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ORGANIC SOLID STATE REACTIVITY

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1. INTRODUCTION

The subject of organic solid state reactivity is a fascinating one. Besides being of great academic interest the exciting class of chemical reactions belonging to this field are also expected to be of synthetic value.[1,2] Generally solid state reactions tend to occur with minimal atomic/molecular motion (topochemical principle).[3] Several other concepts like those of reaction cavity,[4] molecular volume and free space,[5] local stress[6] and steric compression[7] have been used to interpret solid state reactivity. Quite a few research papers and review articles dealing with theoretical and experimental aspects of organic solid state reactivity have appeared during the last few years.[8–16] Because of great topical interest *Tetrahedron* has even published a special issue dealing with *Organic Chemistry in Anisotropic Media*, in 1987 (Volume 43, Number 7).

The purpose of the present article is (i) to discuss the general principles involved in solid state reactivity, and (ii) to review reactions occurring in single solids and between two solids.

2. CRITERIA FOR SOLID STATE REACTIONS

It is necessary to establish criteria for solid state reactions. This enables researchers to focus attention on the true solid state reactions. There are five criteria[17,18] for determining whether a reaction is a true solid state reaction:

(a) A reaction occurs in the solid when in the liquid it either does not occur or is extremely slow. This criterion is particularly important for determining whether a reaction is a true solid state reaction.

(b) A reaction occurs in the solid state when pronounced differences are found in the reactivity of closely related compounds.

(c) Different reaction products are obtained when the reaction is carried out in the solid and the liquid states.

(d) A reaction occurs in the solid state if the same reactant in different crystalline modifications has different reactivities or gives rise to different reaction products.

(e) A reaction occurs in the solid if it occurs at a temperature below the eutectic point of a mixture of the starting materials and products.

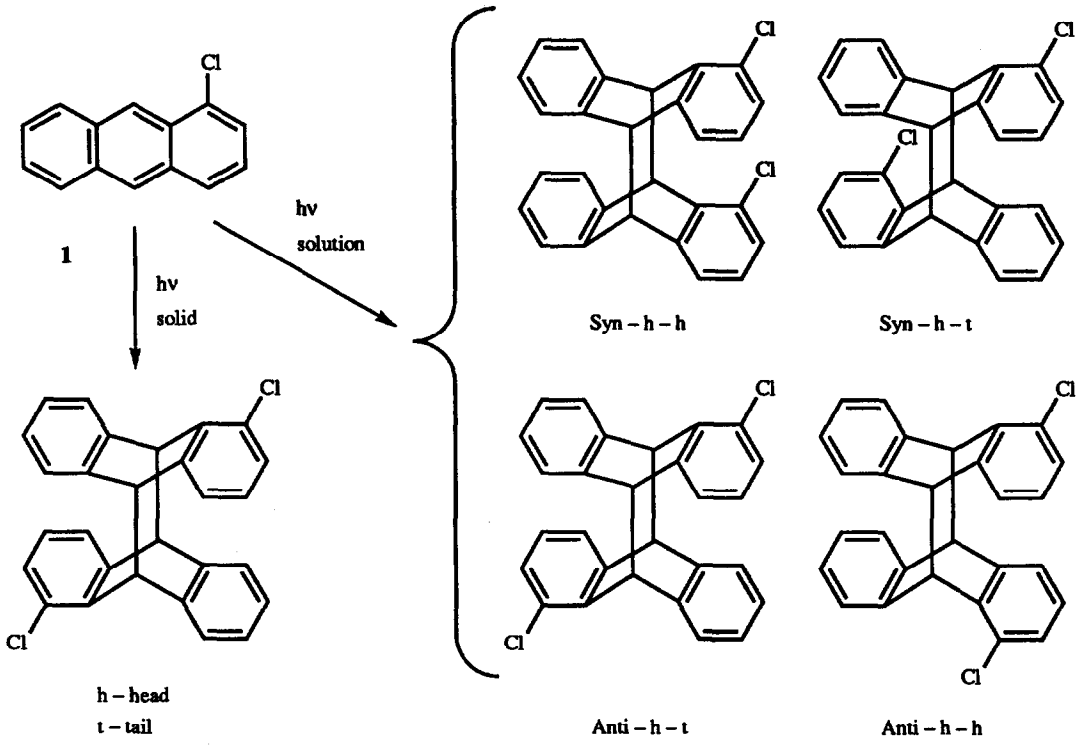
3. FEATURES OF ORGANIC SOLID STATE REACTIONS

There are certain interesting features of organic solid state reactions which are summarized below:

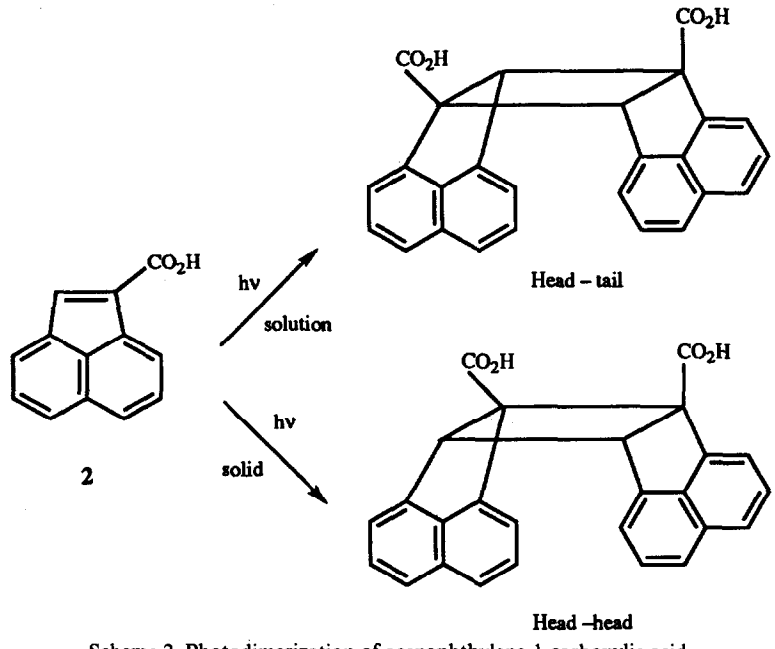
(a) The intrinsic reactivity of a molecule is less important than the nature of the packing of the neighbouring molecules around the reactants.

(b) In a crystal, the possible types of intermolecular contacts, space symmetries with relation to the nearest neighbours and directionality of approach of the relevant molecular moieties are strictly limited and well defined. This brings out dramatic differences between solid and solution state reactivities. For example, 1-chloroanthracene (**1**) gives four dimers in solution whereas a single dimer is formed in the solid state[19] (Scheme 1). Similarly, acenaphthylene-1-carboxylic acid (**2**) yields *syn* head-to-head dimer in the solid state whereas in solution it gives rise to a *syn* head-to-tail dimer (Scheme 2).

(c) In solution the reactivity is mainly dependent on the electronic properties of the reactants. On the other hand, in crystals it depends on a balance between steric packing factors and electronic properties. There are cases of similar behaviour of different compounds in isostructural crystals and of different reactivity of the same compound in different crystal phases, only the phase that allows a favourable topochemistry being reactive. Thus, the molecules that surround a reactive site in a crystal provide a sort of extreme 'solvent effect'.



Scheme 1. Photodimerization of 1-chloroanthracene in solution and solid state.



Scheme 2. Photodimerization of acenaphthylene-1-carboxylic acid.

(d) In the solid state unimolecular reactions are usually easier than processes that require an encounter of two or more chemical entities, unless the crystal geometry is such that reacting counterparts are favourably juxtaposed; thus, there are cases in which proper orientation of reacting groups speeds up the reaction in the crystal with respect to solution or the melt. When this is not

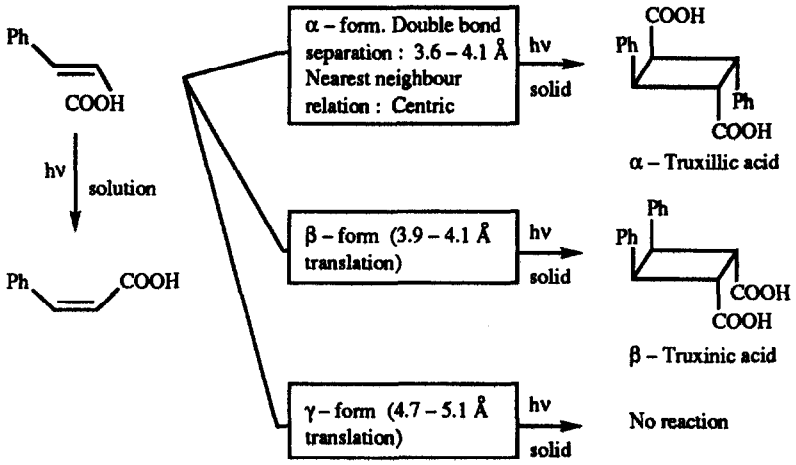
the case, solid state reaction rates are slower than solution ones. Diffusion and/or mother–daughter separation processes are often the rate determining steps in solid state reactions, but in many cases the kinetics are biased by the inhomogeneity of the medium. Hence it is difficult to expect a simple dependence of reaction rate on reactant concentration.

(e) In crystalline solids there are very few conformations taken up by molecules which, in the dispersed state, are very flexible.

(f) Molecular crystals display a rich diversity of polymorphic forms, in each of which a particular conformer or particular symmetry and separation of functional groups prevails.

(g) Many reactions do not involve the movement of molecules but even then the reactions occur very fast. The molecules in the crystals are so designed as to engineer them to react in a particular fashion. This is a diffusionless reaction and this type of reaction comes under the category of crystal engineering.

(h) Because of structural and packing effects, interesting reaction products may be obtained only in the solid state and not in solution. For example, photodimerization of *trans*-cinnamic acids is strictly controlled by the packing arrangement of molecules in the crystals (Scheme 3).



Scheme 3. Photodimerization of *trans*-cinnamic acid.

(i) Solid state reactions are generally initiated at the points of defects or near impurities, which are likely to provide pockets of free space for molecular motion. Sometimes it is possible to induce a reaction in a perfect crystal simply by touching it with a pin.

(j) Most of the solid state reactions are exothermic in nature.

4. STEPS IN SOLID STATE REACTIONS

Solid state reactions are better understood as four-step processes[18]:

(a) *Molecular loosening*: In the initial stages solid state reactions start at one or more nucleation sites and then spread through the crystal. These sites can be produced in a number of ways such as by creating mechanical deformations and defects in the reactant crystals. Deformations occur as a result of molecular loosening. In the case of solid gas reactions also, the diffusion of gas into the crystal begins only when there is molecular loosening in the crystal.

(b) *Molecular change*: This step is similar to reactions in solution where the chemical bonds in the reactants are broken and new bonds formed in the products. Very often the processes of molecular loosening and the resultant molecular change cannot be separated from each other. However, if they do occur as two-stage processes, then the rate of solid state reactions can be explained on the basis of the same factors that account for the rates of reactions in solution. In this

step only a small amount of the product is formed. With the exception of a few cases, solid state reactions are much slower than their counterparts occurring in solution.

(c) *Solid solution formation*: The small amount of product resulting from a reaction in the solid state quickly forms a solid solution within the starting crystal. In general, the extent of solid solution formation and the energies required to form solid solutions probably do not greatly influence the rate of solid state reactions. However, in cases where the energy of the product influences the energy barrier, these factors could play a role.

(d) *Separation of product phases*: Once the concentration of the product reaches a certain optimum value in the starting crystal lattice, it will crystallize. This step would not influence the rate of reaction if the rate is monitored by measuring the concentration change either of the reactants or of the products by chemical methods. However, if the intensity of the X-ray diffraction lines from the crystal lattice of the product is used for measuring the rate, then this step will contribute to the measured rate of reaction. Thus, rates measured using X-ray diffraction differ from those measured chemically.

From the above discussion, it is clear that the rates of solid state reactions depend on several factors, including nucleation and the molecular change involved. Crystal structure and crystal packing profoundly affect the molecular-loosening and molecular-change steps of a solid state reaction.

5. THE TOPOCHEMICAL POSTULATES

The topochemical postulate describes the best examples of control of solid state reactions by crystal packing. A reaction is topochemical if the structure of the product can be explained by the crystal packing of the reactant crystal. Thermochemical reactions deal with the conversion of the molecule of the initial substance into those of the product without disturbing the crystal lattice and without the formation of non-crystalline intermediates.[21–24] The relation between the crystallographic directions of the product obtained from solid state reaction and the initial substance is then referred to as topotaxy.[21] Schmidt and coworkers[3,25,26] at the Weizmann Institute were able to explain a variety of solid state photochemical reactions in terms of the topochemical postulate according to which reactions in crystals proceed with a minimum of atomic and molecular movement. Thus the products of these reactions are controlled by the crystal packing of the starting crystals.[25,26] This postulate explains a large number of reactions; however, it is obviously limited to reactions that occur in a crystalline matrix.

The topochemical postulate implies the concept of a reaction cavity.[4] A topochemically controlled reaction is expected to give the product that best fits the reaction cavity. The photodimerization of mixed crystals of *trans*-cinnamides and of *trans*-stilbenes gives products that are consistent with the dimerization occurring in the bulk phase rather than at defect sites.[27] On the other hand, crystals contain impurities and structural defects of different types, and sometimes they react at these sites. When such a crystal is irradiated, most of the light is absorbed by the perfect part of the crystal. However, in general, energy transfer is fast enough for transfer to the impurity molecules or defect site to occur.[4] Anthracene containing tetracene impurity at a concentration of about 10^{-4} m/m will serve as an example. Anthracene molecules absorb the light, yet it is found that most of the emission is from tetracene. In addition, general experience shows that the rate of a solid state photochemical reaction is faster for impure crystals and for crystals that contain several mechanical defects. There are also exceptions to the rapid energy transfer to defect sites.

Another important example of the influence of the crystal packing of the reactant on a solid state reaction is the phenomenon of topotaxy. Topotaxy is most common in the solid state rearrangement reactions of polyvalent iodine compounds in solid state polymerizations. From studies of topotaxy in polyvalent iodine compounds, the following observations have been made[28]:

(a) Topotaxy is used to describe a solid state reaction whose products have a preferred orientation relative to a crystallographic direction of the parent crystal.

(b) Isomorphism between the reactant and the product phase is not a necessary criterion for topotaxy.

(c) Both bimolecular and unimolecular reactions can give oriented crystalline product.

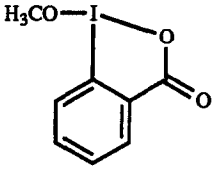
(d) Multiple reaction products can simultaneously be ordered by the reactant lattice.

(e) The symmetry directions of the reactant lattice are not necessarily parallel to the product lattice.

(f) When the reactant and the product lattice symmetry directions are not parallel, twinning of the product phase will occur such that the reactant point group symmetry is conserved.

(g) When 4 Å axis is present in both the reactant and the product lattices, the product will align in such a way that these axes are parallel. The 4 Å axes are not necessarily unique symmetry axes.

Using the principles of topotaxy Etter[28] studied the solid state reaction of 1-methoxy-1,2-benziodoxolin-3-one (**3**). Compound (**3**) crystallizes in two polymorphic modifications (orthorhombic 3-α and monoclinic 3-β) which solid state reaction form the reaction products *o*-iodosobenzoic acid (**4**) and *o*-iodobenzoic acid (**5**).



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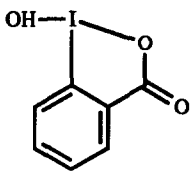

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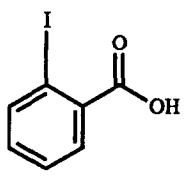

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Specific molecular and geometric lattice properties play an important role in the nucleation and directed crystallization of product molecules. Irradiation of orthorhombic polymorph 3-α leads to the formation of four conservatively twinned crystalline phases of (**5**) which are ordered in such a way that iodine containing planes of the reactant and each of the four product lattices are mutually parallel and have the same ($\sim$ 4Å) interplanar spacing. Irradiation of 3-β gives only a powdered phase (**4**).

6. THE REACTION CAVITY

The concept of reaction cavity in the host crystal lattice was introduced by Cohen.[4,29] The reaction cavity is defined as the space in the crystal occupied by the molecules which directly participate in the reaction. The atomic movements during the reaction would exert pressure on the cavity wall leading to its distortion. However, any such change in the shape will be resisted by the close-packed environment and only those processes which involve minimal change in the external contacts of the reacting molecules will be energetically feasible (Fig. 1).

Recently Gavezzotti[5,30,31] developed a quantitative picture of the concept of reaction cavity by analyzing the volume of the constituent molecules and the size and the location of empty and filled spaces in the crystal lattice. He developed a very valuable computer programme for calculating the volume of a molecule accurately. On the basis of detailed studies, he concluded that "a prerequisite for crystal reactivity is the availability of free space around the reaction site". An interesting example which illustrates the availability of free space in the crystal lattice is the photodimerization of 7-methoxycoumarin where double bonds are not parallel.[32] Ariel *et al.*[7a] have also supported this concept of reaction cavity. Yuji Ohashi *et al.*[33] studied the effect of temperature on the racemization of the chiral 1-cyanoethyl group in cobaloxime complexes (single crystals) when exposed to X-radiation. The rate of racemization could be explained by the size of the reaction cavity for the 1-cyanoethyl group. In order to examine the relationship between the reaction rate and the cavity

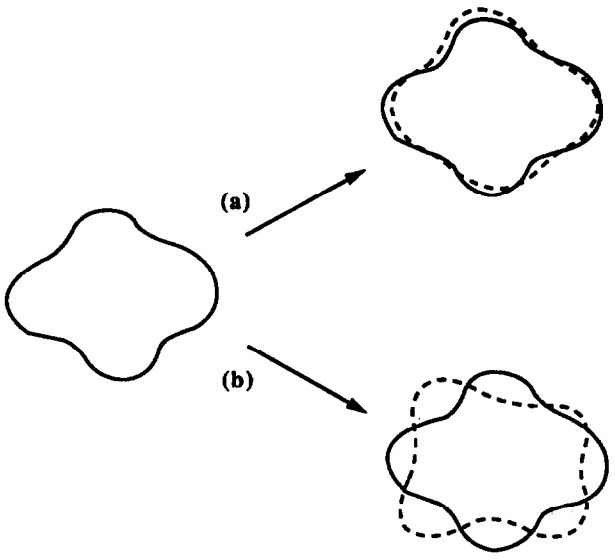


Fig. 1. The reaction cavity before reaction (full line) and in the transition state (broken line) for energetically (a) favourable and (b) unfavourable reactions.

more quantitatively, the rate constants and the crystal structures were obtained at four different temperatures for three cobaloxime crystals with (*S*)-1-phenylethylamine (*S*−*S*), (*R*)-1-phenylethylamine (*R*−*S*), and dimethylphenylphosphine (DMP), as axial base ligands. The volumes of the reaction cavities at different temperatures were calculated from the crystal structure (Table 1) and were found to increase with temperature.

7. ASYMMETRIC SYNTHESIS

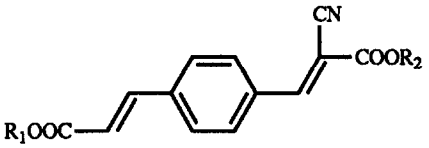
A systematic study of the topochemical reactions of organic solids has led to the possibility of asymmetric synthesis *via* reactions in chiral crystals[34,35] (a chiral crystal is one whose symmetry elements do not interrelate enantiomers). This essentially involves two steps: (i) the synthesis of chiral molecules that crystallize in chiral structures with suitable packing and orientation of reactive groups, and (ii) performing a topochemical reaction in such a way that the chirality of crystals is transferred to the products. Chirality is related to crystal symmetry. There are 230 crystal space groups which can be divided into two categories: (a) the chiral space groups, 65 in number, have symmetry elements of only the first kind, i.e. translations, rotations and combinations of these; and (b) the nonchiral space groups, of which there are 165 in number, may contain symmetry elements such as a mirror plane or glide plane, or a centre of inversion. Thus, the unit cell of a compound belonging to an achiral space group will contain both the object and its mirror image. It is thus obvious that any attempt at achieving asymmetric synthesis *via* photochemical reactions should begin with a compound crystallizing in a chiral space group.

Table 1. Rate constant (k) and cavity volume (V)

T	*S-S*		*R-S*		DMP	
(*K*)	$k \times 10^6$ (s^{-1})	V(Å^3)	$k \times 10^6$ (s^{-1})	V(Å^3)	$k \times 10^6$ (s^{-1})	V(Å^3)
223	1.05	11.56	0.95	14.56	1.53	15.54
253	1.70	11.71	1.40	14.71	1.55	17.07
298	2.38	12.78	3.13	15.35	1.42	17.90
333	2.42	13.94	0.95	16.19	—	—

Furthermore, if the reaction cavity is asymmetric, i.e. it is not superimposable on its mirror image, then the forces acting on the cavity are dissymmetric and the product from an individual cavity will be chiral. This could mean that it is formed in a metastable chiral conformation which can be lost when the crystal is dissolved, or the product molecule may be of chiral constitution which is retained when the crystal environment is removed.

The first step in asymmetric synthesis is essentially a part of the more general problem of crystal engineering. An example of such a system where almost quantitative asymmetric induction is achieved is the family of unsymmetrically substituted dienes (**6**). The system was chosen after careful



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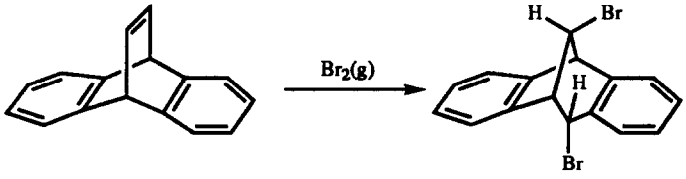
consideration of the relationship between molecular structure and crystal structures. Symmetrically disubstituted benzene derivatives are known to crystallize in structures that undergo photopolymerization. Chiral R_1 groups such as *sec*-butyl induce crystallization in chiral space groups; the *sec*-butyl group also eliminates the packing that would lead to reaction of equivalent double bonds. Nonequivalence of the double bond is ensured by the nitrile function. The ethyl ester (R_2 = ethyl; R_1 = *sec*-butyl) of the diene crystallizes in the space group P1, where the unsymmetrically substituted diene molecules are packed in such a way that the two non-equivalent double bonds are parallel to each other at a distance $\leqslant 4$Å along an infinite stack. When the solid is irradiated at 278 K with $\lambda > 318$ nm, dimers, trimers and oligomers are formed in nearly 100% quantitative enantiomeric yield.

A number of asymmetric solid state syntheses have been described, for example the solid state asymmetric polymerization of *trans,trans*-pentadiene embedded in the chiral inclusion complex of resolved perhydrotriphenylene[36] or in deoxycholic acid,[37] and the addition of gaseous bromine to 4,4′-dimethylchalcone in a chiral single crystal. Lahav and coworkers[39,40] have studied a large number of asymmetric syntheses leading to quantitative enantiomeric yield where the sole asymmetric influence is due to the asymmetric environment of the crystal. Van Mil *et al.*[40] studied the 'absolute' asymmetric syntheses of chiral cyclobutane dimers, trimers, and oligomers from achiral unsymmetrically substituted dienes packing in chiral crystals, where the two nonequivalent double bonds are appropriately aligned for a topochemically controlled ($2\pi + 2\pi$) photopolymerization (Scheme 4). Addadi *et al.*[41] have shown that chirality can be induced by the use of selective additives which modify crystal morphology.

Conformationally controlled gas–solid reactions involving organic solids are known to result in asymmetric syntheses, for example, addition of bromine to achiral alkenes crystallized in chiral space groups.[42] Other examples are the addition of amines to brucine salts of mono-methyl or ethyl fumarate or maleate and Diels–Alder addition of cyclopentadienes to optically active amines such as quinine or α-phenylethylamine salts of monomethyl fumarate.[10] Treatment of chiral crystals of 9,10-etheno-9,10-dihydroanthracene (dibenzobarrelene) (**7**) with bromine vapour results in the formation of the rearranged product 11,12-dibromo-10,11-dihydro-5,10-methano dibenzo-[*a*,*d*] cycloheptene (**8**) in up to 8% enantiomeric excess.[43]



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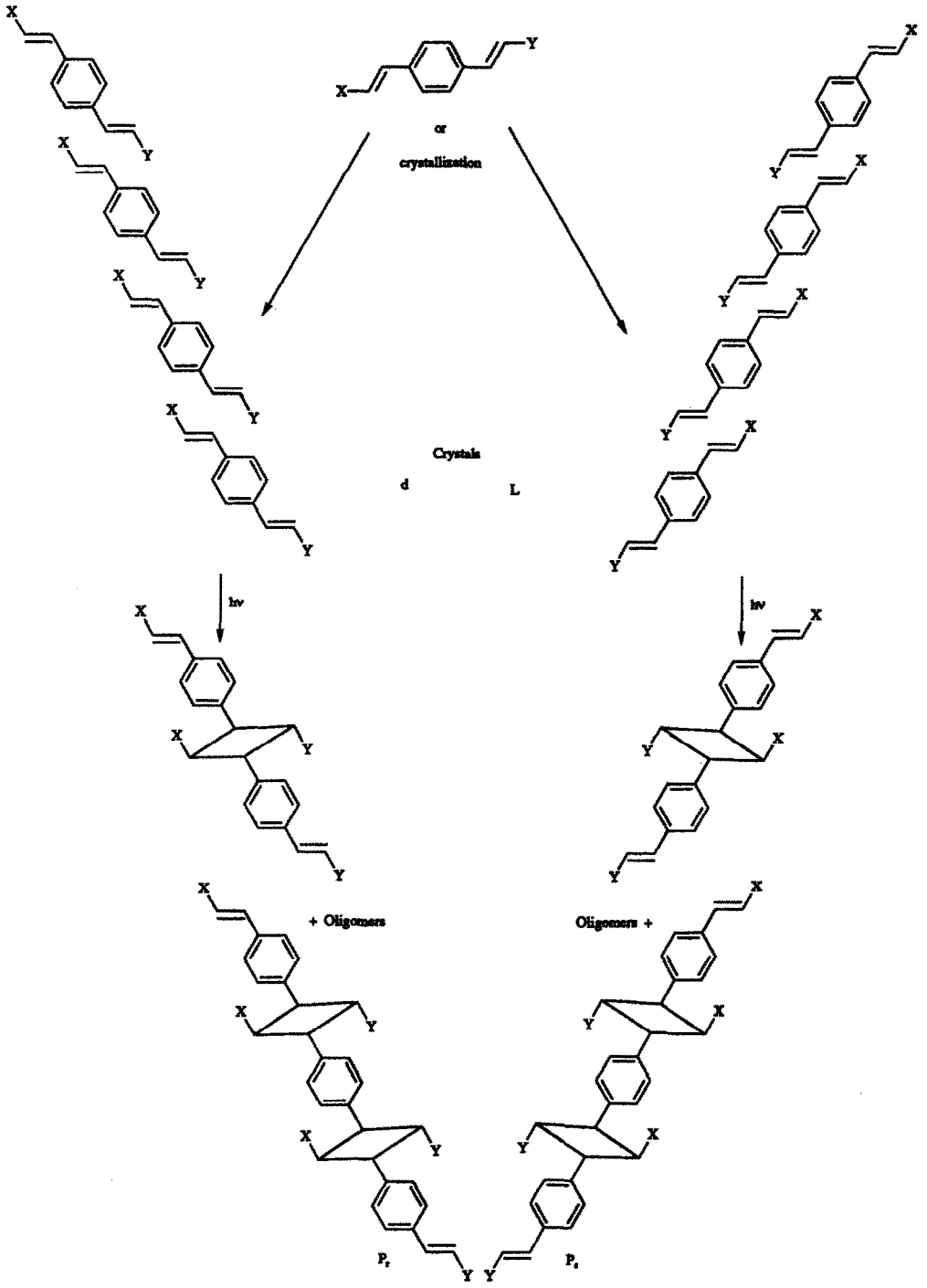


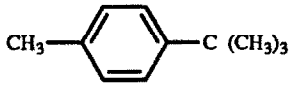
Scheme 4. Topochemically controlled photopolymerization of an achiral crystal.

8. POLAR AXIS AND SOLID STATE REACTIVITY

Formation of crystals possessing a polar axis is one of the most remarkable aspects of the chemistry of the solid state. Some implications of the presence of polar axis to chemical and physical properties of crystals have been reviewed by Curtin and Paul.[44]

8.1. *Molecular structure and crystal polarity*

A crystal is said to be polar if there exist vectors through the crystal such that on progression in a positive sense along the vector the arrangement of atoms is different from that found on progression in the negative sense along the same vector. The compound 1-*t*-butyl-4-methylbenzene (**9**), generally



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agreed to be a non-polar compound, crystallizes in a polar space group with all of the molecules parallel and with all the methyl groups pointed in the same direction (Fig. 2).[45] Such a crystal is polar because one end of the crystal is formed by the methyl group and the other by the *t*-butyl group. Although the molecule does not possess a large permanent dipole moment, the polarity (in the crystallographic sense) of such a crystal could still be chemically of interest; for example, it is not unlikely that crystal faces bounded by the *t*-butyl groups would behave differently from those bounded by methyl groups at the opposite ends of the crystal.

It is difficult to predict and control the crystallization of organic compounds having a desired symmetry. Crystal symmetries are selective towards molecular structure. For example *meta*-di-substituted benzenes are more likely to crystallize in polar forms than are the *ortho* and *para* derivatives.[46] Further, aromatic compounds with certain functional groups, e.g. amino groups, are rather more prone to crystallize in polar space groups than others such as those containing carboxyl groups.

Further distinctions are to be made between a crystal which is polar in a strictly mathematical

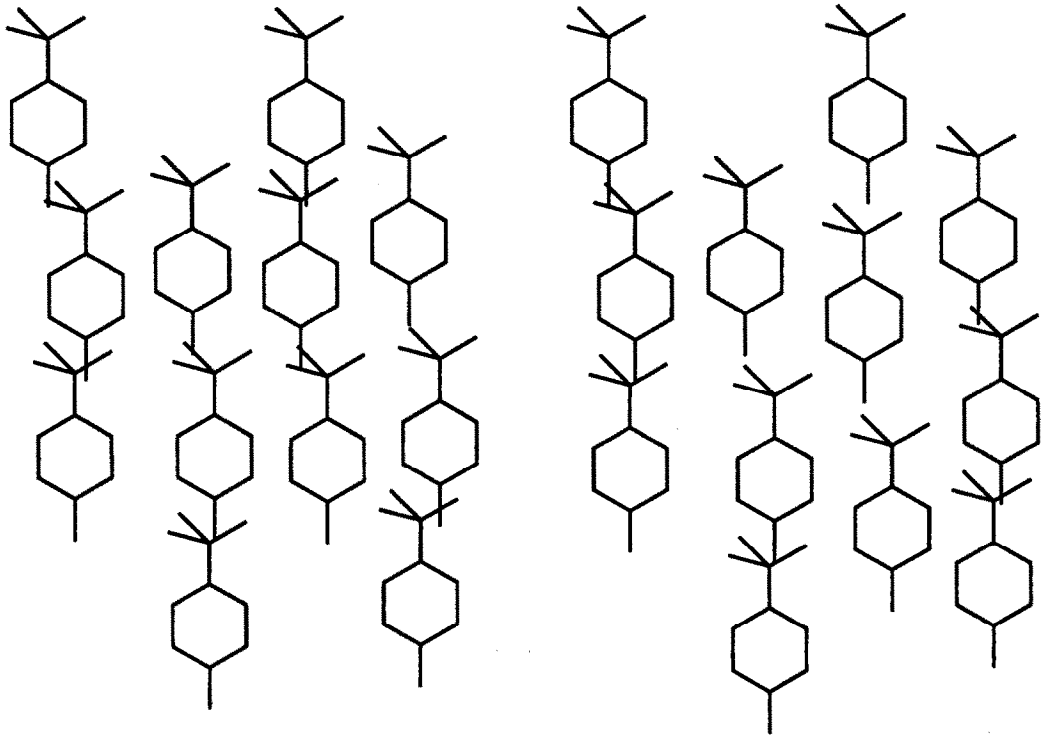


Fig. 2. Stereopair drawing of the polar structure of 1-*t*-butyl-4-methylbenzene.

sense and one whose polarity is of chemical interest. For example, a molecule with a well defined polar direction can be so oriented in the crystal that the molecular polar axis is almost perpendicular to the polar axis of the crystal. One of the examples is *p*-iodonitrosobenzene.[44] Here only a small component of the molecule's polar vector contributes to the polarity of the crystal. Furthermore, crystallization can occur with a pair of molecules in the asymmetric unit, mutually oriented so as nearly to cancel each other's effect on the crystal polarity.

Polarity in a crystal can also be deduced theoretically from the presence and absence of a centre of symmetry. If there is a centre, there can be no polar directions, but if there is no centre, there must be at least some polar directions. The presence and the absence of the centre of symmetry can be inferred theoretically from inspection of space group symbols. However, crystal polarity is affected by crystal disorder, and the inspection of space group symbol is not sufficient to show that a particular substance would crystallize in a structure whose polarity is of interest.

8.2. *The polar axis and the mobile proton*

There are a number of organic compounds which undergo chemical reaction in the crystalline state by rearrangement of one or more hydroxylic or amine protons with only minor perturbations in the positions of the heavier atoms. Such reactions are of possible technological interest because they might be designed in such a manner that proton switching leads to a change in the absorption of electromagnetic radiation or to a change in the crystal symmetry—that is, a change in the direction of one (or more) polar axes. Such processes might be used as the basis for information storage. A number of compounds such as quinhydrones[47,48] and naphthazarines[49,50] exhibit these properties.

8.3. *The polar axis and chemical reactivity*

Crystalline benzoic acid, benzoic anhydride and related compounds have been found to react with ammonia gas to give ammonium salt.[44] These reactions are highly anisotropic. When the

$$C_6H_5COOH + NH_3 \longrightarrow C_6H_5COO^-NH_4^+$$

$$p\text{-}XC_6H_4COOCOC_6H_4X\text{-}p + NH_3 \longrightarrow XC_6H_4CONH_2 + XC_6H_4COO^-NH_4^+$$

$$X = H, Cl, Br$$

single crystals are exposed to ammonia, the side faces at which a functional group (e.g. acid or anhydride) is present are attacked more effectively than the top faces which are dominated by aromatic rings.[44] The reactivities of bromo- and chloroanhydrides are found to be different. A chloroanhydride undergoes reaction at approximately the same rate in any direction parallel to the major face of the crystal, whereas a bromoanhydride reacts much faster along one axis, the polar axis, than along those normal to it. One possible factor contributing to this difference is that the carbonyl–carbonyl dihedral angle of bromoanhydride is larger (49°) than that in the case of chloroanhydride (41°). There are many other factors which affect the rate.

2,6-Dinitrobenzaldehyde[44] crystallizes in space group $Pca2_1$ and has a crystal morphology which clearly shows the orientation of the polar axis. This crystal was allowed to react with primary and secondary amines, and the reactions were favoured along the polar axis.

9. CRYSTAL ENGINEERING AND SOLID STATE REACTIVITY

The understanding of the relationship between structure and reactivity has opened up many interesting areas of research in organic solid state chemistry. An important aspect of this is concerned with the deliberate design of organic molecules so that they pack in a particular manner exhibiting predictable reactivity in the solid state. The concept of designing molecules leading to a particular

crystal structure has been termed "crystal engineering" by Schmidt. The conditions of crystal engineering have been discussed by Desiraju,[9] Rao,[12] and Ramamurthy.[16]

The strategy involves the choosing of appropriate systems and of making specified substitutions in order that they crystallize in desired structures. *trans*-Cinnamic acids are observed to crystallize in three polymorphic forms, namely, α, β and γ and show photochemical behaviour which is determined by the structure type. The shortest cell dimensions of the cinnamic acid polymorphs fall into three ranges: (a) >5.1 Å (α-type), (b) 3.9 ± 0.2 Å (β-type) and (c) 4.9 ± 0.2 Å (γ-type). The α and β forms react in a $2+2$ fashion to give cyclobutane dimers when irradiated in the solid state whereas crystals of the γ-form are photostable. In both the α- and β-forms, potentially reactive double bonds in the crystal are closer than a threshold value of $\simeq 4.2$ Å. However, in the γ crystals, double bond separations are around 4.9 Å and therefore, presumably too great for photoreaction. The key to crystal engineering also lies in understanding the nature of delicate intermolecular forces that control the packing and structure of organic solids. The C–H---O interaction is probably electrostatic in nature and resembles O–H---O and N–H---O bonds in geometrical properties.[51] The long range electrostatic character of the C–H---O bond determines its important role in crystal engineering. The more acidic C–H groups tend to form C–H---O bonds more consistently and these bonds are usually adjusted within the framework of the stronger interactions.

Intermolecular nonbonded interaction such as C=O···Cl, C=O···Ph or Cl···Cl are known to steer molecules to pack in a specific manner. Many chloro-substituted aromatic compounds crystallizing with a short $\sim$ 4Å unit cell axis have been used to engineer crystal structures with a $\sim$ 4Å separation between molecules (β packing).[52] Substituents such as hydroxy, methyl, acetoxy and methoxy have also been investigated for the purpose of engineering organic solids. Methyl and chloro substituents appear to be interchangeable and give isomorphous crystals.[53] The acetyl group seems to favour β-packing, as seen in coumarins.[54] Weak but directionally specific interstack S---S and S---Cl contacts may be used to engineer the 4Å-short axis β-structure for a planar sulfur heterocycle 4-(4-chlorophenyl)-thiazole-2(3*H*)-thione.[55]

The role of acetoxy in attaining desired molecular packing for solid state dimerizations has been explored recently.[56] A few acetoxycoumarins gave mirror symmetric products as a direct consequence of their β-packing. However, the data base analysis does not show clearly that this functional group promotes β-packing.[57] It has been reported that a plane parallel to the stack plane is found along the short C-axis (3.956Å) in 4-(2-carboxyvinyl)-α-cyanocinnamic acid diethyl ester[58] in which molecules overlap completely. Interactions involving the overlap of an ester group of one molecule with the benzene ring of another have been used to steer acrylic acids into packing arrangements suitable for solid state polymerizations.[59]

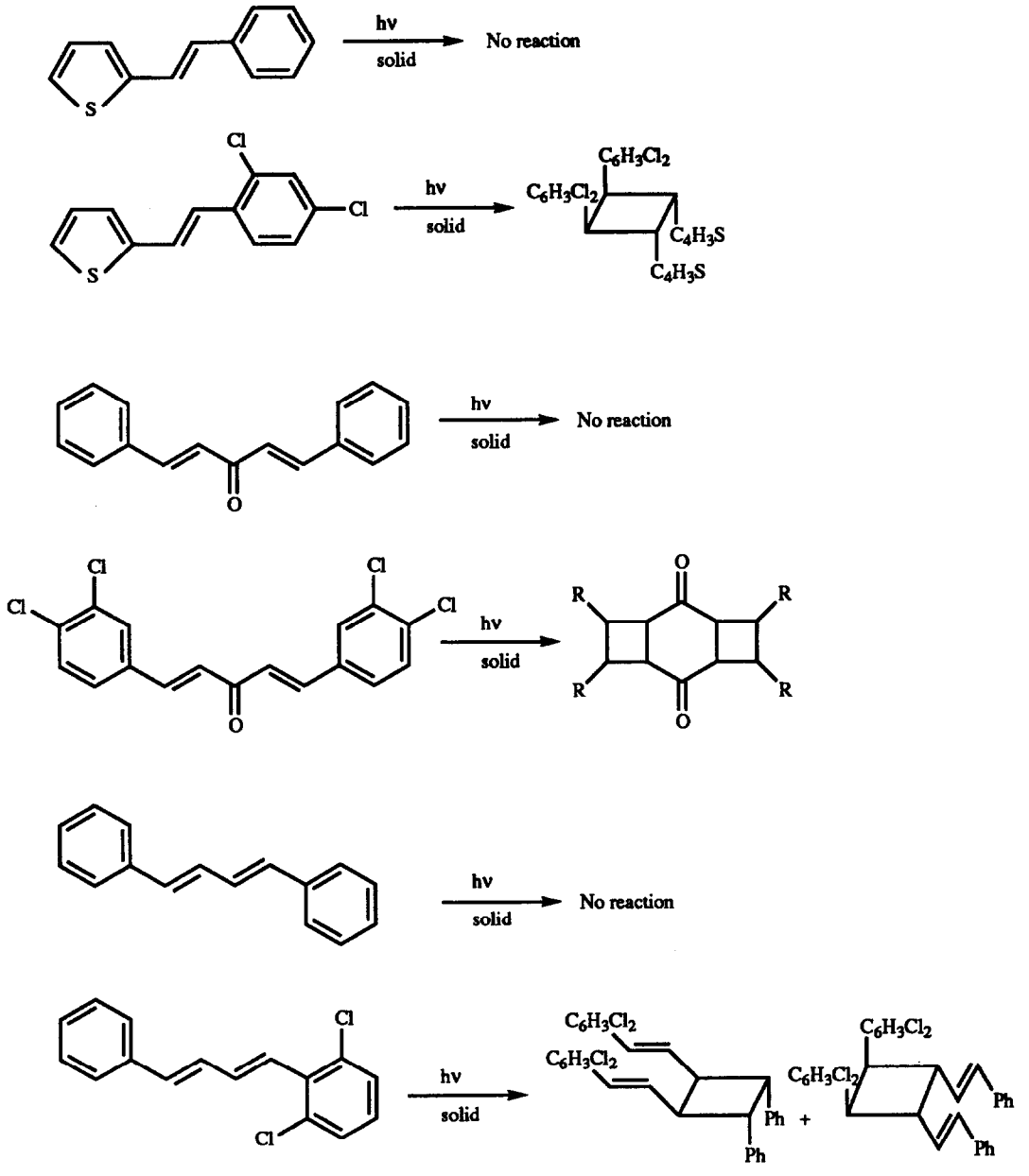
Complexation with Lewis acids has been used for crystal engineering.[60] The technique of mixed crystal or solid solution formation has also been used for this purpose.[61]

Monochloro and (especially) dichloro substitution in aromatic molecules are very effective devices for crystal engineering. By introducing the dichlorophenyl group into unsaturated systems of the type Ar–CH=CHX where X = CHO, COOH, COOMe, CN, Ph, and Ar = 2,4-, 3,4- and 2,6-dichlorophenyl, several groups of workers[61–65] have succeeded in controlling the packing geometry with a unit cell having the shortest axis of about 4Å.

A number of compounds which do not show any reactivity in the solid state have been induced to react through dichloro substitutions. Some examples are given in Scheme 5.

10. THEORETICAL CONSIDERATIONS IN ORGANIC SOLID STATE REACTIONS

A model for crystalline potential field is required for the quantitative theoretical study of the molecular processes in organic crystals.[66] The potential energy of such a crystal is made up of discrete entities in which essentially no ionic bonds are present. It can empirically be described by



Scheme 5. Effect of dichloro-substitution on solid state reactivity.

simple functions of intermolecular distance. Four main types of forces work in such crystals: (i) repulsion between closed shells of electrons (the potential field has the form $E = A \exp(-BR)$ or $E = A'R^{-n}$, where A, A′ and B are empirical parameters, R is the distance between repelling centres, and n lies between 9 and 12); (ii) attractions (essentially electrostatic) between induced instant dipoles or London dispersion forces (the potential has the form $E = -CR^{-6}$, C being an empirical parameter); (iii) coulombic interactions between permanent atomic charges, resulting from moderate bond polarities, also describable as interactions between time-invariant molecular multipoles calculated from the charge distribution in the molecule; and (iv) hydrogen bonds. From this it appears that molecular crystals may in some cases acquire a partially ionic character. Of course, formal

charges, as usually written on organic chemical formulae, seldom have a true meaning in terms of localized electrons in organic molecules.

10.1. *Calculation of crystal energy*

In order to calculate the crystal energy, a model can be built comprising a central molecule surrounded by a number of other molecules arranged according to crystal symmetry. The potential packing energy (PPE) can be calculated from equation (1) for the central molecule by summation of terms (i) to (iv) as above,

$$\mathrm{PPE} = \sum_i \sum_j \mathrm{A} \exp(-\mathrm{BR}_{ij}) - \mathrm{CR}_{ij}^{-6} + \sum_i \sum_j \frac{q_i q_j}{R_{ij}} + E_{\mathrm{HB}}, \tag{1}$$

where the index i runs over the atoms of the central molecule and the index j over those of the surroundings. If zero potential energy is assumed for the molecule at infinity, PPE is the energy needed to bring one molecule to infinity from the bulk of the crystal. It is to be noted that the centres of repulsion and dispersion forces are usually identified with atomic nuclei. The packing energy, PE, is (neglecting zero point energy) the energy for the process of bringing a mole of molecules from infinity to contact in the crystal, each molecule thus acquires an energy equal to PPE and halving is required to avoid counting each contribution twice (Eq. 2).

$$\mathrm{PE} = \frac{1}{2}\mathrm{PPE} \tag{2}$$

This quantity corresponds to the heat of sublimation. In fact, while nonbonded interactions fall off exponentially or with the inverse sixth power of the distance, coulombic terms fall off as the inverse first power of the distance, so that convergence of the summation series is very low.

When a rearrangement takes place in the crystal, the associated intermolecular potential energy barrier can be calculated by estimating the variation of PPE along the reaction coordinates. When an intramolecular process accompanies the rearrangement, the total PE variation is the sum of the inter- and intramolecular parts. The intermolecular contribution can be estimated by usual methods that apply in studies of gas-phase conformation and reactivity.

10.2. *Use of crystal potential energy for solid state reactions*

The use of crystal data in the interpretation of organic reactivity was first proposed by Burgi *et al.*[67] The calculation of dynamical aspects of reactivity in a solid poses a challenging problem, since a model pathway for the reaction in the crystalline matrix has to be proposed and, besides packing energies, bond breaking and bond formation energies must also be evaluated. Quantum mechanical methods have been used to determine intramolecular energy variations. The reaction mechanism of isomerization of *p*-dimethylaminobenzenesulfonate has been studied following a theoretical approach joining PPE and extended Hückel calculations.

The most interesting aspect of the knowledge of reliable crystal potentials is, however, the fact that it opens the way to the calculation of dynamic effects such as libration, rigid body rotation, and even, in principle, phase transitions and reactivity.

The general problem of obtaining information on solid state reactivity from theoretical calculations has not yet been tackled in a systematic way. It is a complex one, but the answers could be rewarding to both organic and physical chemists.

11. RATES OF ORGANIC SOLID STATE REACTIONS

In most of the reactions, a series of steps are involved and the overall process is complicated. Because of this, only the apparent rate constants can be determined. In some cases, rules of physical

organic chemistry are also applicable and the specific rate constants can be determined by Hammett σ-constants of the substituents. Reaction orders generally have no significance. Because of such complexities, rates of reactions between two different solids have been studied less extensively as compared to those involving single solids. In many cases arguments applicable to solution systems are also valid for solid state reactions.[68]

12. KINETIC EQUATIONS FOR SOLID STATE REACTIONS

Solid state reactions show complex rate behaviour that is not easily understood and cannot easily be fitted to a single kinetic equation. These reactions are mainly diffusion controlled and the kinetics proceed through a definite model. Different models have been considered according to the reaction geometry. These are discussed here briefly.

12.1. *Diffusion model*

The rate, in the cases of most reactions between solid substances, is limited by diffusion of the reactant through the layer of the product. As the reaction proceeds in the solid state, a one-dimensional diffusion process with constant diffusion coefficient is governed by equation (3)[69]:

$$D_1(\alpha) = \alpha^2 = \frac{k}{x^2}t, \tag{3}$$

where D_1 is the diffusion coefficient, k is the rate constant, x is the thickness of the reacting layer at any time t and α is the fraction of the total product formed. A two-dimensional diffusion-controlled reaction into a cylinder of radius 'r' follows equation (4)[70]:

$$D_2(\alpha) = (1-\alpha)\ln(1-\alpha)+\alpha = \left(\frac{k_2}{r^2}\right)t. \tag{4}$$

On the other hand the equation given by Jander[71] for a diffusion-controlled reaction in a sphere takes the form:

$$D_3(\alpha) = [1-(1-\alpha)^{1/3}]^2 = \left(\frac{k}{r^2}\right)t. \tag{5}$$

Kroger and Ziegler[72,73] modified Jander's equation[71,74] on the ground that the assumption of a constant diffusion coefficient was not applicable to all solid systems, particularly during the early stages of a reaction, and they suggested equation (6):

$$K_{K-Z}\ln t = \frac{2k\ln t}{r^2} = [1-(1-x)^{1/3}]^2. \tag{6}$$

Zuravlive *et al.*[75] also modified the Jander equation assuming that the activity of the reacting substance was proportional to the fraction of the unreacted material $(1-x)$ and arrived at equation (7):

$$K_{Z-L-T} = \frac{2kDt}{r^2} = \left[\left(\frac{1}{1-x}\right)^{1/3}-1\right]^2. \tag{7}$$

Ginstling and Braunshtein[76] modified the Jander model with the exception of the parabolic rate law and gave the following equation:

$$K_{G-B} = \frac{2kDt}{r^2} = \left[1-\frac{2}{3}x-(1-x)^{2/3}\right]. \tag{8}$$

Carter[77] improved equation (8) by accounting for diffusion in the volume of the product layer with respect to that of the volume of the reactant consumed and arrived at equation (9):

$$K_{C-V} = \frac{2kDt}{r^2} = \frac{z-(z-1)^{2/3}-[1+(z-1)x]^{2/3}}{(z-1)}, \tag{9}$$

where z represents the volume of the reaction product formed per unit volume of the reactant consumed. Valensi[78] developed mathematically the same solid state reaction model from a different starting point and equation (9) is therefore referred to as Valensi–Carter equation.

Dunwald–Wagner[79] derived an equation based on Fick's second law of diffusion and Serin and Ellickson[80] expressed the Dunwald–Wagner equation in terms of the fractional completion of the process and gave equation (10):

$$K_{D-W} = \frac{\pi^2 Dt}{r^2} = \ln\frac{\sigma}{\pi^2(1-x)}, \tag{10}$$

where σ is a constant.

12.2. *Nuclei-growth model*

This model is concerned with the nucleation of the product at active sites and the rate at which the nucleated particles grow. Two common equations for the kinetics of reactions involving nucleation are discussed.

12.2.1. *The Prout–Tompkins equation.*[81] If the rate of a solid state reaction is assumed to be controlled by linearly growing nuclei that branch into chains then equation (11)[81] can be used.

$$\ln\left(\frac{1}{1-\alpha}\right) = kt \tag{11}$$

12.2.2. *The Avrami–Erofeev equation.*[82] If the rate of a solid state reaction is assumed to be governed by random nuclei that grow in three dimensions and ingest other nuclei, then equation (12)[82] can be used. The value of n varies and is assigned to be 1/4,

$$[-\ln(1-\alpha)]^n = kt, \tag{12}$$

1/3, 1/2, 2/3 and 1 for different reaction systems.

12.2.3. *The phase-boundary model.* If the solid state reaction is assumed to be controlled by the advancement of phase boundaries from outside of a crystal to inside, then a series of equations can be derived.

If a crystal is assumed to react along one direction, then the rate is a function of time only and a zero-order rate equation is applied:

$$1-\alpha = kt. \tag{13}$$

If the reaction is assumed to proceed from the surface of a circular disk or cylinder inward, then equation (14) is obtained[69]:

$$1-(1-\alpha)^{1/2} = (u/r)t. \tag{14}$$

When the reaction proceeds from the surface of a sphere inward, equation (15) can be derived

$$[1-(1-\alpha)^{1/3}] = (u/r)t. \tag{15}$$

12.2.4. *Other equations.* (a) The power-law equation: The power-law equation (16) has no theoretical basis but it has been used to analyze solid state rate data, where n = 1/4, 1/3, 1/2 and 1.

$$\alpha^n = kt \tag{16}$$

(b) Equations based on the concept of reaction order: since the concept of molecularity of a reaction is not well defined for solid state reactions, kinetic equations based on order are not widely used. Nevertheless, sometimes data are analyzed in terms of order of reactions. Equations (17), (18) and (19) for first, second and third order reactions respectively have been used.

$$1-\alpha = kt \tag{17}$$

$$\ln \alpha = kt \tag{18}$$

$$1/(1-\alpha) = kt \tag{19}$$

(c) Reactions involving partial liquids: some solid state reactions of drugs involve partial melting or reaction in a liquid layer. In these cases, it is necessary to treat the rate of the reaction as determined by a sum of the rates in the liquid and solid phase.

$$A \rightleftharpoons B + \text{products}$$

For this reaction

$$\frac{dx}{dt} = k_s(1-x-xS)+k_1(xS), \tag{20}$$

where k_s and k_1 are rate constants for reaction in the solid and liquid phases, and S is the molecular solubility of the reactant crystal in the liquid phase. Solution of this equation yields equation (21).[83,84]

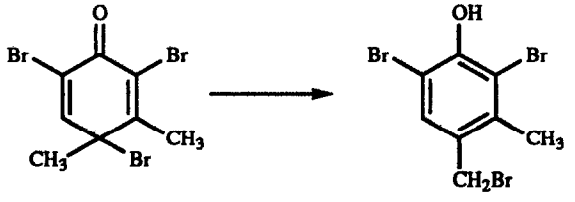
$$x = \frac{1}{K_1S-K_sS-K_s}\exp[(k_1S-k_sS-k_s)k_st-1]. \tag{21}$$

13. SOLID STATE REACTIONS

A variety of solid state reactions under the major headings of (i) Solid–solid reactions, (ii) Solid–liquid reactions, (iii) Solid–gas reactions, and (iv) Reactions of single solids, have been studied. In the present article the salient features of reactions involving only solids will be discussed.

13.1. *Reactions of a single solid*

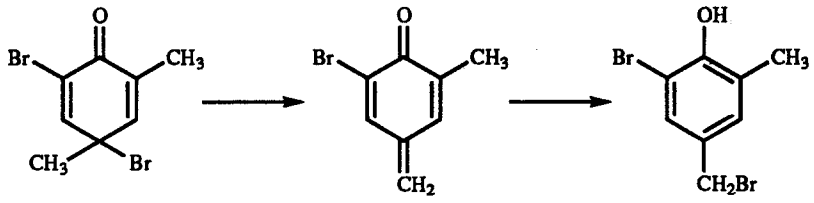
13.1.1. *Reactions involving rearrangement of functional groups and bonds in a single solid.* A large number of such reactions have been reviewed by Shklover and Timofeeva.[8] Some reactions which have been studied recently are considered here. For example, 2,4,6-tribromo-3,4-dimethylcyclohexadienone (**10**) has been observed to rearrange in the solid state to give exclusively 2,6-dibromo-4-bromomethyl-3-methylphenol (**11**).[86–88] Compound (**10**) is stable for a few days at room



10 **11**

temperature but in due course it rearranges autocatalytically and presumably homolytically in the solid phase. Purified samples are stable for longer periods (30 days and more).[87] A similar reaction is reported to occur for 4,6-dibromo-2,4-dimethylcyclohexa-2,5-dienone (**12**), which rearranges

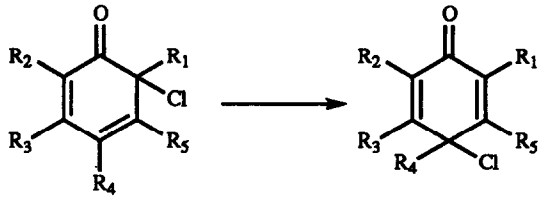
spontaneously in the solid state into 6-bromo-4-bromo-methyl-2-methylphenol (**13**).[89] An addition–



12 **13**

elimination sequence involving a quinone methide is the most likely pathway for this rearrangement.[89]

In a series of studies on the chlorination of phenolic compounds in the solid state, the transformation of a series of *ortho*-chlorodienones (**14a–j**) into the *para* isomers (**15a–j**) by heat or light has been reported.[90–97]

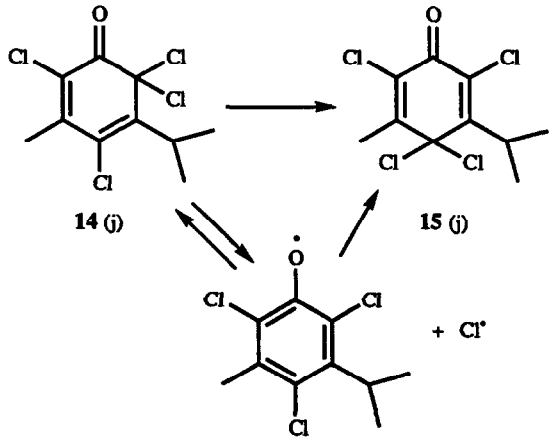


14 (a-j) **15** (a-j)

	R_1	R_2	R_3	R_4	R_5
a	tBu	tBu	H	tBu	H
b	tBu	tBu	H	Me	H
c	Br	Br	H	Br	H
d	Br	Br	Me	Br	Me
e	Br	Br	Br	Cl	Br
f	Br	Br	Br	Br	Br
g	Cl	Cl	Cl	Me	Cl
h	Cl	Cl	Me	Me	Cl
i	Cl	Cl	Me	Cl	Me
j	Cl	Cl	Me	Cl	i-Pr

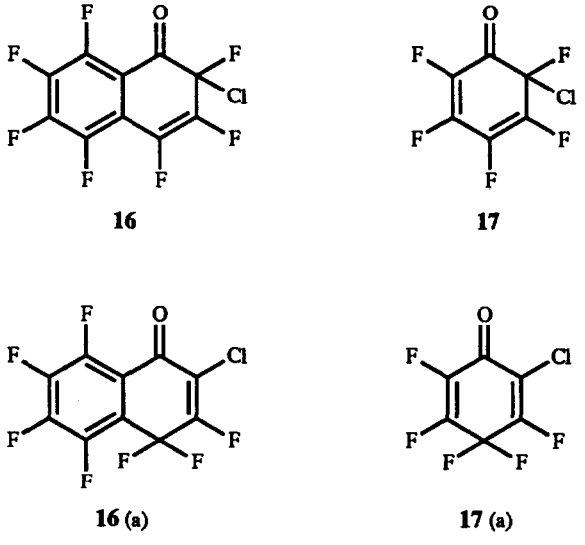
The transformation in the solid state of 2,4,6,6-tetrachloro-3-methyl-5-isopropylcyclohexa-2,4-dien-1-one (**14j**) into 2,4,4,6-tetrachloro-3-methyl-5-isopropylcyclohexa-2,4-dien-1-one (**15j**) is

known to occur with UV irradiation or on heating.[94-96] From microscopic observations of single crystal transformations of **14j** under UV irradiation and from thermal experiments, the solid state mechanism was concluded to be homogeneous[95-97] as defined by Curtin *et al.*[98] ESR signals were observed during the thermal transformation of powders and single crystals of **14j**.[95] A phenoxy radical intermediate was identified. For this process Scheme 6 was proposed by Lamartine.[99] A



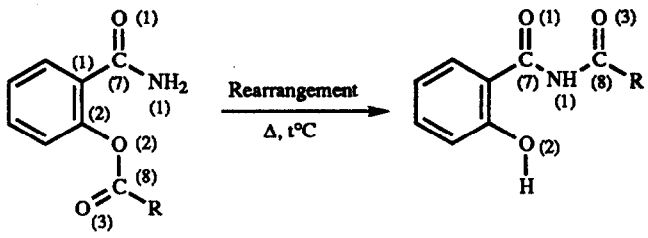
Scheme 6. Thermal decomposition of **14j**.

similar rearrangement has been observed during the heating of compounds (**16**) and (**17**) with Celite in a sealed tube.[100] During these reactions, a fluorine atom is transferred from the *ortho* to the *para* position to produce (**16a**) and (**17a**). From these results, it may easily be deduced that a fluorine



atom migrates preferentially to a chlorine which, in turn, migrates preferentially to a bromine. This order of migration may be explained by electronic factors as well as by steric effects caused by crystal packing.

When *O*-acylsalicylamides (**18**) are heated, O to N migration occurs (Scheme 7).[101]

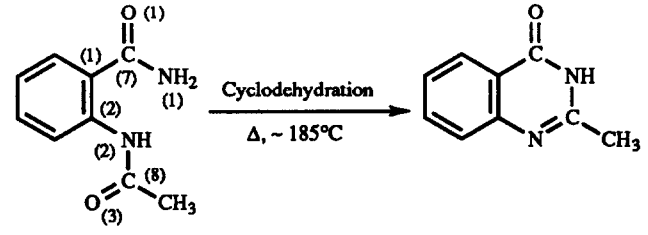


18

Scheme 7. Solid state O to N acyl migration in *O*-acylsalicylamides.

The crystal structures of three *O*-acylsalicylamides (**18**) *viz.* the acetyl, benzoyl and propionyl derivatives, have been determined. The reaction, in essence, involves bond formation between the N(1) and C(8) atoms. The interaction between the N(1) atom and the acyl carbonyl group, C(8)=O(3), is considered as a nucleophile–electrophile interaction, the amide nitrogen N(1) being the nucleophile with a lone pair of electrons. Based on the structural parameters of *O*-acylsalicylamides relevant to N---C=O interactions, such as the N(1)---C(8) contact and the relative orientations of the amide group and the acyloxy groups, an intramolecular mechanism has been proposed for O to N migration. The thermal motion analysis of the reactants has indicated a large thermal motion between C(8) and N(1) and has led to the suggestion that torsional libration about the C(2)–O(2) bond is apparently responsible for the observed solid state reaction.

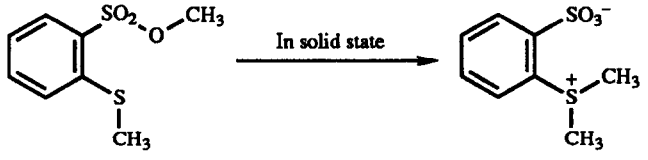
When the *β*-form of *o*-acetamidobenzamide (**19**) is heated in the solid state, cyclodehydration occurs (Scheme 8)[101] and an intramolecular mechanism can again be proposed.



19

Scheme 8. Solid state cyclodehydration of *β*-form of *o*-acetamidobenzamide.

Venugopalan *et al.*[102] studied the transfer of a methyl group in crystalline methyl 2-(methylthio)benzenesulfonate (**20**) to the zwitterionic 2-(dimethylsulfonium)benzenesulphonate (**21**). It has



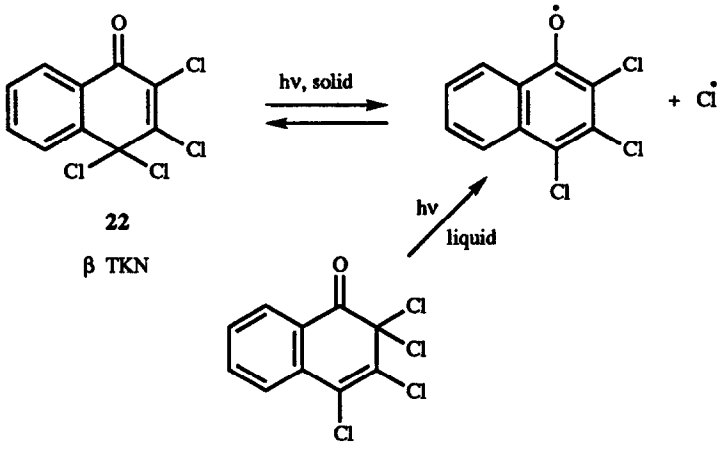
20 **21**

been concluded that in this reaction the crystal packing is quite unsuitable for intermolecular methyl transfer and the reaction in the solid state proceeds not topochemically but rather at defects such as microcavities, surfaces and other irregularities present in the crystal.

13.1.2. *Photochromism.* Photochromism[103] refers to compounds which change colour when

exposed to light and revert to their original colour in the dark. The search for new photochromic materials has been growing in recent years because, in addition to their intrinsic interest, they have potential applications in areas such as communications, computers and display systems.[104] Several classes of organic compounds such as anils, hydrazones, semicarbazones, stilbene derivatives, sydnones and spiro compounds have been found to be photochromic. A number of their important properties such as the reaction rate, reversibility,[105] thermal stability[106] and reusability, have been investigated.

The reversible photochemical transformation of 2,3,4,4-tetrachloro-1-oxo-1,4-dihydronaphthalene β-TKN (**22**), into a coloured species was probably one of the first examples of solid state photochromism. It has been proposed that the absorption of light by the keto group induces a dissociation of the excited molecule into a chlorine atom and an aroxy radical.[107] α-TKN (**23**) shows photochromism in solution but not in the solid state.[108] Perhaps it is the molecular organization of the molecules in the crystal lattice of (**22**) which is responsible for photochromism in the solid state.

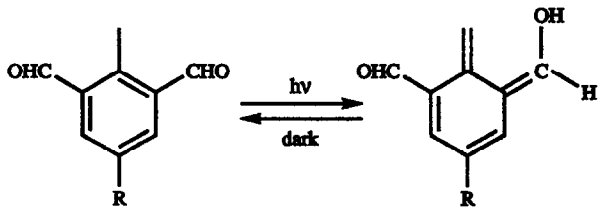


22

β TKN

23

The crystals of 2,5-dimethylisophthalaldehyde (**24**) and 5-isopropyl-2-methylisophthalaldehyde (**25**) were found to be photochromic. These crystals are colourless in the dark but become red in



24

Colourless

24 R = Me

25 R = Pr^i

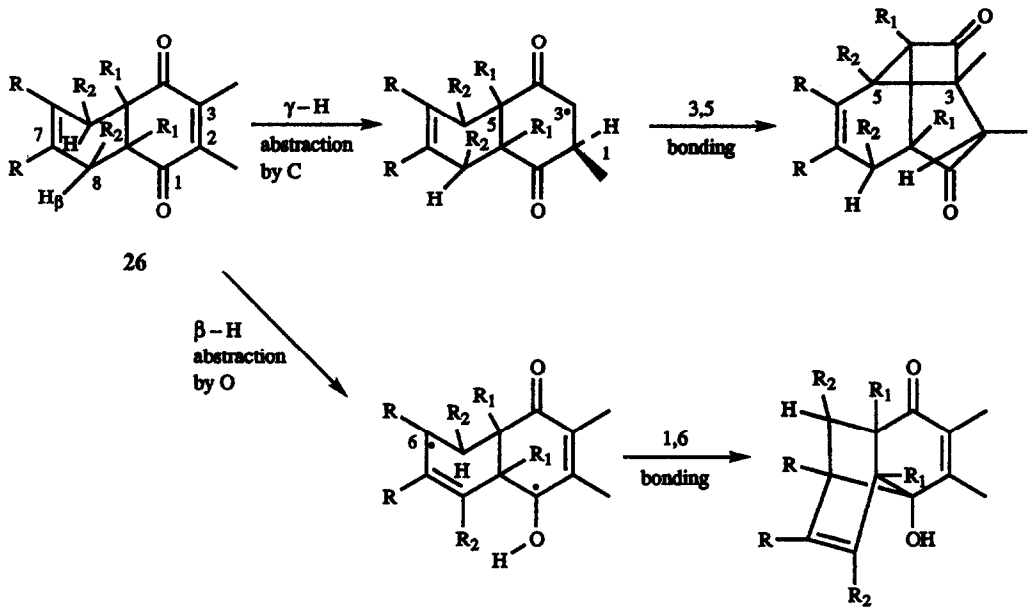
25

Red

sunlight. The process is reversible. It has been postulated that the photochromic property of these compounds is due to photoenolization.[109]

13.1.3. *Photochemical hydrogen abstraction in the solid state.* Most of these photochemical reactions occur with intramolecular abstraction of a hydrogen atom. A number of photochemical

hydrogen abstraction reactions in the crystalline state have been investigated.[110–114] A detailed study of tetrahydro-1,4-naphthoquinones (**26**) has revealed that steric compression controls the reaction (Scheme 9).[7,111,115]



Scheme 9. Hydrogen abstraction in tetrahydro-1,4-naphthoquinones.

X-Ray structure analyses of this series of compounds show that all have a similar 'twist' conformation, with the bridgehead substituents staggered; the cyclohexene ring adopts a half-chair conformation and is *cis*-fused to the more nearly planar ene-dione ring. A major product obtained on irradiation in the solid state is a 1,4-ketoalcohol, whose formation can be interpreted as resulting from 1,6-bonding of the diradical formed by the extraction of H_β by the adjacent carbonyl group (Scheme 9). In fact, the geometry of the molecules seems just right for the abstraction; the H——O distance is of the order of 2.5Å, shorter than the van der Waals distance of 2.7Å, the C–H bond is almost in the plane of the carbonyl group, and the C=O–H angle is about 82°. The occurrence of this reaction can thus be taken as evidence for P_y-electron participation. An important aspect of the reaction is that the overall change in the molecular shape is small, the crystal allowing the 1,6-bonding of the diradical to complete the process. It should be stressed that there may be competitive reactions such as abstraction of H_γ by C(3), followed by 3,5 bonding and leading to a diketone, and even intermolecular cyclodimerization.

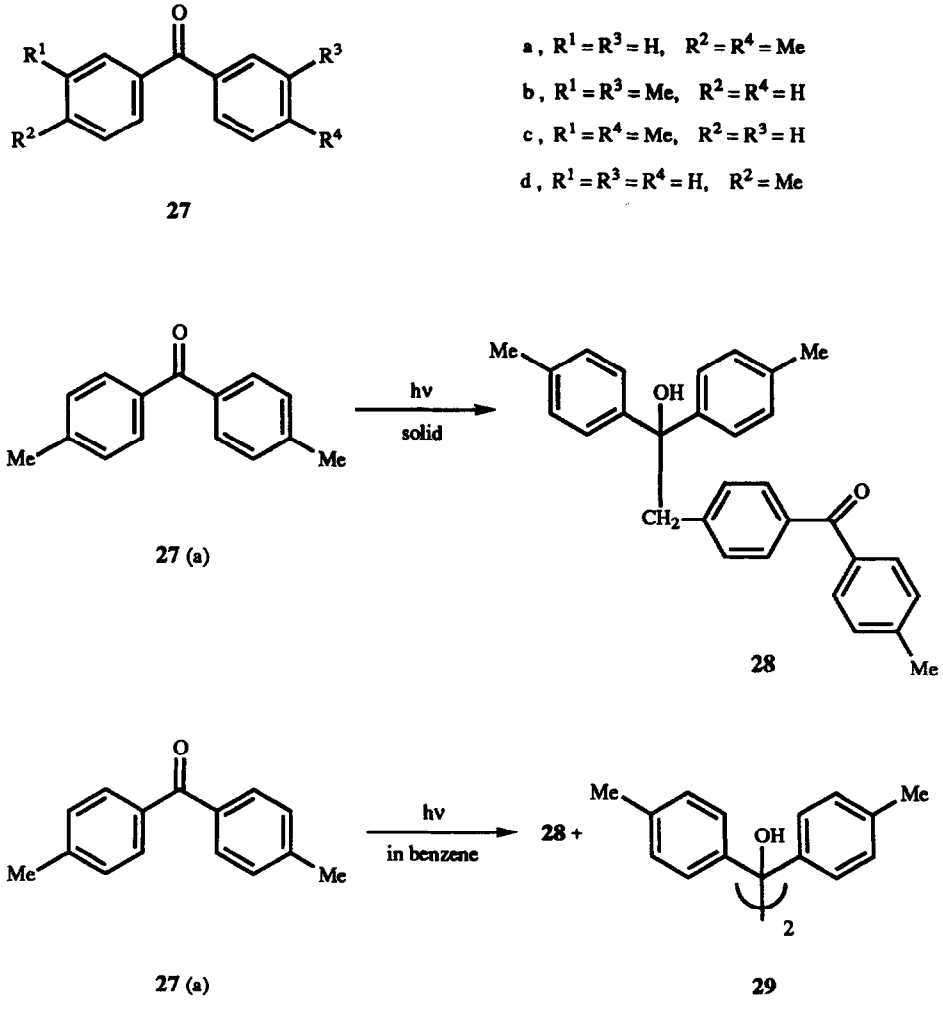
Another example of hydrogen abstraction followed by the formation of a new C–C bond is provided by the recent studies of Tang *et al.*[115] on the regiospecific and stereospecific photo-addition of guest ketones to host deoxycholic acid in the channels of solid bile acids.

Ito *et al.*[116] reported the intermolecular hydrogen abstraction reactions in the crystalline state of 4,4′-dimethylbenzophenone (**27a**) undergoing dimerization to give the compound (**28**). Dimerization in solution gives a mixture of (**28**) and (**29**) (Scheme 10). On the other hand 3,3′-dimethylbenzophenone (**27b**) 3,4′-dimethylbenzophenone (**27c**) and 4-methylbenzophenone (**27d**) are photostable in the solid state. Crystal structure determinations have shown that the long C——C distance and/or the large C=O——H angle is probably responsible for the photoinertness of (**27d**).

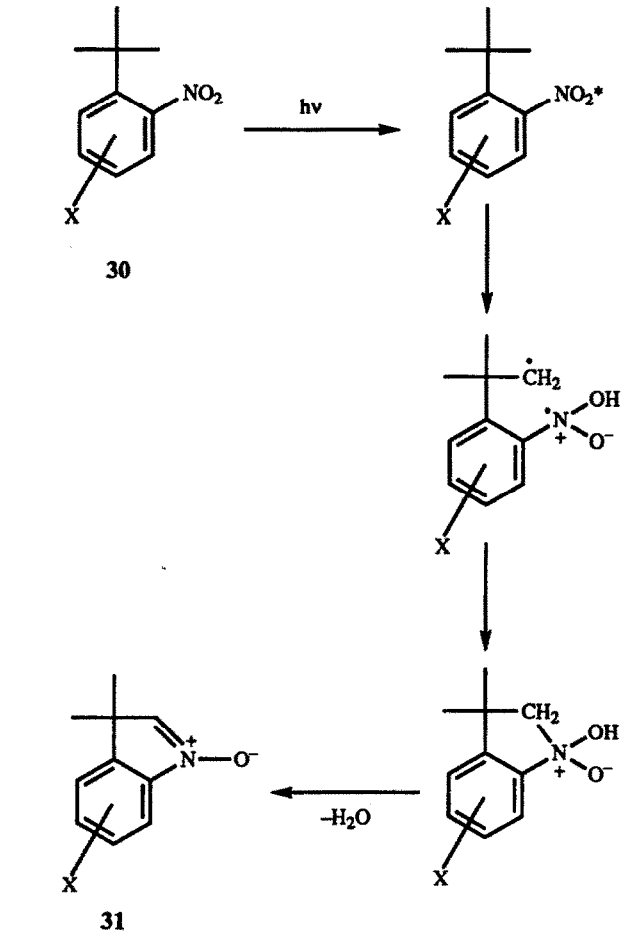
Hydrogen abstraction in many other solid carbonyl compounds has also been studied.[116]

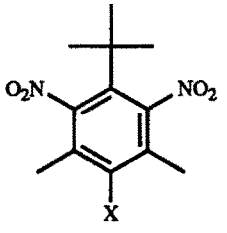
Amongst the compounds studied are α-cyclohexylacetophenones, α-adamantylacetophenones, *N,N*-dialkyl-α-oxoamides, cyclopentane-1,2-diones, 2-*t*-butylbenzophenones and 2,4,6-triisopropylbenzophenones. The hydrogen abstraction reactions occurring in these compounds are intramolecular in type. 2-Nitro-*t*-butylbenzenes (**30**) upon irradiation by UV light ($\lambda > 280$ nm) undergo intramolecular hydrogen abstraction in the solid state leading to the 3*H*-indole 1-oxides (**31**) (Scheme 11).[117] Compounds (**32–34**) also react in a similar manner in solution as well as in the solid state.[118,119]

Padmnabhan *et al.*[120] recently studied the photochemical hydrogen abstraction in 1,4-bis(2-chloro-1,1-dimethylethyl)-2-nitrobenzene (**35**) in the solid state (Schemes 12, 13) and explained the process in terms of intramolecular geometry and molecular packing.



Scheme 10. Hydrogen abstraction in 4,4′-dimethylbenzophenone.



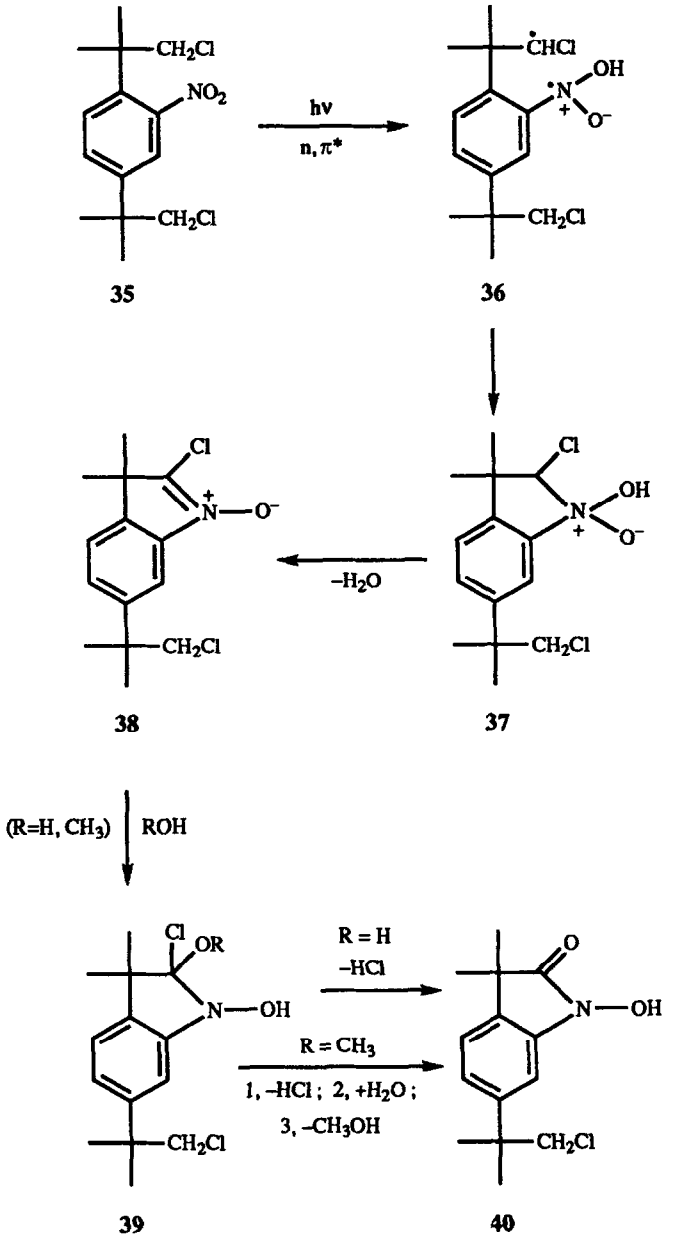


(32) X = NO_2

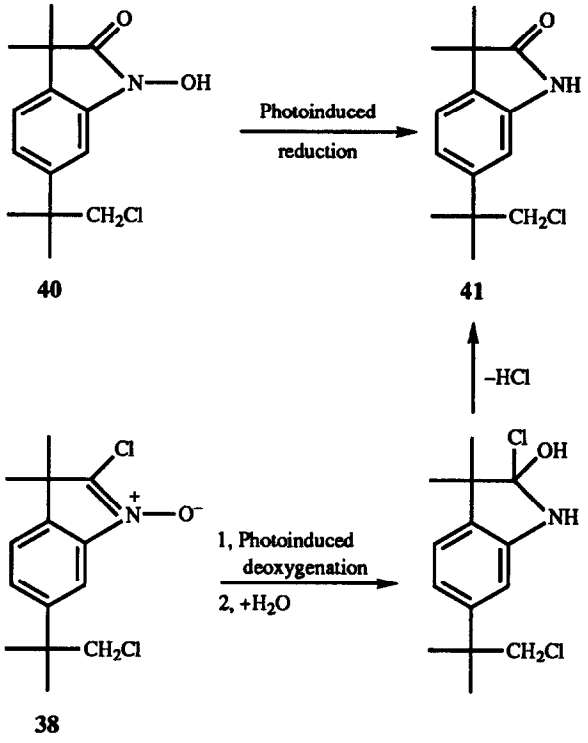
(33) X = CH_3

(34) X = $COCH_3$

Scheme 11. Intramolecular hydrogen abstraction in (**30**).

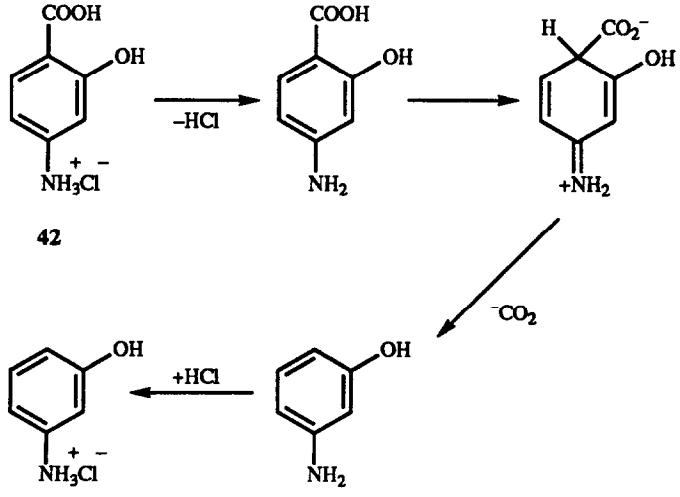


Scheme 12. Intramolecular hydrogen abstractions in (35).



Scheme 13. Intramolecular hydrogen abstraction in (**40**).

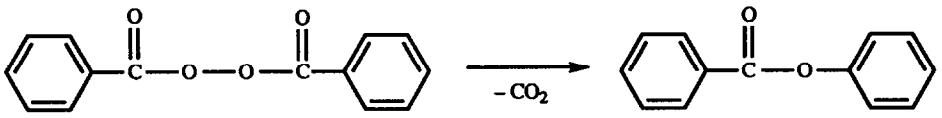
13.1.4. *Reactions with elimination of small molecules.* Chemical reactions in organic crystals accompanied by the liberation of low molecular weight solid, liquid or gas products are very common phenomena. The reaction may initiate at crystal imperfections or surface centres. However, this is not fully understood. There are a large number of solid organic compounds that do not melt but decompose on heating or exposure to radiations.[8] Some of the reactions are desolvation of crystalline solvates, decarboxylation of acids, controlled decomposition of explosive substances, solid aza compounds, etc. Only a few representative examples are discussed here briefly.



Scheme 14. Decarboxylation of *p*-aminosalicylic acid hydrochloride (**42**).

Lin *et al.*[121] have studied the decomposition of salicylic acids. At 100°C *p*-aminosalicylic acid is decarboxylated in 10 h, whereas the other salicylic acids are not decarboxylated even after heating for about a week. This is consistent with the predicted decomposition rate of salicylic acids based on the mechanism of the solution reaction and studies of the solid state decomposition of benzoic acid. The mechanism of decarboxylation[121] of *p*-aminosalicylic acid hydrochloride (**42**) is given in Scheme 14, where molecular packing in the crystals controls the decomposition.

Morsi *et al.*[122] have studied the solid state thermal and photochemical decomposition of dibenzoyl peroxide (**43**). ESR studies have shown that at 4K only phenyl radicals are formed and no benzoyl



43

radicals could be detected. The probable mechanism of decomposition of (**43**) is:

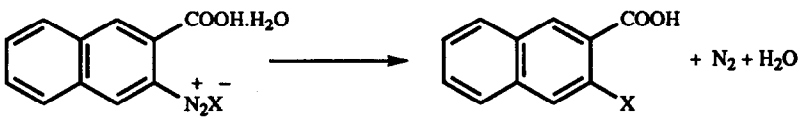
$$\mathrm{PhCOOOOCPh} \longrightarrow \mathrm{Ph^{\cdot} + 2CO_2 + Ph^{\cdot}}$$

$$\mathrm{Ph^{\cdot} + PhCOOOOCPh} \longrightarrow \mathrm{PhCOOPh + CO_2 + Ph^{\cdot}}.$$

The thermal reaction in a single crystal of (**43**) occurs on the 010 face and involves both randomly and [100]-aligned nuclei.

The decomposition of organic explosives has also been extensively studied and reviewed.[123] It is important to note that these reactions begin at and spread from nuclei. The rate of expansion of these nuclei is determined by the heat given off during the explosive reaction. Their nature is not known but could involve mechanical imperfections, impurity sites, or product sites.

The behaviour of diazonium salts **44** has been studied in the solid state.[124,125] The diazonium salts with X = Br and X = Cl are isostructural and decompose to form the corresponding 3-halo-2-naphthoic acids (**45**). The crystals of compounds (**44b**) and (**44c**) are isostructural and, like

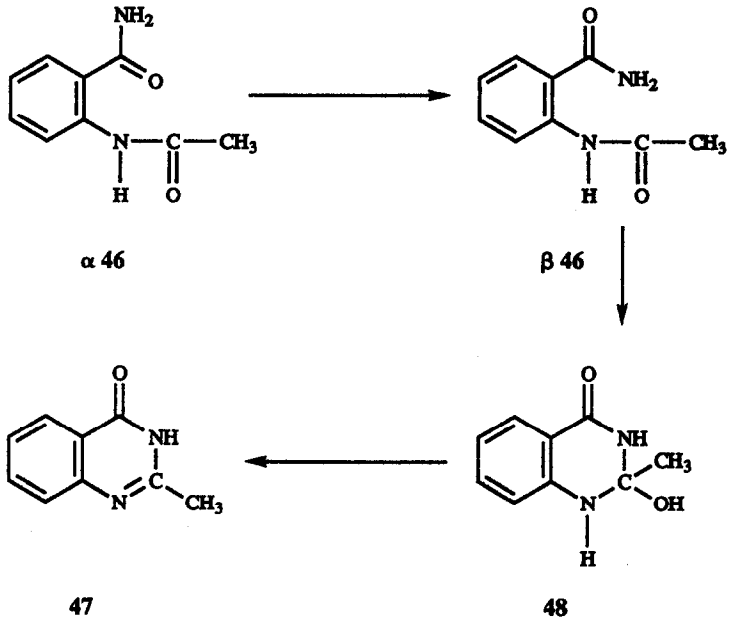


44 **45**

a, X = I
b, X = Br
c, X = Cl
d, X = BF_4

compound (**44d**), crystallize as monohydrates. Data obtained by differential scanning calorimetry, thermogravimetric analysis and X-ray diffraction studies indicate the ability of the triclinic crystals of compound (**44b**) to lose water topotactically. Compound (**44b**), on heating at 65°C, is converted into an intermediate α-phase which is then converted into the β-phase at 90°C. The thermal decomposition of the β-phase at ~100°C is accompanied by the evolution of nitrogen and the formation of 3-bromo-2-naphthoic acid (**45b**).

Errede *et al.*[126] studied the thermal decomposition of *o*-acetaimidobenzamide (**46**). This compound crystallizes in two polymorphic modifications α and β, the solid phase thermal transformation of which leads to 2-methyl-4-quinazolinone (**47**) (Scheme 15).[8]



α 46 β 46

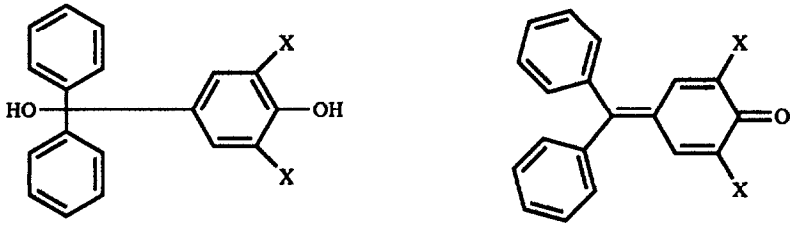
47 48

Scheme 15. Thermal transformation of (α **46**) and (β **46**) to 2-methyl-4-quinazolinone.

The crystals of (α-**46**) and (β-**46**) are made up of the centrosymmetric molecular dimer (Fig. 3) formed by hydrogen bonding with participation of the primary amido group. The structural data indicate that the main role in the destabilization of the structure of (β-**46**) which leads to the solid phase dehydration and formation of compound (**47**) is due to the hydrogen bonds combining the molecules of (β-**44**) into dimers.[127]

Lewis *et al.*[128] studied the thermal, photochemical and photonucleated thermal dehydration of 4-hydroxyphenyldiphenylmethanol (**49a**), (3,5-dibromo-4-hydroxyphenyl)diphenylmethanol (**49b**) and (3,5-dimethyl-4-hydroxyphenyl)diphenylmethanol (**49c**) into corresponding yellow or orange fuchsones (**50**).

X-Ray diffraction studies have shown that the crystal structures of (**49a**), (**49b**) and (**49c**) are



49 **50**

a, X = H a, X = H

b, X = Br b, X = Br

c, X = CH_3 c, X = CH_3

isostructural. The molecules of these compounds are aligned in the solid state with the phenolic OH group hydrogen-bonded to an alcoholic OH group of an adjacent molecule. Thus, these compounds constitute a series in which crystal packing aligns the molecules in a geometry favourable to reaction.

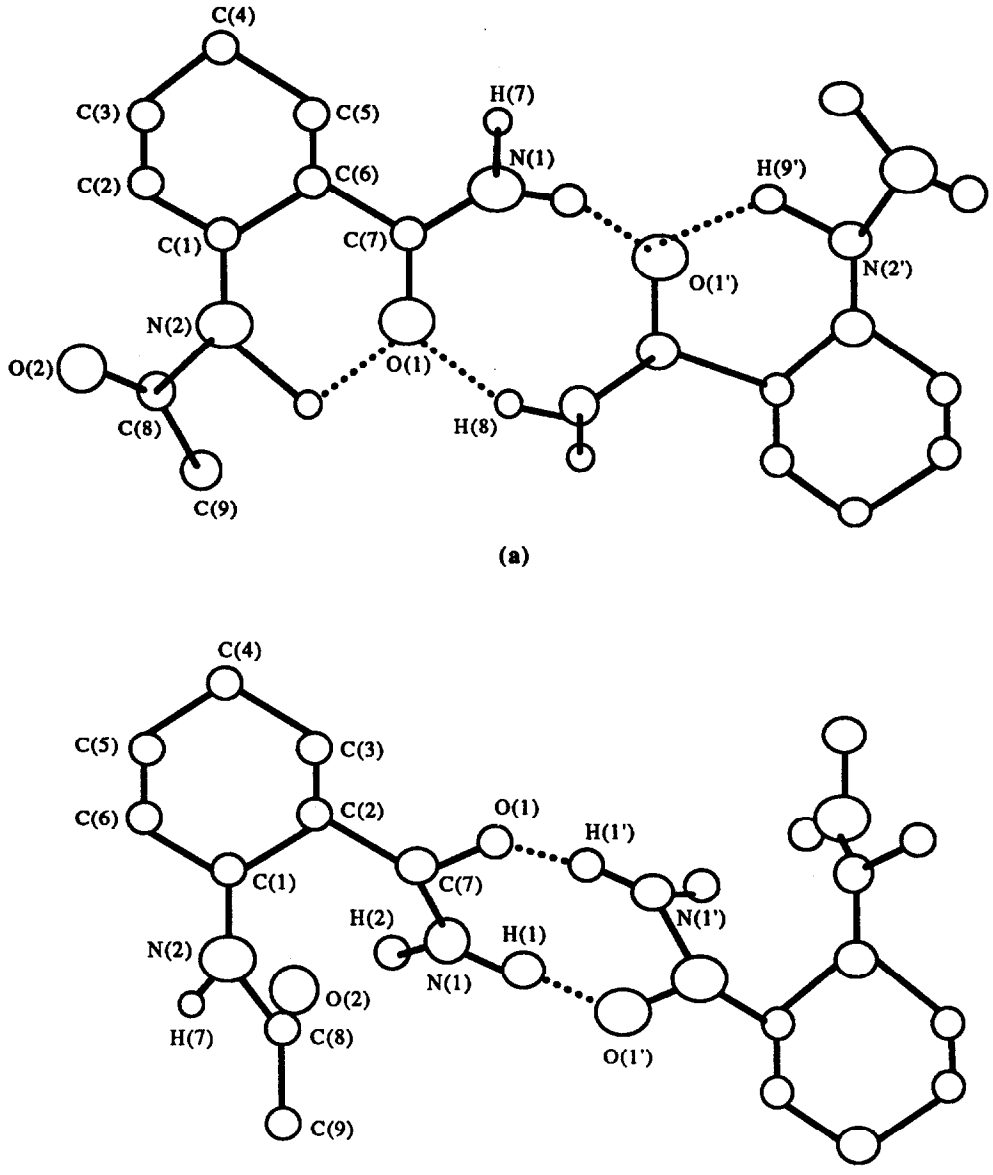


Fig. 3. The structure of centrosymmetric dimers in the crystals of (α-**44** (a)) and (β-**44** (b)).

The dimethyl compound (**49c**) crystallizes in two habits. Figure 4a shows the morphology correlated with the crystal structure for habit I and Figure 4b shows the crystal structure for habit II. Microscopic observation of the thermal dehydration of single crystals of habit I of (**49c**) shows a slight preference for reaction along the hydrogen-bonded chains. The reaction begins by formation of a solid solution of the coloured product in the parent crystal in triangular regions. Then cracks develop and finally the product phase separates as the reaction progresses through the crystal. The behaviour of habit II of (**49c**) is different. In this case reaction begins at random nucleation sites present in the major face and as more sites develop the crystal face gradually becomes opaque.

In spite of its similar crystal structure (**49b**) reacts much faster than (**49c**). At 110°C, 90% reaction occurs within 10 h in the case of (**49b**) whereas (**49c**) takes approximately 100 h. It is also reported that (**49a**) in powdered form is converted to fuchsone (**50a**) on irradiation with sunlight.

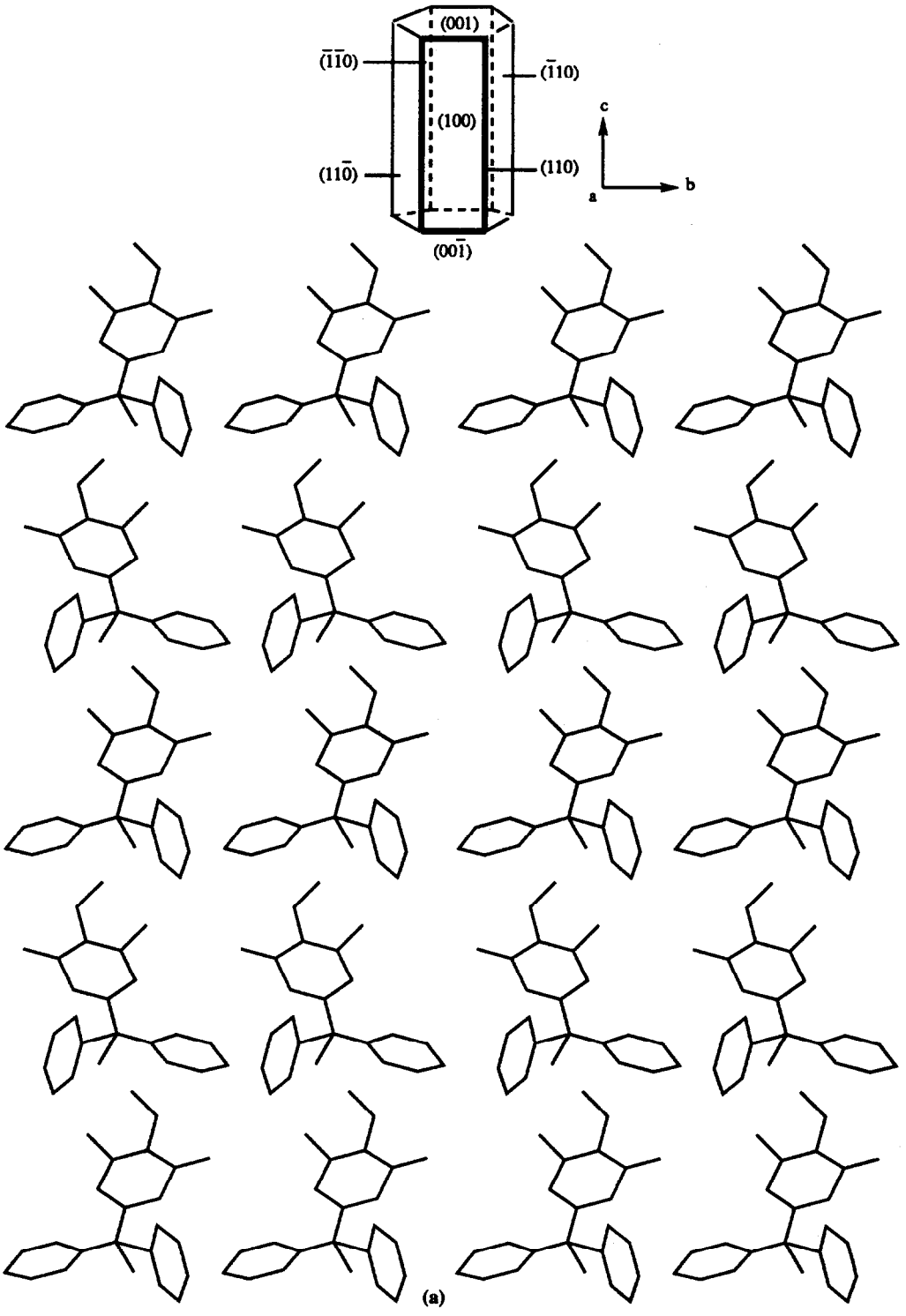
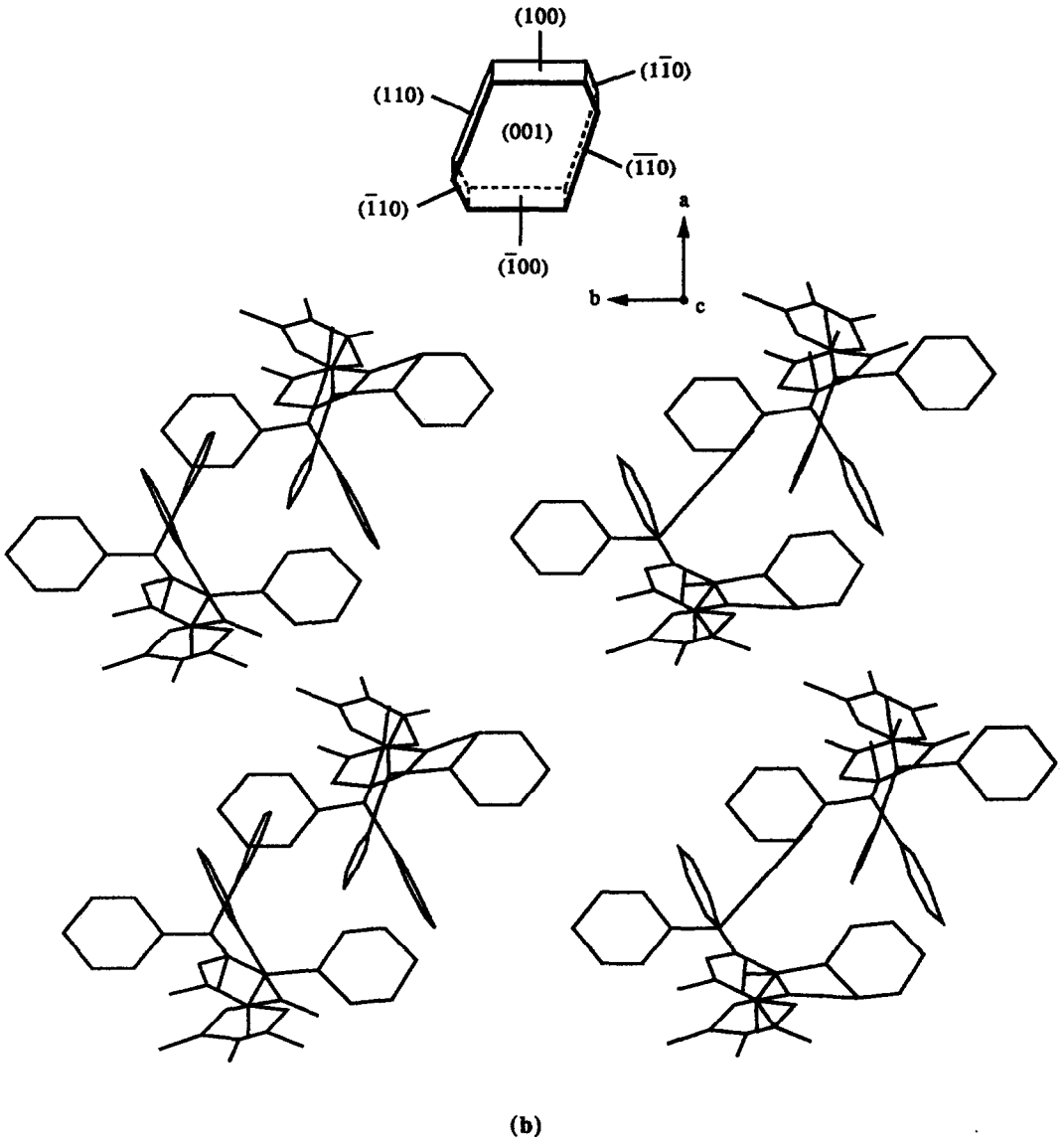


Fig. 4a. The upper drawing shows a crystal of habit I of (**49c**) with major faces indexed. The lower stereopair drawing shows the hydrogen-bonded chains of a crystal of (**49c**) in the same orientation as in the crystal above.



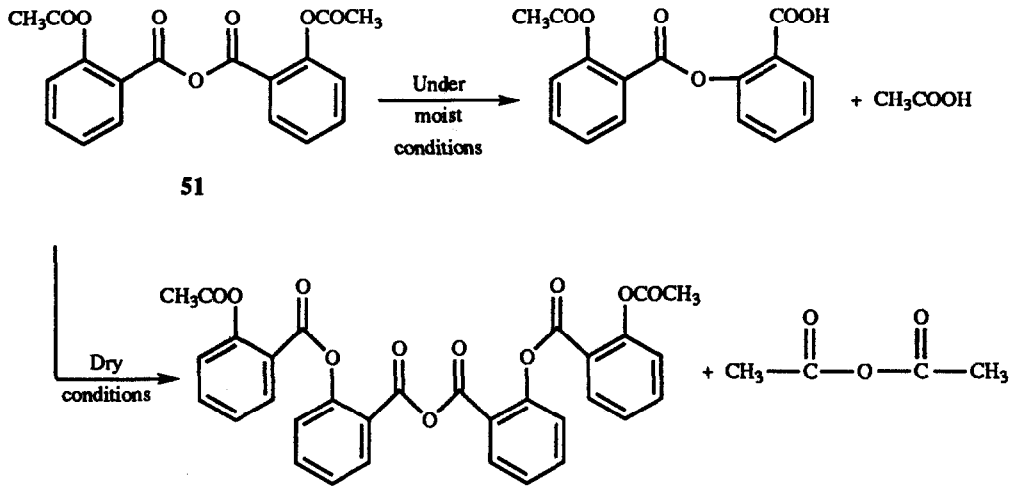
(b)

Fig. 4b. A crystal of habit II of (**49c**) and (below it) the molecular orientation in the crystal.

Both (**49b**) and (**49c**) are found to undergo a change in colour corresponding to conversion into the fuchsone when irradiated with a low intensity UV source (λ = 254nm). It is difficult to explain the mechanism of the reaction, although some explanation could be proposed in terms of enhanced acidity of the excited phenols.[128]

Further, when a part of the crystal of (**49c**) is exposed to ultraviolet light photonuclei are generated which initiate the thermal dehydration process. The reaction begins in the exposed part and then moves to the unexposed part of the crystal. The explanation for photonucleation may require nothing more than the postulation of production of nucleation sites by photolytic formation of fuchsone in the crystals of carbinol (**49**).

Garrett *et al.*[129] reported an extremely interesting study of the solid state decomposition of aspirin anhydride (**51**). This compound decomposes in the solid state at temperatures ranging from 40 to 70°C (Scheme 16).



Scheme 16. Thermal decomposition of (**51**).

Crystalline esters of vitamin A (including the succinate half-ester, the nicotinate, and the 3,4,5-trimethoxybenzoate) decompose by polymerization and oxidation pathways.[130,131] Vitamin A, exposed to air at room temperature for several years or heated at 100°C for 5 h, gave at least five ketones on TLC plates treated with 2,4-dinitrophenylhydrazine.[132]

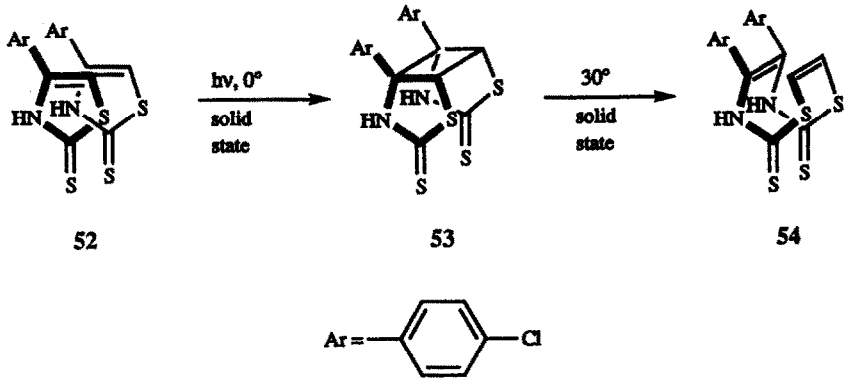
β-Carotene autooxidizes in the solid state in air at 25° and 35°C.[133] The rate of decomposition depends on the oxygen pressure and temperature and occurs through free radicals.

3-Amino-4-hydroxybenzenearsenous acid is an important drug used in the treatment of syphilis; it decomposes even in the absence of oxygen at 100°C in seven days.[134–136] Fumagillin undergoes both solution and solid state photochemical reactions, and the solid decomposes thermally.[137–139]

The study of organic solid state decomposition reactions is very useful in the case of drugs. Once the mechanism of decomposition is established, it is possible to apply the concept of crystal engineering in the development of new drugs.

13.2. *Photodimerization*

Schmidt and co-workers[3,21,140] at the Weizmann Institute have studied systematically the factors that govern the course of organic solid state (especially photoinduced) reactions. The rates of reactions as well as the nature of the products obtained during solid state photocyclodimerization are governed by the packing characteristics, local symmetry and the separation distance between the reactive double bond. The main problem is to engineer the crystal in such a way that reactive partners organize within the favourable distance of 4.2Å and there is β-packing. Further, for topochemical reactions to occur, there should be favourable π orbitals of the reactive partners. These criteria for dimerization are landmarks in organic solid state photochemistry and are used as rules for an understanding of a large number of [2+2] photodimerization reactions. However, recent studies on the photodimerization of olefinic crystals have brought to light several examples which deviate significantly from the well accepted topochemical principles.[141] 4-(4′-Chlorophenyl)thiazole-2(3*H*)-thione (**52**) undergoes photodimerization in solid state forming compound (**53**) which is unstable, and changes to the ten-membered heterocyclic diene (**54**) on warming. It may be noted that both S---S and S---Cl contacts in the structure of thione (**52**) are significantly shorter than the van der Waals values (radii: S, 1.85Å; Cl, 1.80 Å) and that their angular preferences are almost exactly those predicted by a nucleophile–electrophile model (**55**). The S---Cl and S---S contact distances and the angles are given in Fig. 5.



Many photodimerization reactions are broadly governed by the topochemical principles.[142] Pfoertner *et al.*[143] studied the topochemical photoreactions of a number of retinoids. The aromatic retinoid (**55a**) exists in three crystal modifications. The centric (α-**55a**) yields the centrosymmetric photocycloadduct (**56**) whereas the γ-form does not react photochemically. Substitution of the ethyl ester group in (**55a**) by a diethylamide (**55d**) leads to *E*/*Z* isomerization only, although the shortest distance of 3.66Å between two molecules is suitable for [2+2] photocycloaddition across the centre of symmetry. It has been found that substitution of the ethyl ester in (**55a**) by a diethylamide (**55d**) increases the excitation energy. This means that in topochemical reactions, besides distances of the reacting centres and π-interactions, the excitation state may also determine the reaction mode. Crystals of bis-butoxycarbonyl-substituted tetrathiafulvalene (CISTTF) (**57**), which has three reactive double bonds, upon irradiation yield two products, a cage product (**59**) and another (**58**) formed by the participation of one of the pairs of reactive double bonds (Scheme 17).[144]

The main factors controlling the reaction of Scheme 17 appear to be the subtle features of the molecular packing within the broad classification of the α and β type packing modes as well as the degree of molecular motions that the particular crystal permits. It is known that a sulfur atom if present in the structure plays an important role in crystal engineering. However, this does not seem to be a factor in the reactions of Scheme 17.

Venugopalan *et al.*[145] studied the photodimerization of two systems with different topological features but the same steering group (bromo). The systems chosen for detailed investigation were

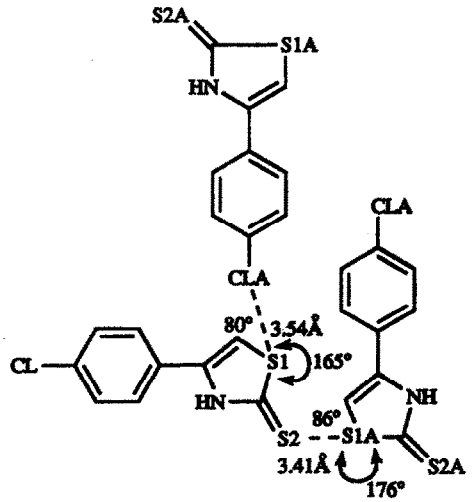
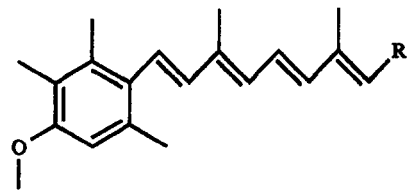


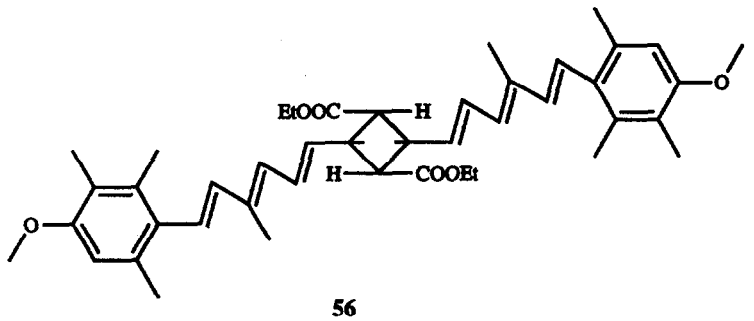
Fig. 5. Intermolecular S—S and S—Cl contacts for thione (**52**).

the planar bromocoumarins (**60**) and the nonplanar 3-(*p*-bromophenylvinyl)-6-isopropylcyclohex 2-enone (**61**). Irradiation of 6- and 7-bromocoumarins yielded *syn* head-to-head dimer (**62**) whereas (**61**) was photostable in the solid state. The results could be explained in terms of packing.

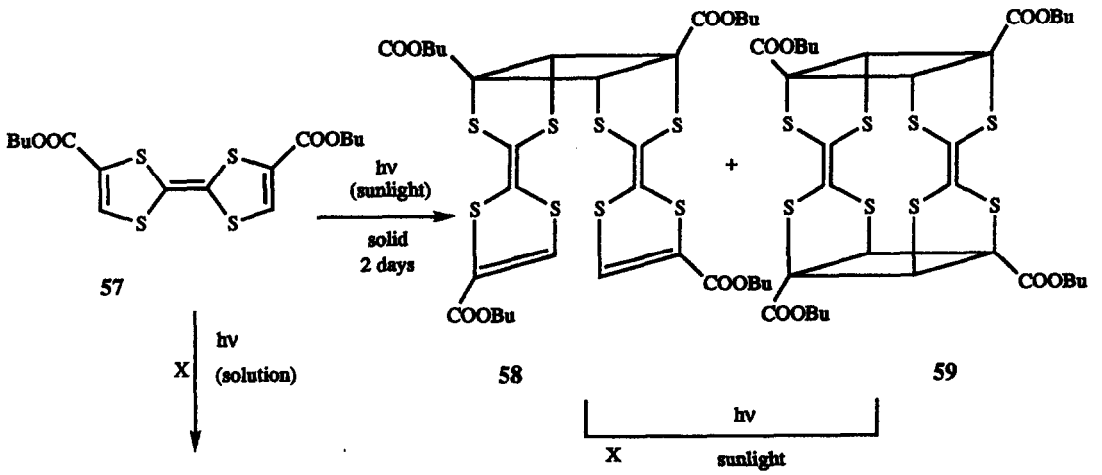


a, R = COOEt
b, R = CONHEt
c, R = COOH
d, R = $CONEt_2$

55

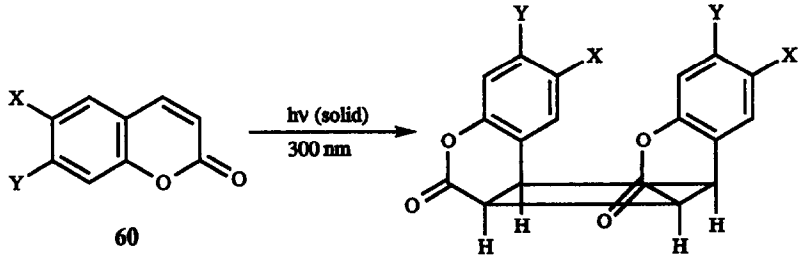


56



Scheme 17. Solid state photochemical [2+2] cycloaddition reaction of (**57**).

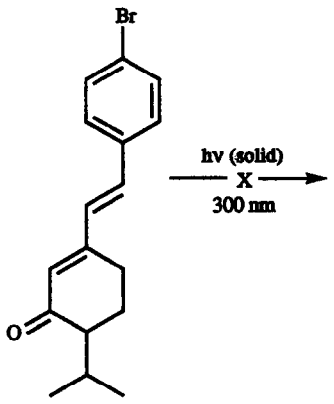
In the crystal structure of unsubstituted coumarin (**60**, x = y = H)[146] the shortest axis is as long as 5.676Å which would not allow it to react in a topochemical fashion to give a mirror symmetric product. On the other hand, bromo-substitution at the 6- or 7- position engineers the molecule to adopt the β-stacked packing mode. The bromoacetylcoumarin[147] also stacks about the shortest repeat axis of 4.229Å. The photoreactive 6- and 7-chlorocoumarins are β-stacked with repeat distances of 4.09 and 4.454Å respectively.[145] The common feature of all these compounds is that they are all planar. Interestingly, all five bromo-substituted *trans*-cinnamic acids reported by Cohen and Schmidt[3] which are β-stacked and photoreactive are also planar. The planarity of the molecules allows an additional π---π interaction to operate between the interstacks which results in the β-packing. The compound (**61**) is photoinert because it is nonplanar and packs in an α-form. Venugopalan and Venkatesan[148] studied the topochemical photodimerization of benzylidene-DL-piperitone in the solid state. Though the molecule possesses two potentially reactive double bonds, it



60

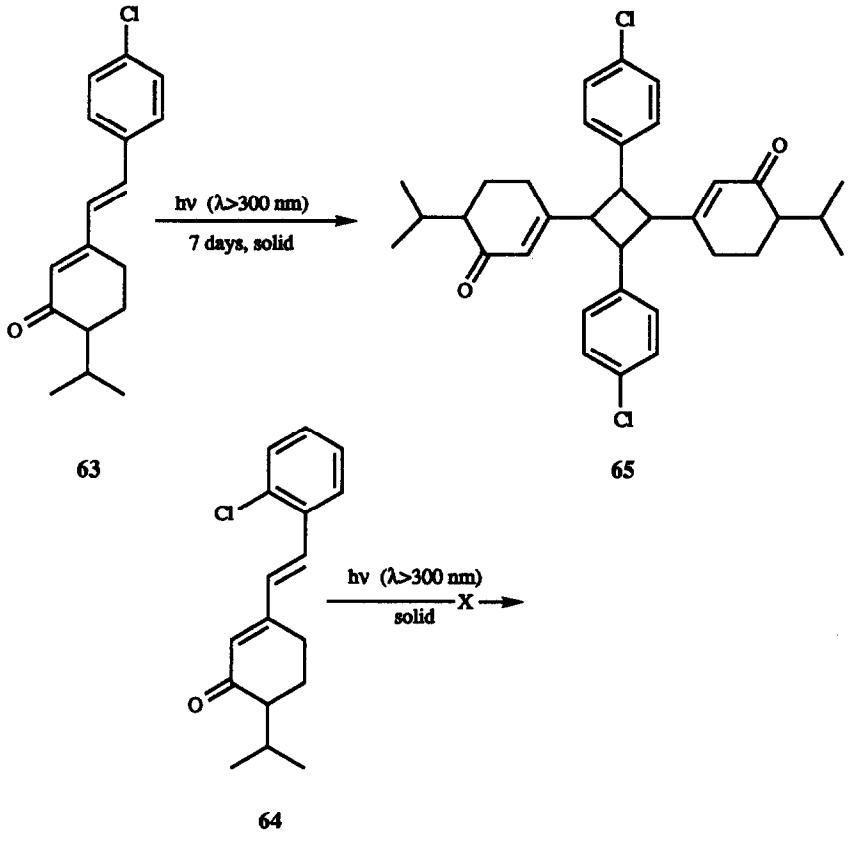
X = H, Y = Br
X = Br, Y = H

62



61

is photoinert in the solid state. Since the chloro-substitution may steer the molecules into β-packing, the topochemical photodimerization of *p*-chlorobenzylidene-DL-piperitone (**63**) yields (**65**) an *anti* head-to-tail dimer. Irradiation of (**63**) yields a single product whereas (**64**) is photostable in the crystalline state. Both *o*- and *p*-chloro derivatives adopt α-type packing in the crystal lattice. The overall nonplanar character of these molecules produced by the cyclohexenone ring adopting a sofa conformation, along with an anisotropically shaped isopropyl group, would prevent efficient close crystal packing in the β-arrangement. This situation seems to lead to the observed α-packing mode taking precedence over the halogen---halogen interaction. α-Packing has also been observed in benzylidene cyclopentanones.[149]



Another important observation is the slowness of the photoreaction of compound (**63**) in the solid state with an induction period. The stability of the crystal lattice would be an important factor in controlling the rate of the reaction. Upon excitation the molecules must undergo the necessary motions to achieve the overlap of the π orbitals. Unlike the case of rigid molecules such as coumarins, there is an additional molecular aspect controlling the rate of reaction, namely the necessity for conformational changes during the course of reaction. Considerable molecular movement must take place, involving changes in the conformations at the anisotropic isopropyl as well as benzylidene groups, in order to release the intermolecular steric pressure. This additional factor may contribute to the presence of the induction period as well as the lower percentage yield of the dimer.

Compound (**64**) is photoinert in the crystalline state. However, the geometrical arrangement of the double bonds can be considered to be conducive to topochemical photodimerization reactions. It is difficult to explain the inertness in this case. There are observations of a similar kind in the literature where, despite favourable molecular packing, the crystals are photostable.[7a,150]

13.3. *Polymerization reactions*

A large number of polymerization reactions have been studied in the solid state. Solid state polymerizations of organic molecules are brought about by thermal or photochemical means. Polymerization of diacetylene (Fig. 6) is probably the most elegant example of the topochemical principle.[151–157] Diacetylene monomers polymerize in the solid state by a 1,4 addition reaction at the diacetylene group to produce a polymer. The solid state reaction transforms the entire monomer crystal without phase separation. When R = *p*-toluenesulfonate, the reaction becomes autocatalytic and the rate is enhanced considerably. The autocatalysis has been attributed to the influence of strain on chain initiation and propagation.

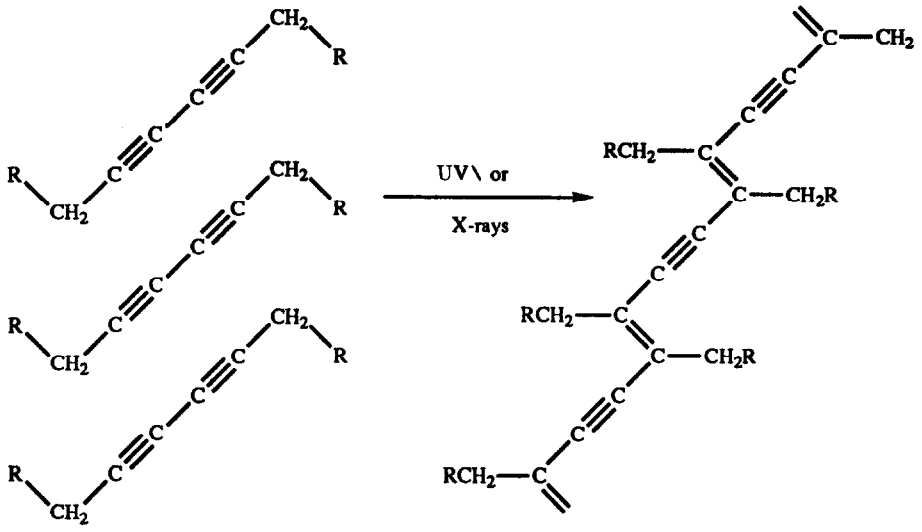


Fig. 6. Polymerization of diacetylene in the solid phase.

Patel *et al.*[158] studied the polymerization of crystals of 2,4-hexadiyne-1,6-diol bis(*p*-toluenesulfonate) (PTS) using the differential scanning calorimetric technique. The heat of polymerization and activation energy were found to be -36.5 and 22.5 kcal mol^{-1} respectively. The results have indicated a biradical dimer as the chain initiation species. At low temperature, the solid state polymerization of acrylonitrile[159–161] with low activation energy is faster than in the liquid state and it increases sharply at a phase transition temperature around $-135°C$.[160,161] Urea-1,3-hexadiene clathrate[162] polymerizes only in the solid and not in the liquid state, implying that the geometrical arrangement of the monomer molecules in the clathrates is particularly favourable for the chain reactions.

The solid state polymerization of trioxane has been studied extensively[163–165] because of its great technological importance in producing highly oriented polyoxymethylene fibres from the needle like crystals of trioxane. Many other cyclic monomers have also been found to polymerize in the solid state.[166–170]

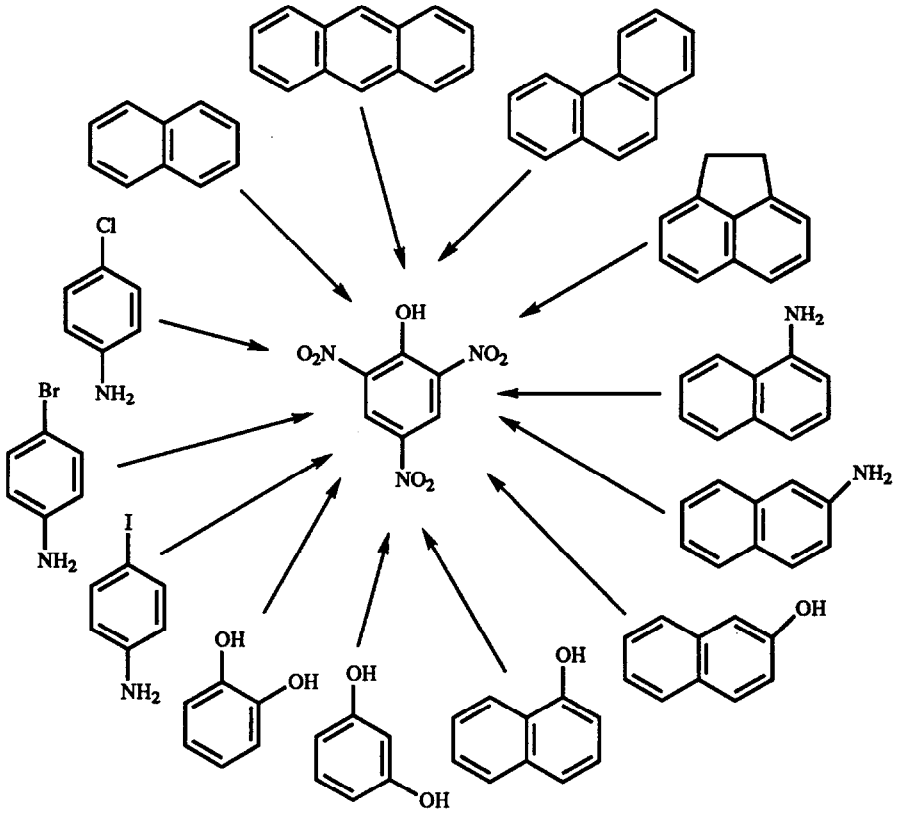
Polymerization reactions are affected considerably by γ-rays, soft X-rays, accelerating electrons and neutrons. Irradiation of crystals of 5-bromo-2-methoxy-*cis*-cinnamic acid yielded a polymer with a structure consistent with the topochemical postulate[171] along with other products. Thus cinnamic acid did not crystallize in either α- or β-type, but has the double bonds related by both translational and screw axis symmetry. Polymerization along the screw axis is consistent with the structure of the polymer obtained. In the polymerization of trioxane[165,172] induced by ionizing radiation and the photochemical polymerization of crystalline 2,5-distyrylpyrazines and 1,4-bis(3-pyridylvinyl)benzene[173–175] chains of the polymer grew in the monomer crystal with the same orientation as the stack of the monomer.

N-Vinylphthalimide polymerizes in the solid state when exposed to γ-radiation.[176] Copolymerization of *N*-vinylcarbazone and acrylamide is effected in the solid state in the presence of γ-radiations.[177] Radiation-induced polymerization processes in crystalline mixtures of acrylic and methacrylic acids have been investigated by Chakiro.[178]

13.4. *Solid–solid reactions*

A number of solid–solid reactions have been studied.[16] They are in general slow and complicated.[179] A novel type of solid–solid reaction between phthalic anhydride and phthaloyl sulfathiazole has been investigated and a second order rate equation was proposed.[180] Diffusion of

phthaloyl sulfathiazole into phthalic anhydride was not measurable but concentration profiles of phthalic anhydride in phthaloyl sulfathiazole were obtained. Diffusivities were calculated and a sharp increase in the diffusivity with porosity indicated the importance of pore surface diffusion. Rastogi and co-workers[181–185] studied a series of solid–solid reactions between picric acid as one component and substituted hydrocarbons as the other (Scheme 18). It was observed that reactions



Scheme 18. Solid state reaction between picric acid and substituted hydrocarbons (arrows indicate direction of diffusion).

propagated as a result of diffusion of substituted hydrocarbons towards picric acid, forming picrates. The nature of interactions in most of the cases is charge-transfer, however some amines could form picrate salts. Diffusion of hydrocarbons in picric acid can be divided in two parts: (1) lateral diffusion, when bulk quantities of reactants are kept side by side and (2) diffusion of the reactant in picric acid grains.

The lateral diffusion can occur by surface migration, grain boundary diffusion, or diffusion through the vapour phase. The energies of activation for reactions when the reactants were kept in contact were found to be lower than the heat of sublimation of hydrocarbons. This shows that the diffusion does not exclusively occur through the vapour phase. The rates of reactions were also measured under two conditions: (i) by keeping reactants in physical contact and (ii) by keeping them separated by air gaps. Different rates observed in the two cases led to the conclusion that the vapour phase diffusion is not prominent when the two reactants are kept in contact with each other. The lower value of energy of activation leads to the conclusion that bulk diffusion also does not occur. Thus, the only alternative left is the surface migration or grain boundary diffusion. Surface migration seems to be more likely because the rate has been found to depend on the surface area of the particles.[184] Surface migration also depends on the size and symmetry of the diffusing molecules.

The results show that the surface migration of bulky molecules is more difficult as compared with the simpler molecules (Table 2). In order to understand the mechanism of surface migration, the rate constants of some of the reactions involving diffusing molecules of different degree of asymmetry are compared. It is found that flat and symmetrical molecules drift on the surface much more easily than do unsymmetrical molecules. It has also been found that the higher the asymmetry (higher dipole moment) the lower the value of the rate constant (Table 3) which implies that rate of surface migration depends on the symmetry of the molecules. If the diffusing molecules have the same symmetry, the rate of surface migration would depend on the end-to-end distance of the guest and the host molecules. The end-to-end distances for picric acid and *p*-chloro-, *p*-bromo- and *p*-iodoanilines have been calculated and compared with the rate constants. It is found that the end-to-end distance in the case of *p*-chloroaniline is the same as in the case of picric acid whereas in *p*-bromo- and *p*-iodoanilines it is greater. As a result, the diffusion of *p*-chloroaniline towards picric acid in solid state is easier as compared to that of *p*-bromo- and *p*-iodoanilines (Table 4).[187]

8-Hydroxyquinoline reacts in the solid state with maleic, succinic and phthalic anhydrides, catechol and resorcinol to give 1 : 1 addition compounds (Scheme 19).[186,188,189] In these reactions, 8-hydroxyquinoline was found to be the diffusing species and the diffusion occurred through surface migration. The results also indicated that the penetration inside the grains took place as a result of the formation of cracks and voids developed during the course of the reaction. Rastogi *et al.*[190] prepared a series of maleamic acids by the reactions of maleic anhydride with substituted amines in the solid state (Scheme 20). Amines were found to be the diffusing species and the reaction

Table 2. Influence of molecular size on rate constant (k_i) for reaction between picric acid and the given reactants (particle size, 100 mesh; temperature $45 \pm 1°C$)

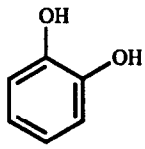
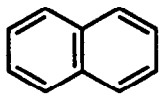
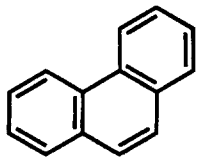
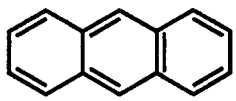
Reactant	Rate constant (k_i) (cm^2/h)	Ref.
	1.51×10^{-3}	184
	4.68×10^{-4}	182
	4.80×10^{-5}	182
	2.39×10^{-8}	182

Table 3. Dependence of rate constant (k_i) on dipole moment for reaction between picric acid and the given reactants (particle size > 150 mesh; temperature 35 ± 1°C)

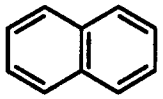
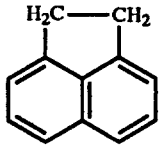
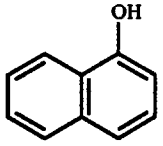
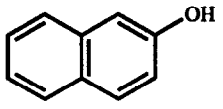
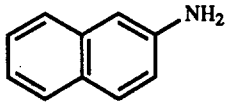
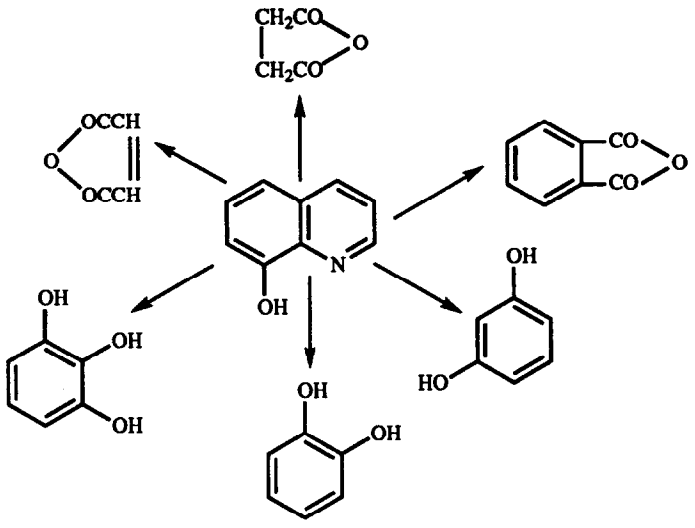
Reactants	Dipole moment of reactants (D)	Rate constant (k_i) (cm^2/h)	Ref.
	0.00	4.22×10^{-4}	182
	0.79	3.35×10^{-4}	184
	1.91	1.84×10^{-4}	183
	2.01	6.74×10^{-5}	183
	2.12	2.44×10^{-5}	184

Table 4. The values of rate constant (k_i) at 31 ± 1°C and perpendicular distance between two groups at *para* positions[187]

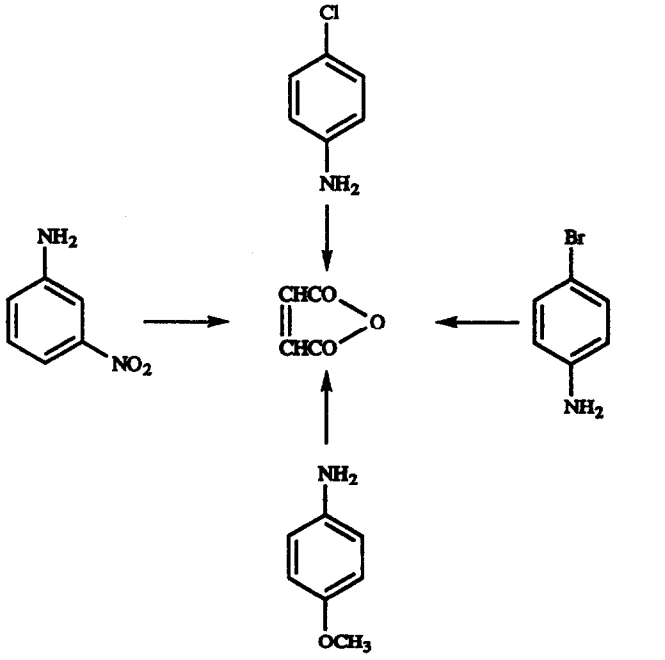
Reactant	Rate constant (k_i) cm^2/h	Groups at *para* positions	Distance (Å)
p-Chloroaniline	5.62	Cl-NH_2	6.4
p-Bromoaniline	1.97	Br-NH_2	6.6
p-Iodoaniline	1.88	I-NH_2	6.8
Picric acid	—	OH-NO_2	6.4

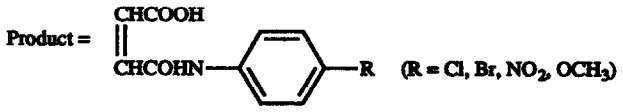
propagated by surface migration. Prasad and Mandal[191] determined the crystal structure of *p*-chlorophenylmaleamic acid and found that the crystal lattice belongs to the monoclinic system with the unit cell dimension: a = 12.68Å, b = 11.69Å, c = 7.35Å, $\beta = 115.5°$, space group = $P^2_{1/a}$, $z = 4$, $d_{calc} = 1.545$ g cm^{-3} and $d_{obs} = 1.54$ g cm^{-3}. They also found that the molecules within the unit cell were arranged in two layers parallel to the (001) plane having normal bond lengths and bond angles. If U_A, U_B and U_P are the cell volumes of maleic anhydride (431Å^3), *p*-chlorophenyleneamine (595.5Å^3) and maleamic acid (1089.5Å^3) respectively, then $\{U_P-(U_A+U_B)\}/(U_A+U_B)$ would be a



Scheme 19. Solid state reaction between 8-hydroxyquinoline as one component and phenols or anhydrides as the other (arrows indicate the direction of diffusion).

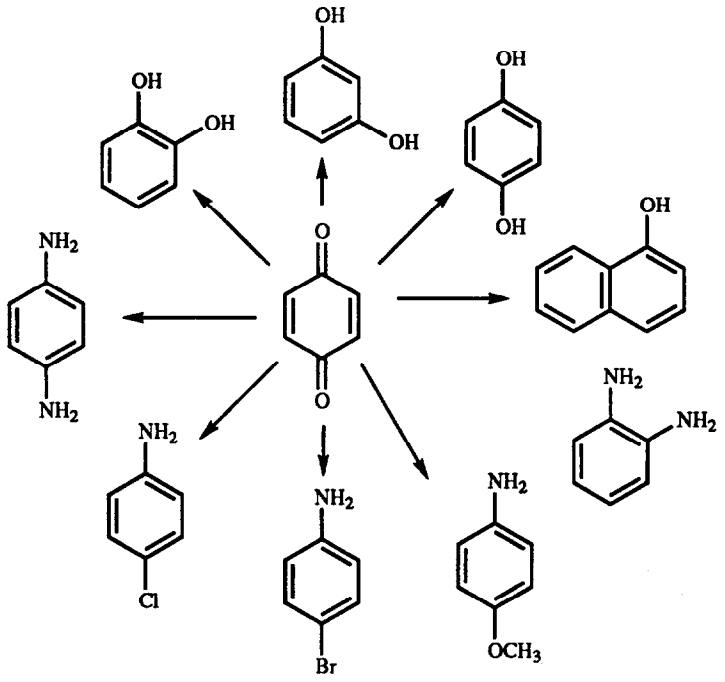
measure of the fractional change of cell volume when the guest molecule enters into the host molecule. The magnitude of the fractional change comes out to be 6.15%. This suggests that entropy change during the reaction is very small. Solid state reactions of *p*-benzoquinone with





Scheme 20. Solid state reaction between maleic anhydride and aromatic amines.

dihydroxybenzenes, phenols and amines (Scheme 21) forming 1 : 1 addition compounds have also



Scheme 21. Solid state reaction between *p*-benzoquinone as one component and phenols and amines as the other component (arrows indicate the direction of diffusion).

been studied.[192–196] The diffusion of *p*-benzoquinone towards the other reactant through surface migration is established.[196] These reactions also show the dependence of surface migration on the symmetry of dihydroxybenzenes. In these systems reactions have been found to undergo completion. It is likely that the first coating of the product layer is formed at the surface of dihydroxybenzene molecules and, due to the internal pressure of the system, cracks develop in the product layer which allow further continued reaction of *p*-benzoquinone molecules with phenols or amines. The diffusion inside the grain may take place through grain boundaries and other imperfections. The overall reaction sequence can be visualized as shown in Fig. 7.

Singh *et al.*[193] studied the reaction of *p*-benzoquinone with α-naphthol and found that the quinone diffused towards the naphthol through surface migration. The reaction carried out with a single crystal indicated the initiation of the reaction at point defects. Recently the authors[194–196] have studied the reactions of *p*-benzoquinone with *p*-substituted anilines. The quinone was found to be the diffusing species. As a result of a solid state reaction, 1 : 1 CT complexes containing free radicals were formed which were found to be polymeric in nature, possessing semiconducting properties. The rate of reaction depended on the symmetry of the host molecules. We reported for the first time that the Hammett equation is applicable to organic solid state reactions also. The energies of activation for a large number of reactions involving surface migration and inner penetration are given in Table 5.

Cohen[10] pointed out that it would be desirable to obtain kinetic data for the "true chemical reaction steps" of the overall solid state reaction, to be able to tell whether the rules of physical organic chemistry, derived almost exclusively from studies of solution processes, are applicable also to crystals. In a number of organic reactions, in solutions, it is reported that in the case of *m*- and *p*-substituted acids and bases of the same series, the rates of reactions are related with the dissociation constants of the acids and bases.[198] Bassi *et al.*[199] reported such a correlation for inorganic solid

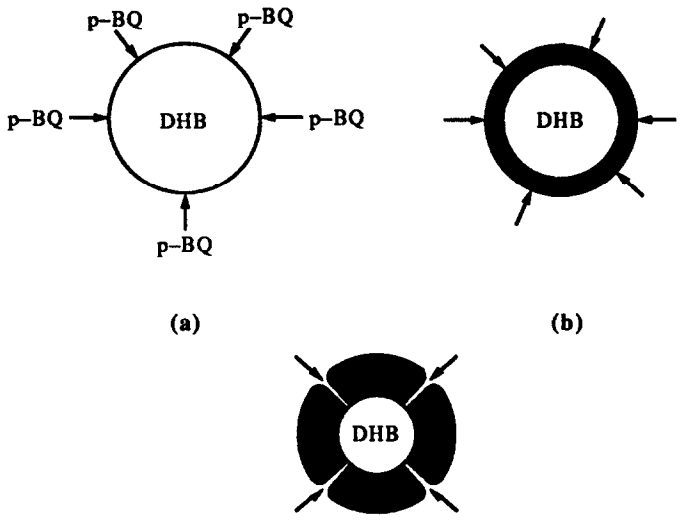


Fig. 7. Penetration of *p*-benzoquinone (*p*-BQ) in the grains of *o,m* and *p*-dihydroxybenzene (DHB) (a) first contact of the reactants, (b) formation of reaction products at the surface of DHB, (c) formation of cracks in the reaction product and further diffusion of *p*-BQ.

state reactions. Recently the authors have proposed the existence of such a correlation in organic solid state reactions between *p*-substituted anilines and *p*-benzoquinone.[196] Linear plots (Fig. 8) between log k_i (rate constant) *vs.* log k_b are obtained showing the validity of equation (21).[196]

$$\log k_i = \rho \log k_b + C, \tag{21}$$

where k_b is the dissociation constant of the *p*-substituted aniline, and C and ρ are constants. If the values of k_i and k_b are compared to that of *p*-phenylenediamine (k_0 and k_{b0}) we get the Hammett equation (22):

$$\log (k_i/k_0) = \rho \log (k_b/k_{b0}) \tag{22}$$

or

$$\log (k_i/k_0) = \rho\sigma',$$

where $\sigma' = \log (k_b/ k_{b0})$, is also known as the substituent constant. When log (k_i/k_0) is plotted against σ' a straight line is obtained (Fig. 9) showing that the Hammett equation holds good even for organic solid state reactions.

Qureshi *et al.*[200] studied the solid state reaction between 2,4-dinitrotoluene (**66**) and *p*-dimethylaminobenzaldehyde (**67**) and found that a yellow coloured 1 : 1 CT complex (**68**) is formed (Scheme 22) and diffusion of *p*-dimethylaminobenzaldehyde occurred into the crystal lattice of 2,4-dinitrotoluene through surface migration and the vapour phase. The energy of activation was found to be 42 kJ mol^{-1}. Recently Patil *et al.*[201–204] prepared a series of quinhydrone complexes by the reaction of substituted quinones and hydroquinones in the solid state. They found that, as the

Table 5. Energy of activation for solid state reactions

Reactants		Energy of activation for surface migration (kJ mol^{-1})	Energy of activation for inner penetration (kJ mol^{-1})	Ref.
Static species	Diffusing species			
Picric acid	α-Naphthol	80	102	183
Picric acid	β-Naphthol	42	—	183
Picric acid	Acenaphthene	46	—	184
Picric acid	β-Naphthylamine	46	—	184
Picric acid	Pyrocatechol	42	—	184
Picric acid	Naphthalene	44	—	181
Picric acid	Phenanthrene	36	—	182
Picric acid	Anthracene	24	—	182
Picric acid	*p*-Chloroaniline	21	—	187
Picric acid	*p*-Iodoaniline	22	—	187
Picric acid	*p*-Bromoaniline	25	—	187
Maleic anhydride	Pyrocatechol	37	—	189
Phthalic anhydride	8-Hydroxyquinoline	19	96	188
Maleic anhydride	8-Hydroxyquinoline	19	—	188
Catechol	8-Hydroxyquinoline	54	—	188
Maleic anhydride	*p*-Anisidine	27	64	190
Maleic anhydride	*p*-Chloroaniline	32	54	190
Maleic anhydride	*p*-Bromoaniline	21	86	190
Maleic anhydride	*p*-Nitroaniline	—	58	190
o-Dihydroxybenzene	*p*-Benzoquinone	32	117	192
m-Dihydroxybenzene	*p*-Benzoquinone	26	117	192
p-Dihydroxybenzene	*p*-Benzoquinone	15	100	192
α-Naphthol	*p*-Benzoquinone	13	57	193
p-Phenylenediamine	*p*-Benzoquinone	18	29	194
p-Anisidine	*p*-Benzoquinone	19	120	196
p-Bromoaniline	*p*-Benzoquinone	22	—	196
p-Chloroaniline	*p*-Benzoquinone	30	—	196
o-Phenylenediamine	*p*-Benzoquinone	20	33	195
p-Chloranil	8-Hydroxyquinoline	32	110	196
Pyrogallol	8-Hydroxyquinoline	29	75	197

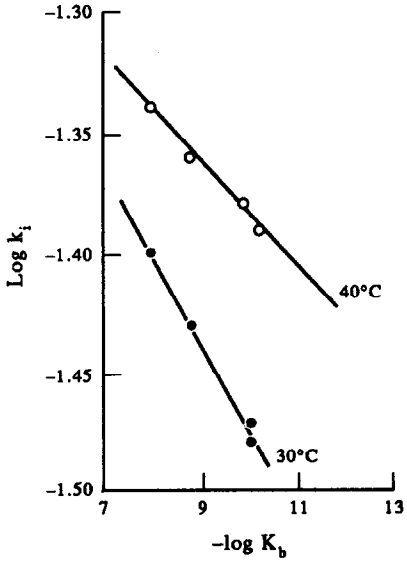


Fig. 8. Plot of k_i vs k_b at different temperatures.

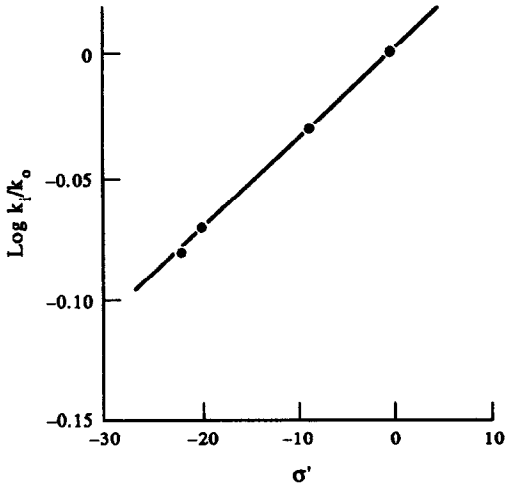
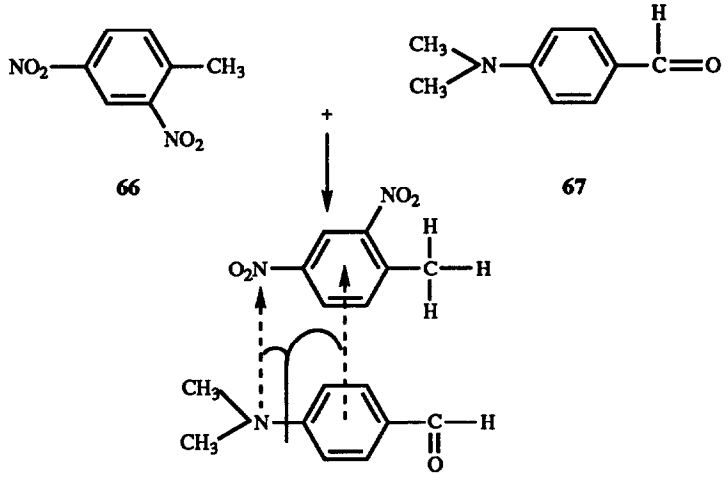


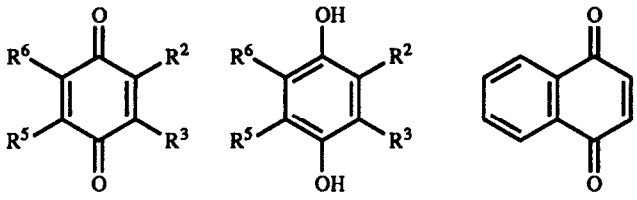
Fig. 9. Plot of log k_i/k_0 vs σ' at 30°C.



Scheme 22. Solid state reaction between (**66**) and (**67**).

degree of substitution increased, the reaction became more difficult. Methyl substitution on the hydroquinone moiety generally leads to the formation of a complex with components in 1 : 1 ratio whereas methyl groups on the quinone moiety form the complex in the ratio of 1 : 2 of quinone to hydroquinone. A few reactions of methylated quinones and hydroquinones are given in Table 6.

The mechanisms of such reactions are complicated. Patil *et al.*[201] attempted to explore the details of the process by examining the structural changes that occur during the course of reactions. Hydroquinone exists in three crystalline forms whereas naphthohydroquinone crystallizes in a relatively simple structure.[205] In the crystal of hydroquinones, the molecules are linked by hydrogen bonds forming chains or rings. For the formation of quinhydrone complexes the hydrogen bonded structures are to be broken. The structures of monoclinic and triclinic quinhydrones, 1 : 1 complex of naphthoquinone and hydroquinone, and the symmetrically substituted phenyl- and *p*-chlorophenyl quinhydrones have been reported.[205] All of them have chains of alternating hydroquinone and quinone molecules linked via hydrogen bonds; adjacent chains are held together by π-complexing. It is interesting to note that both monoclinic and triclinic forms of quinhydrone formed by the



(1) (2) $R^2 = R^3 = R^5 = R^6 = H$
(3) (4) $R^2 = Me, R^3 = R^5 = R^6 = H$
(5) (6) $R^2 = R^6 = Me, R^3 = R^5 = H$
(7) (8) $R^2 = R^3 = Me, R^5 = R^6 = H$
(9) (10) $R^2 = R^5 = Me, R^3 = R^6 = H$
(11) (12) $R^2 = R^3 = R^5 = Me, R^6 = H$
(13) (14) $R^2 = R^3 = R^5 = R^6 = Me$
(15) (16) $R^2 = Ph, R^3 = R^5 = R^6 = H$
(17) (18) $R^2 = p\text{-}ClC_6H_4, R^3 = R^5 = R^6 = H$

Table 6. Effect of multiple substitution on quinhydrone formation

Complex	Position of methyl group		Composition ratio
	Quinone	Hydroquinone	
(1).(2)	0	0	1:1
(3).(2)	2	0	1:2
(1).(4)	0	2	1:1
(3).(4)	2	2	1:1
(7).(2)	2,3	0	1:1
(1).(8)	0	2,3	1:1
(7).(8)	2,3	2,3	1:1
(9).(2)	2,5	0	1:2
(1).(10)	0	2,5	1:1
(9).(10)	2,5	2,5	1:1
(9).(10)	2,5	2,5	2:1
(5).(2)	2,6	0	2:1
(1).(6)	0	2,6	1:1
(5).(6)	2,6	2,6	1:1
(11).(2)	2,3,5	0	1:2
(1).(12)	0	2,3,5	1:1
(11).(12)	2,3,5	2,3,5	1:1
(13).(2)	2,3,5,6	0	1:1
(13).(2)	2,3,5,6	0	1:2
(1).(14)	0	2,3,5,6	2:1
(13).(14)	2,3,5,6	2,3,5,6	1:1

reaction in the solid state are exactly similar to that obtained from solution using standard methods of crystallization. These solid state reactions are in many ways similar to certain gas–solid reactions which have been studied at the surface of a crystal. In both cases the structure is disrupted on the surface as the product is formed and then diffusion takes place through the disrupted regions. A preliminary examination of the reaction of single crystals of the α-form of hydroquinone showed a rapid and rather uniform surface attack by the vapours of 1,4-benzoquinone. When the quinone was removed the colour of the complex disappeared in a few minutes leaving a somewhat fritted surface. There was no evidence of anisotropic attack. However, with the large number of molecular orientations in the structure (54 molecules per unit cell), this is not surprising.

13.5. *Diffusionless reactions in organic solids*

Most of the reactions in solids are diffusion controlled and have been discussed in the previous sections. Chemical reactions are generally sluggish in solids.[206] It often comes as a surprise to discover that crystals of certain organic molecules can be induced to react rapidly, and in a pre-ordered fashion even at cryogenic extremes. The secret is to design these organic molecular crystals

to 'engineer' them in such a way as to pack together in potential reactive monomer units which entail no diffusion, but merely minor reorganization—a slight rotation or a subtle shift of a part or all of the reactant molecules. Such reactions fall in the category of diffusionless reactions named by Thomas.[207] A practical consequence of diffusionless organic solid state reactions is their potentialities in preparing materials which are anisotropic in their optical, mechanical and electrical properties.

One can identify several distinct types of diffusionless reactions in organic solid state chemistry. There are three main categories:

(i) Thermally induced processes which, in turn, may involve conformational changes that take place continuously or discontinuously.

(ii) Stress-induced processes where a distinct crystallographic change takes place.

(iii) Photochemically induced processes where UV or ionizing radiations may set off dimerizations or polymerizations and oxidations.

A series of polymerization, dimerization, hydrogen abstraction and electron transfer reactions in the solid state occur at very low temperatures[208–210] and can be considered as diffusionless reactions in solids. Detailed studies are still needed to explore the mechanisms of such reactions.

14. FACTORS AFFECTING REACTIVITY IN THE SOLID STATE

14.1. *Effect of molecular size and geometry*

Rastogi and Singh[184] have shown that the shape and the size of the molecules affect the reactivity in the solid state. Planar and less bulky molecules diffuse at a faster rate.

14.2. *Effect of particle size*

The rate of chemical process occurring in the solid state is often controlled by the surface area of the reactants.[211] The reactions are frequently initiated at surfaces which are the regions of contact between the reactants. This may be the reason for the dependence of solid state reaction rate on the particle size of the reactants.

14.3. *Effect of impurity*

It has been observed by various workers[212] that impurities markedly influence the rate and sometimes the activation energy of solid-phase reactions of the type

$$\text{Solid I} + \text{Solid II (impurity)} = \text{Solid III}.$$

Impurities can affect the solid state kinetics in two ways: firstly, the impurities may affect the defect structures of the reactants and may change the rate of reaction. Secondly, the reaction rate would become very fast when the liquid appears due to lowering of the eutectic point. However, if the eutectic point is not lowered below the reaction temperature, no significant change in kinetics is expected, provided the impurities do not affect the diffusion coefficient.[185]

14.4. *Effect of imperfection*

Lattice vacancies play an important role in solid state reactions. The presence of dislocations in solids develops highly energetic regions and hence of higher total free energy than the equilibrium solid lattice. Such a region would clearly be a favourable site for the formation of a new phase. The strain energy compensating for the creation of surface energy at the interface opposes nucleation. Thus, the dislocations are generally the centres for nucleation. However, more experimental information is needed to confirm this proposition. Organic solid state photochemical reactions are also controlled by defects.[213] The defect sites may function as energy traps during excitation. If the rate of excitation energy transfer in a crystal is faster than that of a reaction, the energy is transferred to the defect sites.[2] As a result, the molecules with abnormal orientation or separation distances get

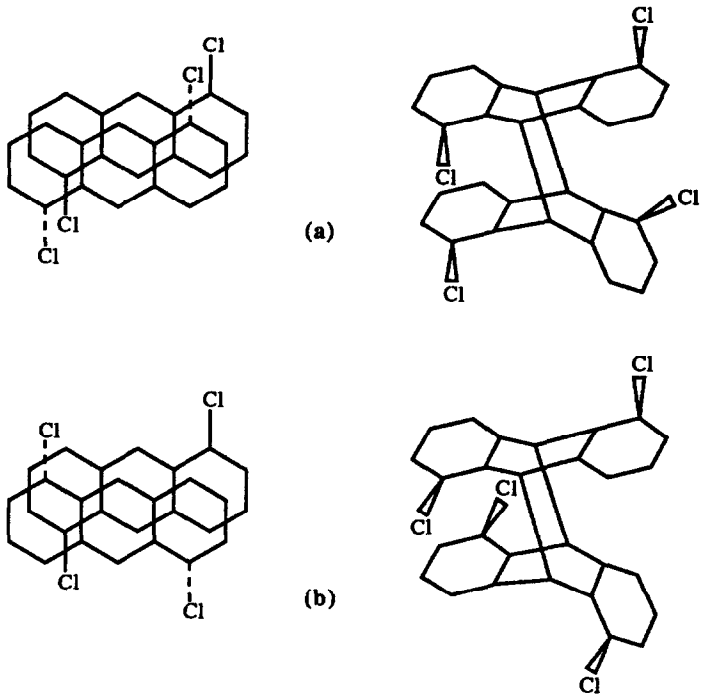


Fig. 10. Photodimerization of 1,5-dichloroanthracene: (a) head-to-head and (b) head-to-tail dimerization.[215]

photoactivated, leading to unexpected products. This means that dislocations can function as favoured reaction sites. Since the number of molecules at these sites is small, the reaction must be accompanied by defect multiplication to yield products in appreciable amount. They are autocatalytic in nature, i.e. as the reaction proceeds, the quantum yield increases.[3] Unusual photoreactivity of 4-methyl-7-methoxycoumarin has been observed at defect sites.[4]

There are several well documented cases known where photoreaction in the solid state involves crystalline imperfections. Examples where photodimerization has been shown to take place preferentially at dislocations and at stacking faults are acenaphthylene and 1,8-dichloro-9-methylanthracene.[214] In the triclinic phase of 1,5-dichloroanthracene it has been shown[215] that an orientational point defect can account for the unexpected course of photoreaction in the solid state which is 20% of the head-to-tail dimer and 80% of the head-to-head dimer rather than 100% of the head-to-head dimer if the reaction were to take place slowly in the perfect regions of the crystal (Fig. 10). Apparently a 'flipped' molecule (Fig. 11), which results from a rotation through 180° about an axis parallel to either the long or short molecular axis, is accommodated as a point defect in the parent monomer crystal.

Since most of the solid state reactions have been studied in polycrystalline materials, grain boundaries play an important role. The dislocation models of grain boundaries and sub-boundaries imply the existence of paths of more rapid diffusion than the volume migration. If boundary migration is of importance, then the reaction rate will depend on the particle size.

14.5. *Effect of radiation*

The effect of radiation on the reactivity of solids has been studied by many workers. Higher energy radiations introduce defects in the solid and these defects may influence various manifestations of solids. Bromination of various *trans*-cinnamic acids has been studied by Hadjoudis

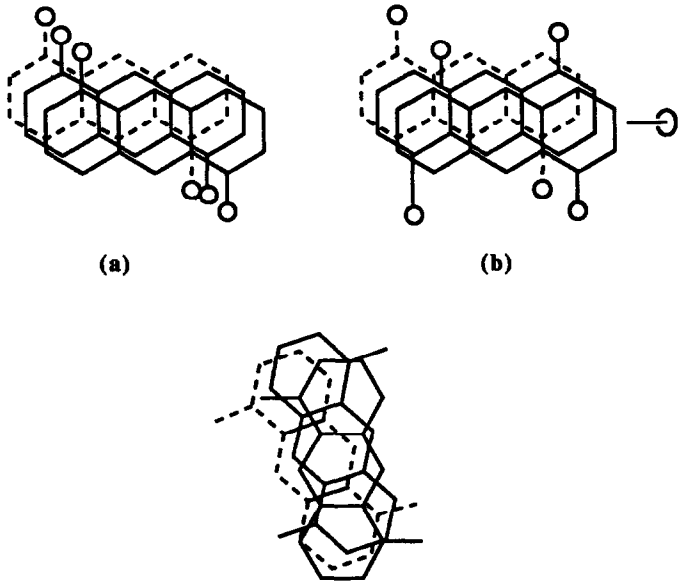


Fig. 11. There is no conformational change brought about by in-plane rotation parallel to the stack axis (a), a flipped molecule (present as an orientational defect), (b), give rise to the incipient head-to-tail registry in the dimers. The final location of the molecule that constitutes the point defect is represented by the dotted figure (c).

and his group[216] in the dark as well as in light. It has been observed that light slows down the rate of reaction of gaseous bromine with solid organic compounds.

14.6. *Effect of molecular packing*

A major point of interest in solid state organic chemistry is on the utilization of the crystalline state to lock molecules into proper orientations favouring a desired reaction. Examples have included conformational locking of substrate molecules to favour a stereospecific elimination produced by a gaseous reagent. A second approach involves the juxtaposition of two or more reactant molecules with reactive positions correctly aligned for the intermolecular reaction desired. The latter category includes photochemical (2+2) cycloadditions and nucleophilic displacement reactions. It is now realized that thermal and photochemical reactions taking place within the bulk or at the surfaces of organic molecular solids may result in high yields of stereoselective products which are not usually, or cannot be, generated by the analogous reaction in solution.

In the reaction of ammonia with acenaphthylene-1-carboxylic acid,[217] it is found that there is preferred attack at the (001) and (100) faces and reaction is extremely slow at the (001) face of the acid. Further, dislocation etch-pit studies demonstrate the facile occurrence of many slip systems. These results have been interpreted in terms of the nature of the packing of molecules in the ideal structure and the creation of fresh sites of attack as a result of the occurrence of particular structural imperfections.

14.7. *Effect of polymorphism*

Polymorphic changes in reacting solids usually cause a considerable increase in the rate of reaction, since polymorphic changes require a loosening and rearrangement of lattice units. It is to be expected that lattice mobility will be high at and near the transition temperature.

15. CONCLUSION

Organic solid state reactivity has been studied extensively during the last few years and has been correlated with molecular structure and crystal packing. It is possible to engineer a molecule so that a desired reaction product can be obtained. However, theories of crystal engineering are not fully understood. Amongst different types of solid state reactions, solid–solid reactions are more complicated and less extensively studied. The major advantage of this class of reaction is that the choice of reactants is practically unlimited and hence a variety of reaction products could be obtained. Fractal type kinetics should also be studied in the solid state.

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