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Rapid Communication

Kinetic treatment of photochemical reactions

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In a number of recent papers, the photochemical degradation of a drug substance has been described, and the rate of photodegradation has been quantified in terms of a rate constant, generally of the first order, but in some cases a zero-order rate dependence has been reported at the higher concentration range. Among the many recent examples which can be listed are studies on midazolam (Andersin and Tammilehto, 1989), furosemide (Bundgaard et al., 1988), ketrolac tromethamine (Gu et al., 1988), fluorochloridone (Chang et al., 1988) and nifedipine (Tucker et al., 1985; Majeed et al., 1987).

The main considerations involved in drug photodegradation studies are (i) whether the drug is stable in a particular formulation and container, (ii) whether different light sources of different wavelength ranges produce differing effects, (iii) the nature of the photodegradation products, and (iv) whether factors such as oxygen, metal ions, pH and impurities affect the rate of the degradation. In experiments of the last category, rate constants are frequently used to express the effect of a particular agent. It is the purpose of this communication to point out that some caution must be exercised in the interpretation of rate constants derived from the study of photochemical reactions. Given the importance that must be placed on the possibility of impurity production by photochemical degradation, it is suggested that a standardised manner of reporting the kinetic treatment of photochemical reactions is required, so that experimental data may be reproduced in different laboratories.

For a thermal reaction, e.g., hydrolysis, the rate constant determined in one laboratory may be readily reproduced in another without any significant consideration of the nature of the reaction vessel in which the reaction is performed. On the other hand, the rate of a photochemical reaction is critically dependent on the wavelength and intensity of the irradiating source as well as the shape and position of the reaction vessel in relation to the light source. In other words, the number of quanta of the relevant wavelength region being absorbed per unit time is one of the two factors which determines the rate at which a photochemical reaction occurs. This factor, which can be designated as n, varies from one experimental apparatus to another, and depends as well on the concentration and specific absorptivity at the relevant wavelength(s) of the absorbing substance.

The other factor is akin to the specific rate constant, being the photochemical efficiency or quantum yield of the reaction (ϕ), and defined by:

$$\phi = \frac{\text{Number of molecules transformed per s}}{\text{Number of quanta absorbed per s}}$$

Thus, the rate of a photochemical reaction is given by:

$$\begin{aligned}\text{Rate} &= \text{Number of molecules transformed per s} \\ &= \phi n\end{aligned}$$

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Although it is possible to know the concentration and absorptivity of the compound, there is no standard for the apparatus and light source to be used for photochemical reaction studies. Therefore, it is important that quantitative expressions of photochemical rate be given in terms of the quantum yield. A quantum yield usually refers to one or another of a set of mutually exclusive primary events such as fluorescence emission or chemical reaction, and the set of all possible events should total unity. An exception is the case of a photochemically initiated chain reaction when an apparent value well in excess of unity may be recorded. It should be clear that quantum yields are normally wavelength-dependent; they are not very meaningful unless reported for at least a fairly narrow wavelength range.

Menderhall (1984) and Connors et al. (1986) have explained the meaning of the quantum yield, and have given a kinetic interpretation of photochemical reactions, with the conclusion that the rate of photodegradation of a drug, or the rate of product formation, follows approximate first-order kinetics for dilute solutions, but approaches pseudo-zero-order kinetics in more concentrated solution. The reason for the change in reaction order was stated by Connors et al. (1986) as "the reaction becomes limited by the number of incident quanta of energy and, in concentrated solution, quenching of excited molecules becomes more efficient."

The use of rate constants is useful for comparative purposes when studying a number of different reaction mixtures under the same irradiation conditions. However, the reaction order and numerical values of the rate constants are all relative to those conditions, and that qualification should be stated.

The photochemical reaction is limited, and the apparent order determined, by the number of quanta absorbed by the substance. The authoritative treatment of kinetics studies in photochemical reactions is given by Calvert and Pitts (1966) who state that the measured total or average rates of reaction are not always truly representative of the individual local rates to which the usual theories apply, unless the absorption of light is entirely uniform over the reaction volume. This condition can be approached only for solutions having very low absorbance at the irradiating wavelength(s).

The value for the number of quanta absorbed is given by:

$$n = I_0 - I_t = I_0(1 - 10^{-A})$$

where I_0 and I_t are the incident and transmitted light intensities, respectively, and A is the absorbance of the substance at the wavelength of irradiation. This expression can be expanded as a power series:

$$n = 2.303 I_0 (A + A^2/2 + A^3/6 + \ldots)$$

When the absorbance is low, the expression simplifies to the first term, and given the Beer's Law relation between absorbance and concentration, n can be seen to be directly proportional to concentration:

$$n = 2.303 I_0 A = 2.303 I_0 \epsilon\ b\ C$$

where ϵ is the molar absorptivity and C the molar concentration of the absorbing species, and b is the optical path length of the reaction vessel.

Thus,

$$\text{Rate} = 2.303 I_0 \epsilon b \phi C = kC$$

whereby first order kinetics apply, although the rate constant k depends critically on the particular experimental arrangement, as well as the reaction taking place.

The non-linearity effect at high concentration occurs as the second and higher order terms become significant, in exactly the same manner as non-linearity occurs in fluorescence, for which the same relationship applies (Udenfriend, 1962; Guilbault, 1973).

When the rate of the photochemical reaction is observed as a function of concentration of the drug substance the data is often presented as a semi-logarithmic plot of the residual drug concentration (expressed as a percentage of the original) vs time. Such treatment produces a family of straight lines whose 'apparent rate constant' varies in inverse proportion to the drug concentration.

This will always be the case if the source of irradiation remains constant and the same amount of substance is therefore transformed in a given time.

The determination of photochemical quantum yield should be used to report photoreaction rates in an absolute sense. The most convenient method relies on calibration of the experimental arrangement with the ferrioxalate chemical actinometer system of known quantum yield. The procedure has been adequately described (see, for example, Calvert and Pitts, 1966; Moore, 1987). Alternatively, a comparison could be made through the photodegradation of a drug of known quantum yield, studied in the same experimental arrangement. A convenient example of a readily available drug is naproxen, for which the quantum yield of photodegradation in aerated aqueous solution is 0.012 (Moore and Chappuis, 1988).

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