PHARMACEUTICAL SCIENCES

TOPOCHEMICAL PHOTO REACTIONS IN DRUG PRODUCTS AND DRUG PREPARATIONS

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Summary

Under the action of light, drug products may be transformed into different products according to whether they are in solution or in a crystalline form. In topochemical reactions the product is dependent upon the conformation immobilized in the crystall lattice, as well as, occasionally, on the surrounding atmosphere. In order to exclude any solvent effects, the light stability testing of solid drug preparations or crystalline drug substances has to be carried out on solid samples. Suitable testing methods will be considered.

INTRODUCTION

Every pharmacist is familiar with the fact that many crystalline drug products and solid drug preparations undergo topochemical reactions under the influence of light.

These reactions may result in a decrease in activity and an increase in toxicity. In many cases these rearrangement processes are manifested by development of a colour (santonin, amidopyrine, sulphonamides—Reisch and Niemeyer, 1972), a deepening of the colour (chloramphenicol —Reisch and Weidmann, 1971), bleaching or a change in crystalline structure (methadone—Reisch and Schildgen, 1972). The widespread view that drugs are more stable against light while in a crystalline form than when in liquid or dissolved state is true in as much as that, in case of crystals and solid drug formulations (e.g., tablets), always only a small surface with respect to volume is exposed to light and therefore higher photostability is apparently obtained.

TOPOCHEMICAL PHOTOREACTIONS

Exposure of a substance to light would lead to different products being formed dependent upon whether the substance is in gaseous, amorphous, crystalline or dissolved state (Reisch and Schildgen, 1972; Schmidt *et al.*, 1976. Scheffer and Dzakpasu, 1978). In the latter case, the most numerous photoproducts are formed due to the reaction of excited molecules with the solvent. In many decomposition reactions involving radicals the solvent influences, additionally, the composition of products by means of so called "cage effect" (of e.g., Reisch and Kobberling, 1974). The reactions of solid substances differ from those of the same species in mobile phases mainly by the fact that, in the latter states neither specific comformation exists nor do the molecules undergo any rapid conformational isomerisation processes, whereas in the solid aggregate state both diffusion and rotation are hindered and the molecule is held firmly in a defined conformational arrangement. Consequently, the reactions in the solid state proceed with a minimum atomic or molecular motion. Photoproducts deviating from those of the mobile phases may be especially expected under circumstances when the orientation of the molecular packing in the crystal would promote a reaction between the neighbouring molecules or their parts.

The significance of crystal geometry as a controlling factor in topochemistry of a species will be made evident by the following facts—viz:

(*i*) chemically closely related molecules frequently do not react in the crystalline state in an analogous way;

(*ii*) topochemical photoreactions of polymorphous modifications lead to different products; and

(*iii*) the spatial orientation of crystalline reaction products is very often impressed by the crystalline structure of the starting materials, especially when certain elements of structure are retained*.

Since X-ray cristollographic structural analysis gives a real and faithful three-dimensional image of a crystalline molecule, there is a "symbiotic relationship" between topochemistry and X-ray crystallography.

Almost all the photoreactions in the solid state as described till now deal with lattice-controlled [2+2] and [4+4] photodimerisations (photocycloaddition reactions). Most recently, the reactions have been reported which consist in intermolecular or intramolecular hydrogen-abstraction by an excited carbonyl group (Scheffer and Dzakppasu, 1978; Reisch and Abdel-Khalek), a reaction type which is prevalent in photoprocesses involving mobile molecules.

BIMOLECULAR (2+2) PHOTOADDITION OF CINNAMIC ACID

A prerequisite for a bi(inter-) molecular (2+2) photoaddition is a parallel arrangement of the reacting double bonds in the neighbouring molecules so that the bonding centres come closer than 0.41 nm to one another. In addition to this -C = C- distance, the spatial location of the molecules will determine the result of cycloaddition. It may

°Topochemistry (("site—dependent" chemistry) · the name derived from Greek 05 (topos = site) is the designation for all the chemical processes taking place in a solid starting material, and influenced by its spatial arrangement (e.g., crystalline structure). In topechemical reactions (e.g., photochemistry in crystalline phase) the properties of products are basically determined by a spatially defined chain of transformations.

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*This reaction type is referred to as a topotactical reaction.

be illustrated by taking, as an example, the thoroughly studied topochemical dimerisation of trans-cinnamic acid (Cohen and Schmidt, 1964).

Trans-cinnamic acid is trimorphous. Owing to a different orientation of molecules in the lattice of the modifications, two photoproducts are formed (Fig. 1) (Schmidt, 1967; Cohen *et al.,* 1964). For the stabile modification (d), the distance between the double bond of the neighbouring molecules equals 0.36—0.41 nm (Fig. 2); they are placed in a head-to-tail arrangement. The exposure to light of this modification gives the expected α—truxillic acid (1).

The structure of photoproducts from metastable (β) form were, in the first instance, controversial; first of all β—truxillic acid (II) should have been formed, but according to some other authors, a mixture of I and II was formed. In the crystalline lattice of the β-form, the intermolecular distance is nearly the same as that of the α-form (o.39-0.41 nm) but the molecules are in a head to head arrangement. Consequently, only β-truxillic acid should be formed.

This problem makes it clear that, in case of reactions involving solids in metastable crystalline forms, possible errors may be easily committed. In some experiments involving β -cinnamic acid, a thermal rearrangement into the (stable) α-form occured to a certain extent and this resulted in the dimerisation to α-truxillic acid. If the exposure to light is carried out at a temperature below 20°C (within this range no noteworthy $\beta \rightarrow \alpha$ conversion takes place) the β- form would give β- truxillic acid exclusively.

The third modification, γ-cinnamic acid, is photostable because the intermolecular distance between the double bonds is too great (0.47—0.51 nm) for a cyclobutane ring to form.

Contrary to earlier suppositions (Bernstein and Quimbi, 1943), cis-cinnamic acid is not able to form a four-membered ring adduct directly but it must first undergo isomerisation to trans-cinnamic acid (Bergmann *et al,* 1964; Schoñberg, 1968). Not until recrystallisation of the trans-form into one of its polymorphous modifications has been effected, may the characteristic photoreactions depicted in Fig. 1 set in.

In a molecularly dispersed phase cinnamic acid is liable, like other mono-olefins, to cis-trans isomerisation. In most cis-trans isomer pairs their trans configuration is thermodynamically more stable (Meyer, 1975).

The photodimerisation of cinnamic acid is of a certain technical importance. Using this way, for example, esters of α-truxillic acid were obtained that have proved to be effective muscle relaxants, (.e.g., III-V, Fig. 3). The light-induced cycloaddition of polymeric cinnamic acid esters (e.g. from cinnamic acid polyvinyl ester) has been utilized for photocopying paint.

Also, from pharmaceutical-biological view-point, the topochemical photodimerisation of cinnamic acid and its derivatives are noteworthy with regard to the association of truxillic and/or truxinic acid esters, as well as cinnamic acid esters, with the alkaloids accompanying cocaine; the problem that arises is whether or not the above mentioned esters—provided any fermentation process is left out of consideration—are formed in connection with cinnamoyl cocaine under the influence of light.

PHOTOSTABILITY TESTING OF DRUGS IN SOLID STATE

In order to determine whether or not photochemical processes occur in solid drug substances or drug preparations, one must examine the solid, preferentially well defined, crystalline samples. On the basis of the afore-said relationship, the studies on dissolved samples are rather of little evidential value.

For the stability testing, the sample must be exposed to the most appropriate kind of light whose spectral composition corresponds closest to that of storage conditions or that which is expected to produce degradation. In warm climatic zones sun light is the most suitable source because more consecutive sunny days, necessary for irradiation, are available and a great number of samples can be investigated simultaneously. According to our own practical experience, the colour manifestations can be followed up and determined simply and quickly with the aid of a "colour guide" (Schwanenberger, 1965).

More expensive is the procedure proposed recently by Matsuda *et al.,* 1978) for recording colour changes induced by light on the surface of tablets or crystalline films (Fig 4). As a light source, a 400 W Hg—lamp is employed. The cooling of the sample is effected by a blower. On completion of the experiment the change in colour can be quantitatively evaluated either by reflection spectroscopy (for tablets) or by a specially developed method in which the colour of crystalline sample is measured by means of absorption spectroscopy in gaseous phase (for crystalline films).

A simple method for the investigation of photostability of solid pharmaceuticals was described earlier (Reisch and Schildgen, 1972). This involves adsorption of the examined sample on a TLC plate, followed by exposure to light and finally developing the chromatogram (Fig. 5). Although the method presents some advantages due to its apparatus and time requirements, its very simple procedure and practical conditions, as well as the possibility of making comparisons with dissolved samples in the course of operation, it conceals, at the first sight, several sources of errors. First of all, the crystalline form of the irradiated sample is not defined, secondly, due to the taking up of moisture by the adsorbent (thin layer), participation of water in the photoreaction to follow cannot be ruled out; finally, the composition of the adsorbant layers might also influence the course of the reactions. However, numerous experiments have shown that these objections are largely not well-founded*. Comparative tests performed on crystalline powders and on adsorbed samples have led to the same results (cf. also Reisch and Schildgen, 1972).

For scientific purposes, a solid state reactor has been developed only recently (Schmidt and Dzakpasu, 1978) as shown in Fig. 6. The inner vessel consists of a brass

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double-wall cylindrical container on whose gold-plated reaction surface area the samples are placed. The vessel has a pyrex window through which the crystals are irradiated from outside. The system is hermetically sealed and can be evacuated. The rest of the apparatus consists of an ultracryostat which cools down a refrigerent circulating in the inner vessel, thermo-couple indicator, a 450 W mercury-lamp, and a filter (for $\lambda \leq 340$ nm and for $\lambda < 355$ nm, that is located between the radiation source and the pyrex window of the reactor.

The experiments carried out at the Cairo University (1976) and the University of Ife, Nigeria (1977) during the "Pharmaceutical Photochemistry" workshop.

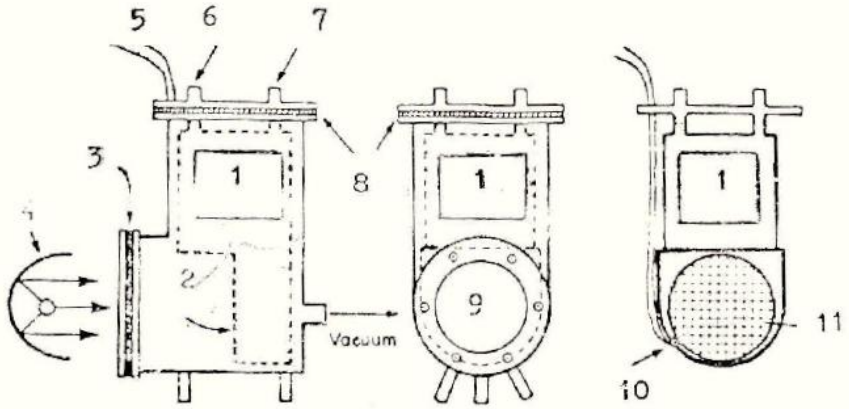

Fig. 6: Apparatus for the irradiation of solid substances (acc. to Scheffer and Dzakpasu, 1978).

1. Inner vessel; 2. Reaction surface area; 3. Ring gasket; 4. Reflector; 5. Thermo-couple leads; 6. Cooling inlet; 7. Cooling outlet; 8. Top ring seal; 9. Pyrex window; 10. Thermo-couple connexion; 11. Gold-plated reaction surface area.

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