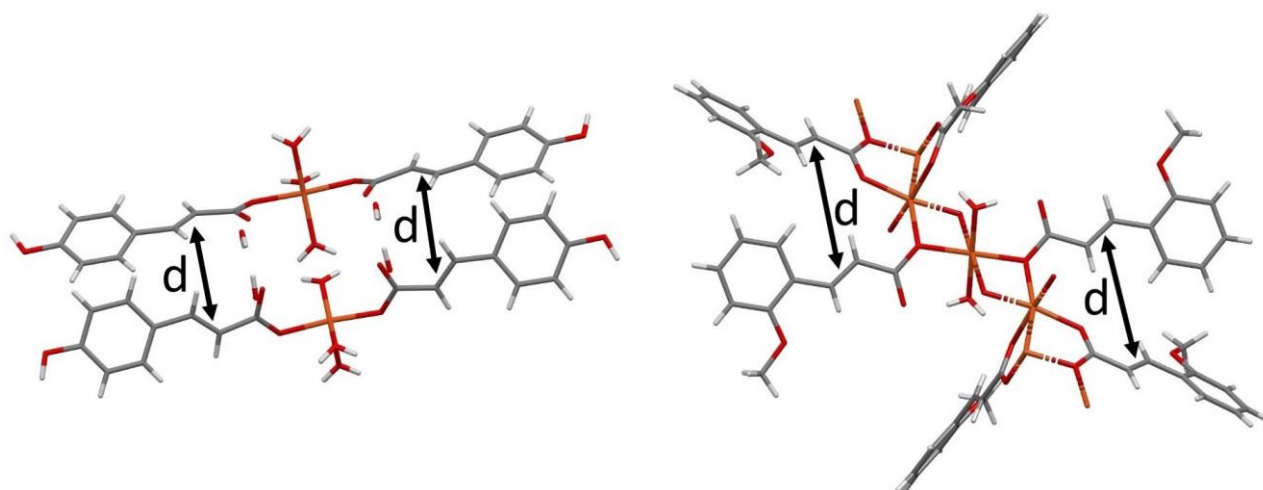


Figure 7. Crystal packing of $\text{Cu}(\text{p-OH-TCA})_2(\text{H}_2\text{O})_4$ (left, $d = 4.7 \text{ \AA}$) and $\text{Cu}_3(\text{o-OMe-TCA})_6(\text{H}_2\text{O})_2$ (right, $d = 5.3 \text{ \AA}$).

4. Conclusions

We aimed to alter the photoreactivity of TCA and four of its derivatives by forming complexes with Ag and Cu. Although their photobehavior altered when forming metal complexes, in most cases this led to non-photoreactive structures. Only the complex between silver and o-Cl-TCA leads to a hydrated phase of the β -type. This latter was shown to be photoreactive, leading to β -truxinic acid. For the anhydrous complex, as well as the silver complexes of TCA, p-OH-TCA, o-OMe-TCA, and o-OEt-TCA, a γ -type packing was observed. When using copper, hydrated γ -type complexes formed in all cases.

Controlling regioselectivity during the dimerization of TCA-like compounds using metal-complexation is feasible, as highlighted by the Ag complex presented here. However, in most cases, non-reactive species were obtained. This is likely due to the strong metal–carboxylic acid interaction, which would be the main interaction responsible for orienting the compounds instead of the π -stacking interactions, which one would use to align the TCA molecules in a manner so that Schmidt’s rules are respected.

Ultimately photoreactive complexes are less likely to result, which makes identification of an ideal complex a tedious and time-consuming task.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/cryst14060530/s1>, Figure S1: $^1\text{H-NMR}$ spectra of the irradiated $\text{Ag}(\text{o-Cl-TCA})(\text{H}_2\text{O})$; Figure S2: XRPD data of the complex $\text{Ag} + \text{o-Cl-TCA}$; Figure S3: XRPD data of the complex $\text{Ag} + \text{TCA}$; Figure S4: XRPD data of the complex $\text{Ag} + \text{p-OH-TCA}$; Figure S5: XRPD data of the complex $\text{Ag} + \text{o-OMe-TCA}$; Figure S6: XRPD data of the complex $\text{Ag} + \text{o-Et-TCA}$; Figure S7: XRPD data of the complex $\text{Cu} + \text{TCA}$; Figure S8: XRPD data of the complex $\text{Cu} + \text{p-OH-TCA}$; Figure S9: XRPD data of the complex $\text{Cu} + \text{o-OMe-TCA}$; Figure S10: XRPD data of the complex $\text{Cu} + \text{o-Et-TCA}$; Table S1: Main crystallographic data of o-Cl-TCA (Polymorph I); Table S2: Main crystallographic data of o-Cl-TCA (Polymorph II); Figure S11: Structural comparison between both polymorphs of o-Cl-TCA; Table S3: Main crystallographic data of $\text{Ag}(\text{o-Cl-TCA})$; Table S4: Main crystallographic data of $\text{Ag}(\text{TCA})$; Table S5: Main crystallographic data of the complex of $\text{Ag}(\text{o-OEt-TCA})$; Table S6: Main crystallographic data of $\text{Cu}(\text{p-OH-TCA})_2(\text{H}_2\text{O})_4$; Table S7: Main crystallographic data of $\text{Cu}_3(\text{o-OMe-TCA})_6(\text{H}_2\text{O})_2$.

Author Contributions: conceptualization, G.W., K.P. and T.L.; methodology, G.W.; validation, G.W.; formal analysis, G.W. and K.P.; investigation, G.W. and K.P.; resources, T.L.; data curation, K.R.; writing—original draft preparation, G.W. and T.L.; writing—review and editing, G.W., T.L. and K.R.; visualization, G.W.; supervision, T.L.; project administration, T.L.; funding acquisition, T.L. and K.R. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: The authors declare no conflicts of interest.

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