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BIOMIMETIC CHEMISTRY IN THE SOLID STATE[1]

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Abstract Because of the precise ordering of molecules in crystals, chemists developing organic chemistry in the solid state have been able to produce solid chemical systems which imitate and simulate biological processes. Several examples taken from the literature are given.

INTRODUCTION

More than twenty years after the pioneering work of Cohen and Schmidt[2] introducing the topochemical principle as a consequence of studies of (2 + 2) π photodimerization in the solid state, the literature still abounds with reports concerning new developments on solid state reactions. Initiallly the effort of investigation was mainly directed to correlations of reactivity with X-ray structure determination and in showing evidence of the effect of the crystalline structure of starting material on reaction pathways and final product structure. This effort was done to improve synthetic methods and to afford precise details on molecular mechanism in relationship to reactions in solution. A certain number of general reviews and articles has shown a variety of examples of such effort and how

different disciplines can provide fruitful cooperation on particular phenomena[3-8]. Although there has been a great proliferation of investigations on reactions occuring in the solid state and/or in heterogeneous conditions, application possibilities were not well defined probably because solid state chemistry was a new field of research. More recently new trends and developments in solid state chemistry have been shown to contribute to fields of application : photodimerization is correlated to photographic developments[6], solid state polymerization is applied to preparing superconductors[9], investigations of solid-gas reactions are useful for pharmaceutics[7], crystal structure determination and molecular packing studies are essential for designing synthetic metals[10].

The object of this review is to present tentative correlations between processes involved in solid state systems and biological systems. These correlations are based on the following idea : organized biological systems are able to perform selective functionalizations on substrate molecules. This high specificity is due to the strictly defined geometry and the ordered proximity of the reactants undergoing the desired reaction. The reactive functionnal groups attached to the reactant molecules adopt mutual orientations and relative positions which induce and facilitate the reaction. With respect to these observations biomimetic chemistry has been developed in two directions :

i. to imitate and stimulate the high specificity of biological reactions and to apply it to efficient synthetic chemistry[11].

ii. in a wider use, to contribute to the basic understanding of living phenomena by the construction of chemical models presenting in their three dimension structure very similar functions to substances acting in biological systems[12].

Organic solid state chemistry is mainly directed to studying chemical changes of organic molecules in the solid phase. In the reactive crystalline phase the molecules are precisely ordered in close contact. Molecular interactions are rigid and severely constrained by the crystalline packing. The separation distances and the orientations of the interacting functional groups are made rigid by the crystal lattice and the reactivity of molecules thus depends on the crystal structure in a cooperative way. From this topological point of view, organic chemistry in the solid state has been able to produce solid systems able to imitate and simulate biological systems. And one can speak of biomimetic models in the solid state.

Previous examples of correlations of solid state chemistry with biological processes have been proposed in the literature. Cohen noticed that solid state photolysis of dicroïc crystals of various diazocompounds show the dependence of these crystals with a suitable orientation with polarized light[13]. An application of this effect has become apparent from studies of visual processes in which microscopic observation of a rod shows it to be highly

dicroïc[13]. In a different paper the same author proposes that the process in the transfer of energy in anthracenes photodimerization is similar to the transfer of energy in DNA damage reactions[14]. On the one hand the non-topological photodimerization of anthracenes is shown to occur preferentially at specific defect sites in the crystal rather than at random[14]. On the other hand in the multidamaged DNA, the thymine dimers are located in clusters rather than at random[14]. In both cases it is suggested by Cohen that mobile excitation energy is trapped near preliminary formed dimer, leading to "aggregates" of photoproducts[14]. Adler reported that irradiation of solid amides, fatty acids and related compounds yields radicals reacting with ambient gases such as O_2, NO_2 and SO_2[15]. The diffusion of gas through the crystal lattice was rationalized by a dependence on a particular kind of structure named "bilayer structure"[15].This bilayer structure was claimed to bear a superficial resemblance to bilayer structure of cell membranes[15].

PHOTOREACTIVITY OF THYMINE-THYMINE SOLID COMPLEX.

Figure 1 represents the thymine dimerization occuring in irradiated nucleic acids.

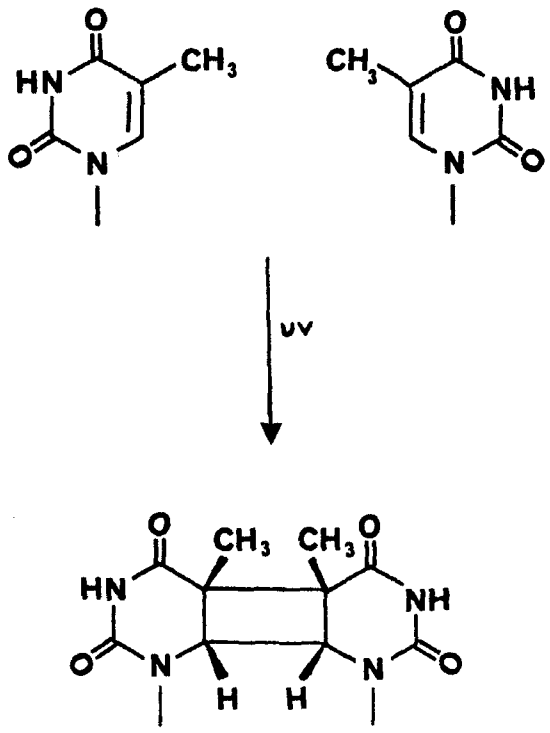
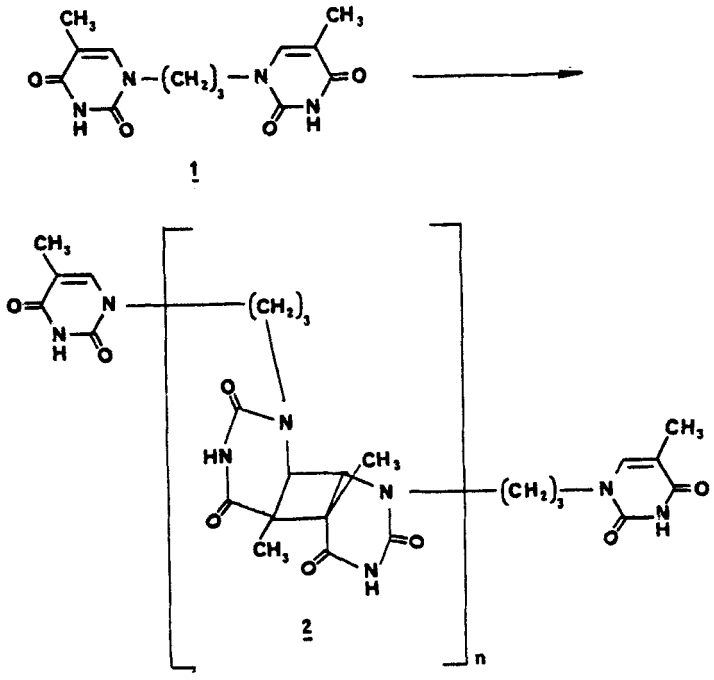


FIGURE 1. Photocycloaddition of pyrimidine bases (the pyrimidines shown are thymines)

In relationship to DNA damage due to the photocycloadditions of pyrimidine bases,(Figure 1), the photodimerization of a model molecule, 1, having a trimethylene chain between two thymine residues was investigated[16].



SCHEME I. Crystal state irradiation of 1.

Crystal state ultraviolet irradiation of 1 at 300nm yields a polymer 2 made up of trans-syn thymine cyclobutane dimer units, each joined to the next by a trimethylene chain (Scheme I)[16]. Irradiation of 1 in acetone (10%)-water solution yields practically exclusively the cis-syn internal cyclobutane dimer[16]. The crystal structure of 1 has been determined and shows that the thymine rings in the

crystal of 1 are arranged such that both intramolecular and intermolecular photoreaction could occur [17]. In each case a trans-syn geometry for photoproduct would be anticipated[17]. The intramolecular separation, 3.501 Å, of the double bonds is shorter than the intermolecular separation (3.688 Å)[17]. However the thymine moieties are aligned so their π orbitals probably interact more intermolecularly than intramolecularly [17]. The orientation of the orbitals involved in the cycloaddition has more influence than the distance between the reacting atoms [17].

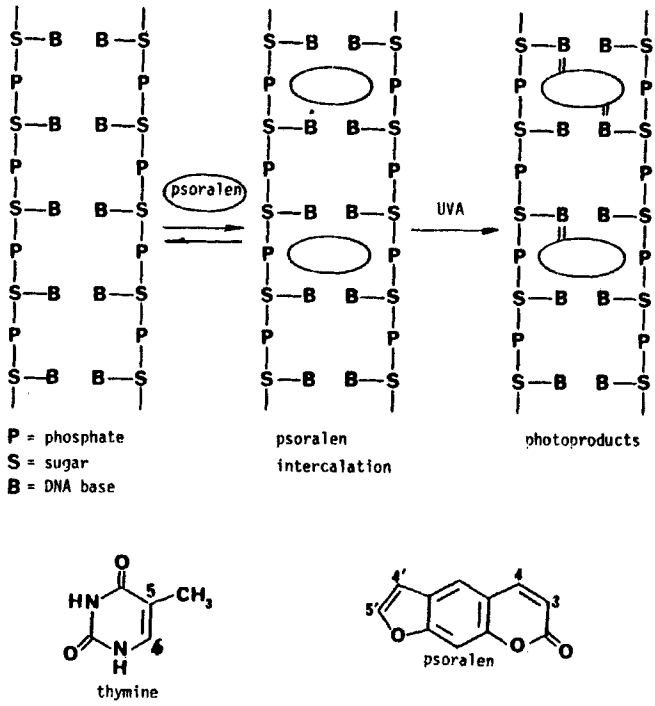
PHOTOREACTIVITY OF PSORALEN - THYMINE COMPLEX.

The photochemical activity of psoralens with nucleic acids is the subject of intense investigation. This interest is due on one hand to the application of psoralens in combination with uv irradiation in the treatment of DNA damage[18]. On the other hand, psoralen - nucleic acid reactions are used as a probe of nucleic acid structure and function [19].

The whole process of the activity of psoralens towards DNA involves two main steps (scheme II) :

1. The formation of a non covalent molecular complex by intercalation of one molecule of psoralen between DNA bases.

2. The photoreaction of the complex leads to the formation of covalent bonds between psoralen molecules and DNA bases.



SCHEME II. Activity of psoralens towards DNA.

During the second step irradiation gives rise to mono-and di-adducts deriving from cyclization reactions. Mono-adduct is initially formed by cycloaddition of a first thymine residue to the [4',5'] double bond (furan side) of psoralen. [20,21] Then a second thymine residue cycloadds to a [3,4] double bond (pyrone side) of the precedent mono-adduct [20,21]. Di-adduct is represented in Figure 2. The stereochemistry of the adducts is determined by the geometry of the non covalent molecular complex formed in step 1 prior to irradiation [20,21]. This complex allows for maximum π bond overlap and is observed to lead to cis-syn

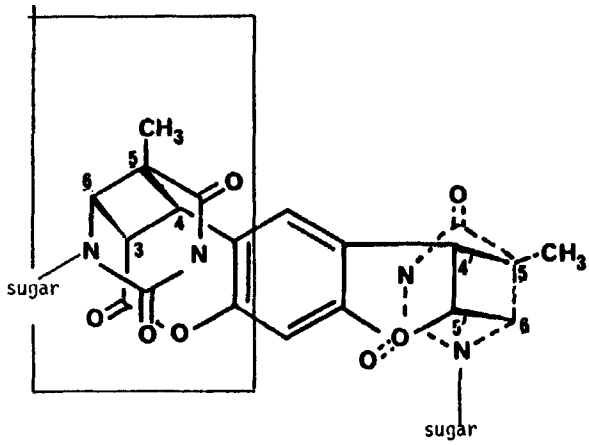


FIGURE 2. Diadduct of psoralen-DNA reaction.

configurations for both cyclobutanes formed[20,21]. This was consistent with a computer generated model[20] (Figure 3).

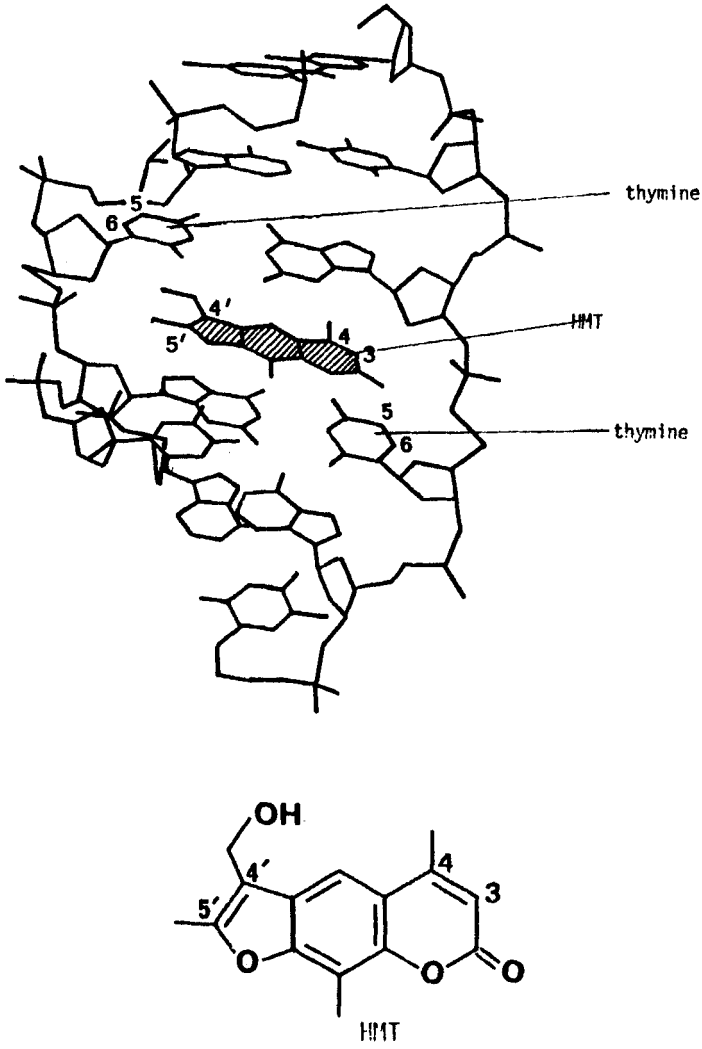
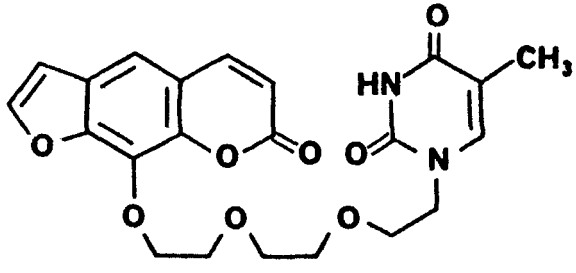


FIGURE 3. Computer-generated display of the proposed psoralen-DNA intercalation site (from reference 20).

SOLID STATE MODEL.

In a recent work a model molecule, 3, was designed having a trioxyethylene chain between thymine and psoralen residues [22,23] (Figure 4).



3

FIGURE 4. Model molecule 3.

Due to the flexibility of the polyoxyethylene link, analysis of the molecular packing of 3 shows formation of coplanar pairs of bases associated by H-bonds and complexation of the psoralen ring with the pairs of bases [22,23]. The planes formed by the thymine bases and psoralen are nearly parallel (angle≈3°C). The distance between double bonds of pyrone ring [3,4] and the [5,6] double bond of pyridine ring is 3.5Å [20,21].

Irradiation of single crystals of 3 leads to the formation of a cyclobutane between the [5,6] double bond of the thymine residue with the [3,4] double bond of the pyrone ring in a cis-syn configuration [20,21]. The solid state reaction is shown in Figure 5.

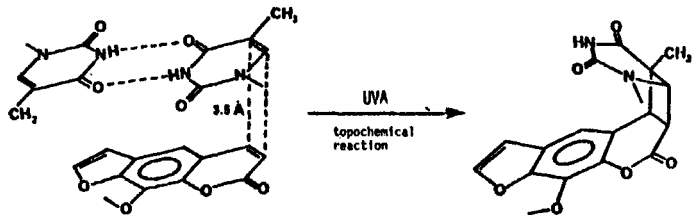
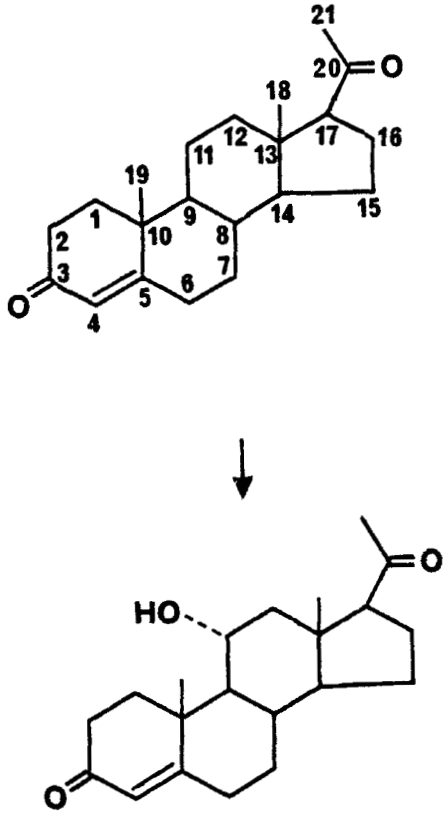


FIGURE 5. Solid state irradiation of 3.

The stereochemistry of the crystalline cyclization corresponds to the stereochemistry of the cyclization observed in the reacting living systems. Such a study is therefore of interest in mapping the conformation of molecules irradiated in DNA intercalation. From this mapping precise details may be informative for the subsequent photoreactive process.

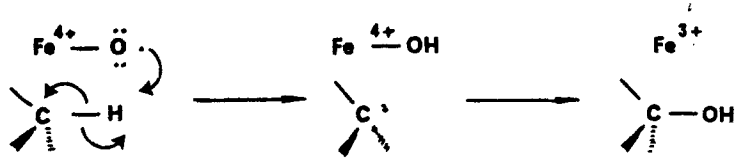
HYDROXYLATION OF STEROIDS.

The use of a micro-organism to introduce the hydroxy-group into an organic molecule by performing the direct conversion of a non-activated carbon-hydrogen bond to carbon-hydroxyl with defined regio-and stereo-specificity has given the organic chemist the ability to produce a wide range of compounds requiring synthetic ingenuity and skill[24,25]. Scheme III represents the microbial conversion of progesterone into its 11-α -hydroxy derivative by the fungus Rhizopus arrhizus[26]. Generally the



SCHEME III. Microbial conversion of progesterone into its 11-α-hydroxyderivative.

hydroxylation of steroïds at unactivated positions occurs exclusively with net retention of configuration[27,28]. For the catalytic cycle of cytochrome P450 dependent steroïd hydroxylations a free radical mechanism (Scheme IV) is believed[29].



SCHEME IV. Cytochrome P450 dependent hydroxylation free radical mechanism.

SOLID STATE MODEL.

Two recent publications report the solid state photochemistry of guest ketones inside the channels of host deoxycholic (DCA) and apocholic (APA) acids[30,31]. When DCA complexes with aliphatic ketones are irradiated in the presence of air, one photoproduct corresponds to a regio-and stereo-selective hydroxylation of C5 of DCA (Figure 6)[30]. It is suggested by the authors that the excited ketone in the channel of DCA produces a radical on C5 which may be trapped by molecular oxygen available in the channel leading to the isolated C5-OH hydroxy product[30]. The geometrical requirements of the C=O function and C-H

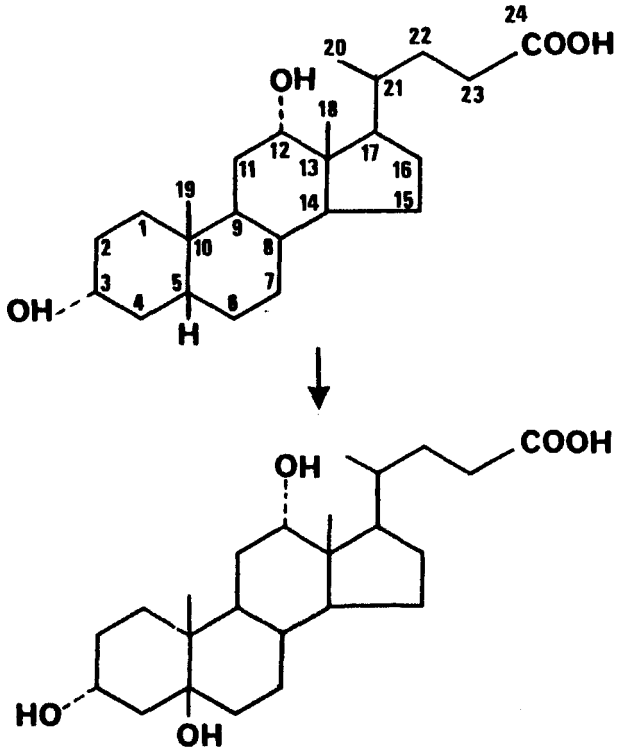
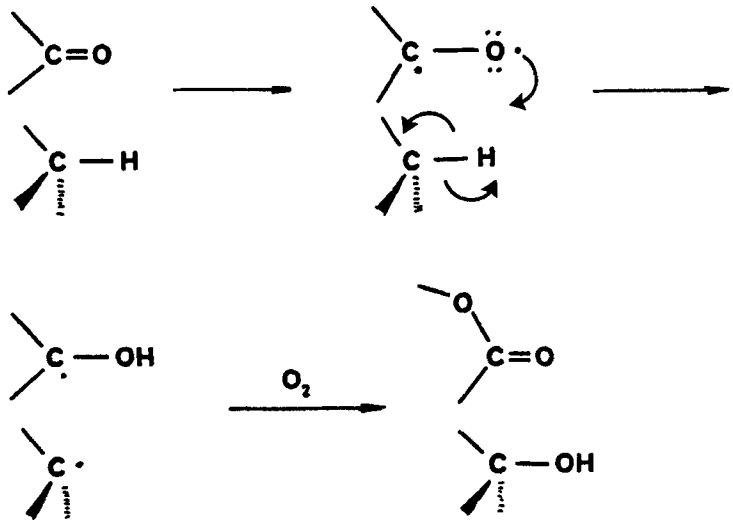


FIGURE 6. Regio-and stereo-specific C5 hydroxylation of DCA in solid state.

direction for the reaction to occur is described in reference 30 and will not be discussed here. A rough mechanism is depicted in Scheme V[32].



SCHEME V. Proposed mechanism of formation of C5 hydroxylation product of DCA.

It is obvious that the details obtained from such studies are of interest for interpreting detailed mechanism of microbial transformation of steroïds in living systems (mode of substrate binding, required geometries of atoms, intrinsic nature of reactions). A theoretical evaluation of hydroxylation mechanisms by living systems has been reported and no neat conclusion was given[33]. Finally it is to be noticed that the reaction occuring in DCA channels correponds to a hydroxylase present in Python liver[34].

CHLORINATION OF PHENOL AND DERIVATIVES.

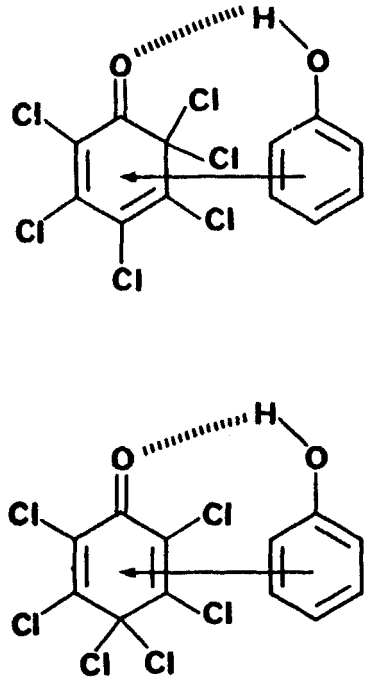
Chloroperoxidase is a heme protein (mol.wt. 42000) which has been isolated from the mold Caldariomyces fumago[35]. Chloroperoxidase catalyzes the peroxidative formation of the carbon-halogen bond according to Scheme VI[36].

$$H_2O_2 + X^- + HA \dashrightarrow AX + OH^- + H_2O$$

SCHEME VI. Chloroperoxidase catalysis.

X^- represents an oxidizable halogen anion (chloride, bromide a iodide) and HA represents an acceptor molecule with a replaceable proton[35]. Chloroperoxidase exhibits a broad specificity with respect to halogen acceptors. Among them phenol, substituted phenols and related aromatic compounds serve in an acceptor capacity in chloroperoxidase reactions[35,36]. The enzymatic chlorination of anisole only produces the para (p) and ortho (o) isomers at a p/o ratio of 1.9[36]. Chlorination by hypochlorous acid (HOCl) in presence of α-cyclodextrin (αCD) yields monochloration products at p/o ratio of 24[11]. This biomimetic effect was suggested to result from a chlorination occuring specifically on the para position because of a shielding of the ortho position in the αCD complex[11]. A similar biomimetic control by directing the topology of the reactants during chlorination was reported to take place during the regiospecific chlorination of phenol substrates by hexachlorocyclohexadienones[37]. The selectivity is obtained by

maintaining the reactants in the right position by building systems interacting as donor and acceptor (DA) and by hydrogen bonding (Scheme VII)[37].



SCHEME VII. Systems interacting as DA and by H-bonding used for selective chlorination.

In another system chlorination of phenol is promoted at the ortho position by micelles[38].

SOLID STATE SYSTEMS.

Gaseous chlorination of single crystals of 2-methylphenol showed that the p/o ratio varies according to the crystallographic orientation of the reactant surfaces[39]. It is suggested by the authors that the crystallographic faces exposing non reactive OH and CH_3 groups give less para chlorinated product than the crystallographic faces presenting the para position which, in turn, yielded more para chlorinated product (Figure 7)[39].

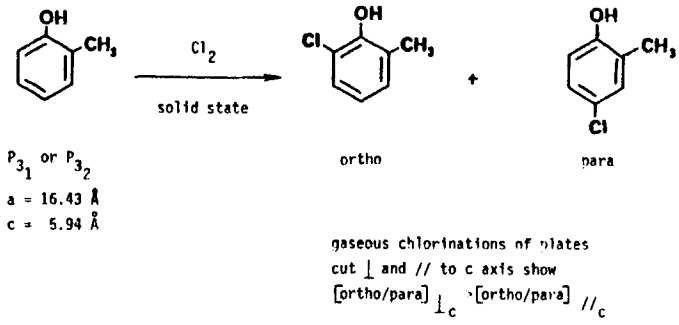


FIGURE 7. Chlorination of 2-methylphenol.

More spectacular is the reaction of gaseous chlorine on solid 18-crown-6 : H_2O : 3,5-dichlorophenol ternary complex[40]. In that case the reaction in solution leads to a p/o ratio < 1 while the reaction in the solid state leads to a p/o ratio > 1[40]. It is suggested from the crystalline

structure of the ternary complex (Figure 8) that the chlorine attacks preferentially at the para position because of a shielding of one ortho position of 3,5 dichlorophenol by interactions with 18-crown-6[40].

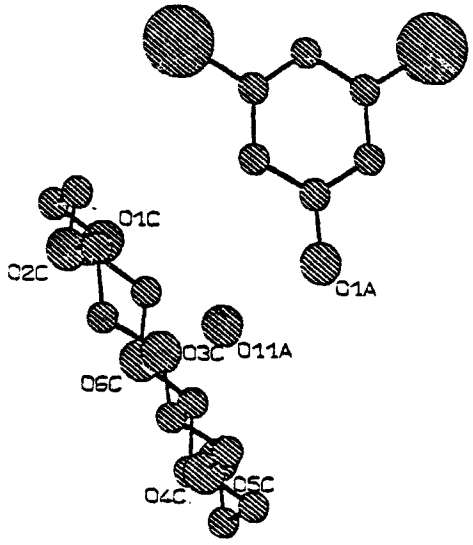


FIGURE 8. 18-crown-6 : H_2O : 3,5 dichlorophenol ternary complex.

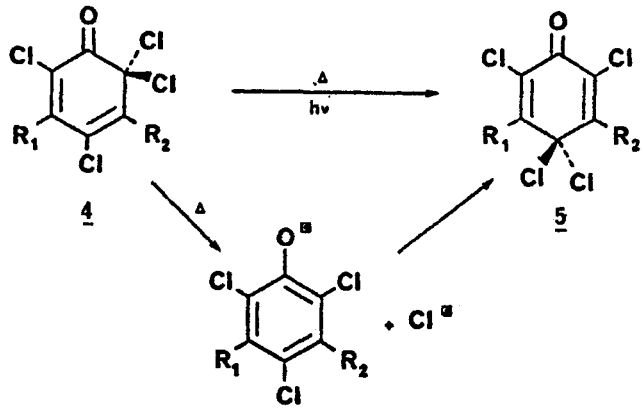
It becomes apparent that understanding the influence of the molecular packing of the complex gives a tool for planning new models and matrices for directing selective chlorinations. This may be helpful for synthetic purposes and of interest for creating systems involving other substrates than phenols and derivatives.

Moreover the methodology used in such organized systems performing selective chlorinations in anisotropic

media involves at one step of the reaction electrophilic chlorination of an aromatic ring. This reaction is characterized by the conversion of an sp2 carbon into an sp3 one by formation of a new C-Cl bond (Scheme VIII)[41].

SCHEME VIII. Electrophilic chlorination of an aromatic ring.

The disposition of atoms participating in such a reaction is well represented as shown on Figure 9 by the bimolecular system found in the reacting crystalline 2,4,6,6-tetrachloro-3-methyl-5-isopropyl-cyclohexa-2,4-dien-1-one, 4[42]. This compound was observed to react in the solid state to give the isomer 2,4,4,6-tetrachloro-3-methyl-5-isopropyl-cyclohexa-2,5-dien-1-one, 5[42]. This transformation occurs via a radical process involving a phenoxy radical, (Scheme IX).



SCHEME IX. Transformation 4 ⟶ 5.

The molecular mechanism is rationalized upon viewing the crystalline structure of 4 (Figure 9).

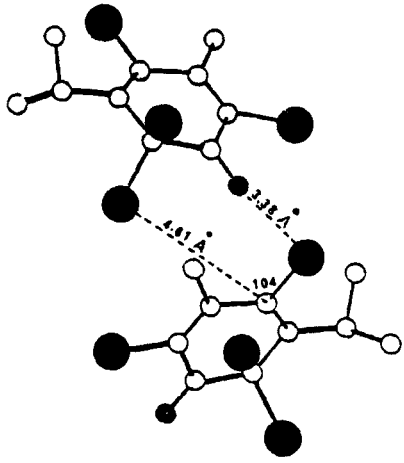
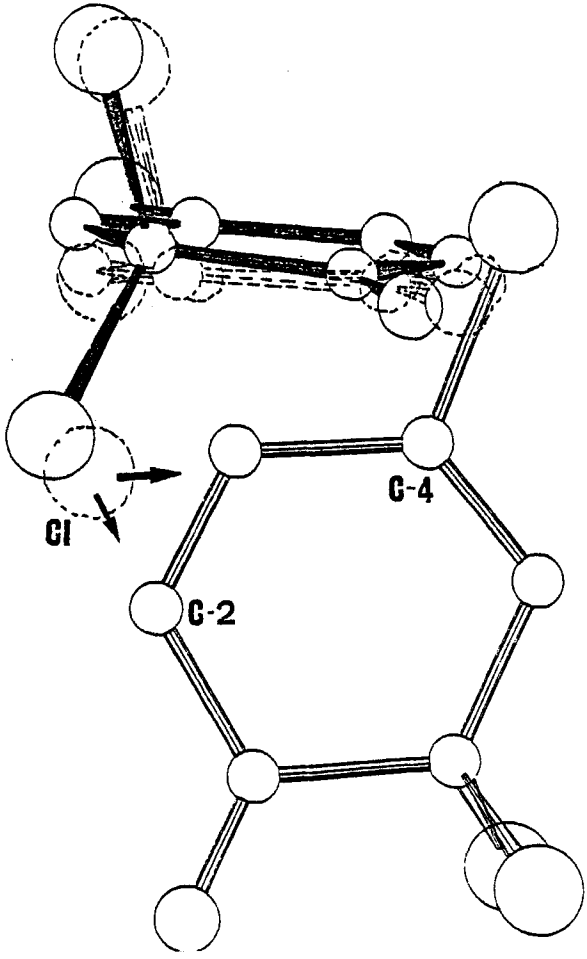


FIGURE 9. Two reacting molecules of 4 in the crystal phase.

The distance between one chlorine atom attached to the C6 position of the neighbouring molecule is 4.6Å. In agreement with the topological disposition it is assumed that a radical chlorine atom migrates along C4...C6 direction[42]. Application of the Caillet and Claverie program for molecular packing calculations[43] provides a theoretical model of reacting crystals, 4[42]. By elongation of the C-Cl bond a new dispostion of molecule 4' is obtained and gives a molecular motion picture of the beginning of the reaction of crystal 4 (Scheme X)[42]. This new disposition shows that the migrating chlorine atom brings the C4 position of the neighbouring molecule nearer[42].

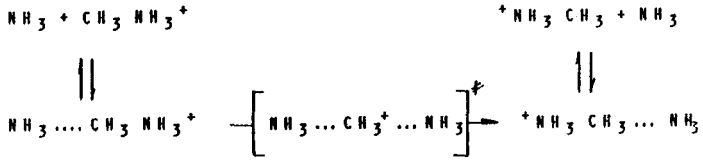
Although the shape and the volume of atoms and molecules participating in the enzymatic process and in solid state reactions are equivalent, molecule-molecule, atom-molecule, ion-molecule and radical-molecule interactions may play a role in the molecular process and in the prefered pathway. They have to be determined in more detail in order that the model given by the solid state reaction may be applied to the enzymatic or biomimetic model. Work is needed in this direction.



SCHEME X. Theoretical model of two reacting molecules of 4 in the solid state.

METHYL TRANSFER GROUP.

Transmethylation from S-adenosylmethionine to a wide range of acceptors is an important reaction in biochemistry[44]. In a recent communication its enzymatic catalysis was described in terms of a methyl-group transfer from an electrophile to a nucleophile by an SN2 mechanism[45]. A theoretical model was proposed for the methyl transfer process (Scheme XI)[45].

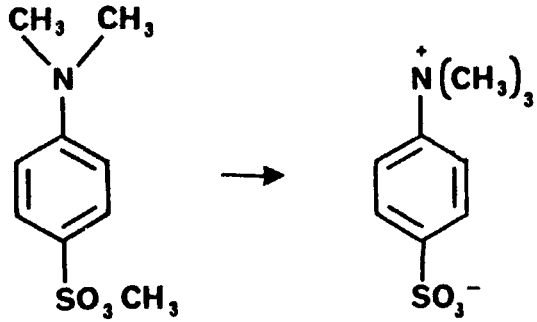


SCHEME XI. Theoretical model for methyl transfer process.

The model catalyst comprises (a) a pair of helium atoms located at fixed distance apart on the N...C...N axis so as to compress the reacting system by repulsive interactions and (b) a cage of point charges serving to stabilize both the reactant ion-molecule complex and transition structure by attractive interactions[45].

SOLID STATE MODEL.

This model is reminiscent of the methyl transfer during the solid state transformation of methyl p-dimethylaminobenzenesulfonate, 6, into p-trimethylammoniumbenzenesulfonate, 7, (Figure 10)[46].



6 7

FIGURE 10. Transformation 6 --→ 7.

In agreement with a catalysis by inter- and intra-molecular interactions due to the crystal packing and arrangement of atoms the intermolecular methyl transfer proceeds at a considerable faster rate in the crystal than it does either in melt or in solution[46]. The X-ray structure of crystalline 6 shows the molecules are nearly ideally oriented for methyl transfer in the solid state (Figure 11)[46].

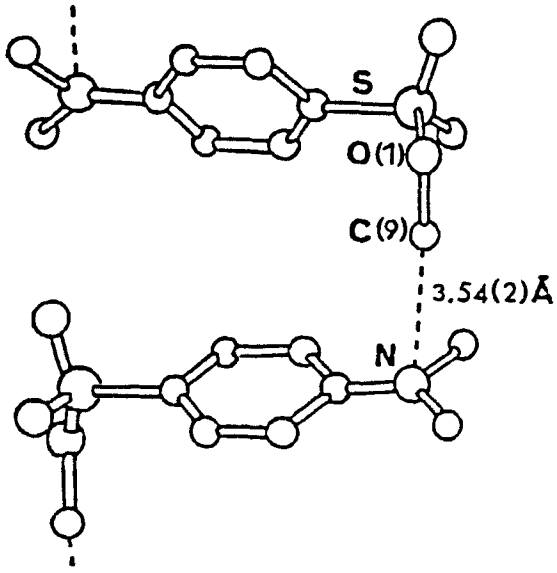
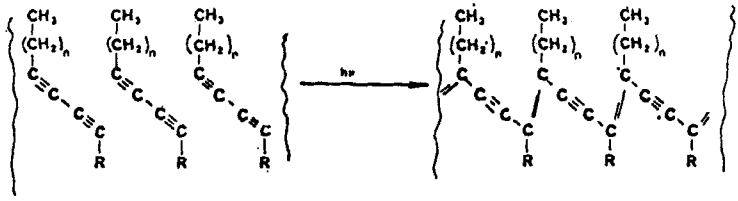


FIGURE 11. X-ray structure of 6.

It is apparent that information given by the molecular process in the solid state may be useful in the application of theoretical models to understand and gain insights into the nature of molecular interactions and atom affinities controling the enzymatic process.

POLYMERIC MEMBRANES.

The main component of lipids in a membrane consists of phospholipids with hydrophobic alkylchains[47]. In order to build up membranes of high stability chemists synthesized lipids containing polymerizable groups able to produce after polymerization the rigidity required[47].



the spectroscopic investigation of the polymerization of diacetylene surfactants and lipids in monolayers shows that it is comparable to the polymerization of these systems in a crystal.

schematic representation of the synthesis of polymeric monolayers by UV-irradiation, orientation of the molecules being preserved (x = polymerisable groups).

$$CH_3-(CH_2)_{12}-C\equiv C-C\equiv C-(CH_2)_8-O-\overset{\overset{O}{\|}}{\underset{\underset{O^{\ominus}}{|}}{P}}-OR$$

$R = H$

$R = CH_2-CH_2-NH_3^{\oplus}$

$R = CH_2-CH_2-\overset{\oplus}{N}(CH_3)_3$

SCHEME XII. Polymerization of diacetylene lipids in monolayers.

The spectroscopic investigations of the polymerization of diacetylene lipids in monolayers[48] (Scheme XII) shows that it is comparable to the polyreaction of related systems in a crystal [49]. The blue (λmax = 620 nm) as well as the red (λmax = 540 nm) form of the polymer can be detected. The polymerizability of the diacetylene lipid 8 proves that the required packing of molecules for a topochemical reaction is found in monolayers and bilayers [48].

This is an example of the application of the topochemical concept [2] in both studies of solid state and biochemical systems.

HYDROLYSIS OF BENZOXAZINONES AND RELATED COMPOUNDS.

Benzoxazinones, quinazolones and anthranilates have been reported to belong to a new class of serine proteases inhibitors [50,51]. Benzoxazinones are compounds useful as models for hydrolysis during proteolitic and related enzyme reactions [52, 53]. In a series of papers the solid state chemistry of these compounds (hydrolysis and dehydration which correspond to two steps of the enzymatic reaction) has been reported [54,55]. Work is in progress to show evidence of similar mechanisms of solid state hydrolysis and cyclodehydration in relation to enzymatic mechanisms.

CONCLUDING REMARKS.

In this report we presented a certain number of similarities between reactions occuring in living systems and reactions taking place the crystalline state. The starting idea was that the topochemical concept [2] applied to solid systems is also applicable to biosystems. The statements found in biomimetic models in the solid state, not only in the context of the topological sequence of events

but also in the context of steps in the process, may afford details on the mechanisms occurring in enzymes [56]. From a general point of view intermolecular conformation analysis in relation to geometrical approaches during chemical reactions and the directionnal requirements upon the reactants is an increasing field of research. In this respect we mention : Koshland (theory of orbital steering)[57], Breslow (biomimetic chemistry)[11], Cram (molecular recognition)[58], Lehn (supramolecular chemistry)[59], Baldwin (rules for ring closure)[60], Brown (selective catalysis in micelles)[61], Delongchamps (theory of stereoelectronic control)[62], Bürgi and Dunitz (method of correlation of structures)[63], Menger (directionnality and proximity in organic and enzymatic reactions)[64]. From a philosophical point of view we mention the words of Monod in "Le hasard et La nécessité" : " Que par ce critère, aussi bien que par ceux de régularité et de répétitivité, les structures cristallines et celles des êtres vivants dussent être rapprochées, pourrait donner à reflechir au programmeur, même ignorant de la biologie moderne : il devrait se demander si les forces internes qui confèrent leur structure macroscopiques aux êtres vivants ne seraient pas de même nature que les interactions microscopiques responsables des morphologies cristallines." [65]

The similarity described by Monod of the internal forces leading to structures of crystals and biological molecules is well represented by the presence of DNA supercoiling effects [66] and chiral turnover phenomena in molecular crystals [67].

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