Φ-Order kinetics of photoreversible–drug reactions

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Background: Drug photodegradation data are usually treated by zero–, first– or second–order kinetic equations. Such treatments would lack reliability since the aforementioned equations have been originally developed for pure thermal reactions. In this respect, it has recently been shown that unimolecular photodegradations obey Φ–order kinetics (Maafi and Maafi, 2013). However, no similar information is, thus far, available for other reactions including photoreversible AB(2Φ) systems. This paper aims at filling this gap for AB(2Φ) kinetics.

Methods: Runge–Kutta numerical integration data for photoreversible reactions traces were combined with a template equation in order to derive an optimized (semi–empirical) integrated rate–law equation for AB(2Φ) reactions. The proposed model equation was test by examining its ability to fit synthetic Runge–Kutta data that have not been used for the optimization. The obtained fitting parameters are then compared to their theoretical counterparts.

Results: Both an integrated rate–law and an analytical equation for the overall reaction rate–constant were set for photoreversible drug reactions. The values of overall reaction rate–constant and initial velocity obtained theoretically correlated well with those obtained by fitting the kinetic traces of reactions with the derived integrated rate–law. AB(2Φ) photodegradation reactions have been proven to obey Φ–order kinetics. The equation proposed describes faithfully their kinetic behaviour in solution. The formula of the overall rate–constant involves both reagents characteristics and experimental parameters. These

equations facilitated the rationalisation and prediction of the individual effects of each reaction parameter. Specially, our results proved a self–photostabilisation with increasing initial drug–concentration and demonstrated the potential for actinometry of drugs obeying AB(2Φ) mechanism.

Key words: drugs photodegradation, kinetics modelling, AB photosystems, actinometry.

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1. Introduction

The ICH recommendations for photostality testing of drugs and formulations (ICH, 1996) do not provide clear specifications or protocols on the treatment and analysis of the kinetic data of drug photodegradations. In the literature, the photokinetic data of the initial drug, usually extracted by a separation method, were treated according to the well–known classical zeroth–, first– or second–order kinetic model equations (Ming, 2012; Piechocki and Thoma, 2010; Tashtoush et al., 2008; Tonnesen, 2004; Albini and Fasani, 1998). These three kinetic options were used irrespective of the photochemical overall mechanism governing the drug and its photoproducts, and despite the fact that the aforementioned equations were originally developed for pure thermal reactions. It is also noticeable that most often the application of this approach meant that only data corresponding to the early stages of the reaction (up to the half-life time) were effectively used for the kinetic treatment (Piechocki and Thoma, 2010). In addition, the determined overall rate–constants of drug photodegradation reaction could neither be compared to those obtained by other studies or lead to the determination of the photochemical quantum yield of the reaction (the overall rate–constant and the quantum yield are generally achieved by separate experiments).

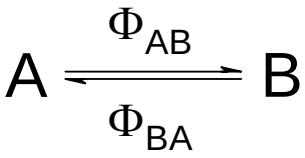
Recently (Maafi and Maafi, 2013; Maafi, 2010; Maafi and Brown, 2007), it has been shown that a drug unimolecular AB(1Φ) photodegradation reaction, where the initial species (A) phototransforms into a product (B) with an efficiency $\Phi_{A\rightarrow B}$, obeys a specific kinetic order, the so-called Φ–*order*, that significantly differs from the mathematical formulation of 0^{th}–, 1^{st}– and 2^{nd}–order equations. The Φ–order kinetic was found to describe well the whole set

of AB(1Φ) photodegradation data and readily allows the determination of the reaction photochemical quantum yield from the reaction overall rate–constant. Nonetheless, the above findings have a limited application as they are specific to unimolecular drug photodegradations of the AB(1Φ) type.

Despite the relative mathematical similarity of the differential equations (DE) of drug photoreactions obeying more elaborate mechanisms than AB(1Φ), there are no known procedures to achieve their solutions, i.e. deriving the corresponding integrated rate–laws of such systems, through a closed–form integration (Maafi and Maafi, 2013; Maafi, 2010; Klan and Wirz, 2009; Mauser and Gauglitz, 1998). In this respect, it has been shown that it is not even possible to solve the DE of AB(1Φ) systems for the case where both (A and B) species absorb the incident light at a non–isosbestic wavelength (Maafi and Maafi, 2013).

In order to circumvent this tedious problem, a new approach (Maafi and Maafi, 2013) was proposed to develop semi–empirical rate–law equations for drug photodegradation DEs that cannot conventionally be solved. It combines the results generated by a numerical method, such as Runge–Kutta (RK) method, to a plausible template equation. The various parameters involved in the rate–law equation would then be optimized and their analytical expressions defined.

In order to explore further the usefulness of the above approach, it is applied in the present study to propose an integrated rate–law equation for drugs that obey a photoreversible AB(2Φ) photodegradation reactions, as given in Scheme 1.



Scheme 1. Generic photodergadation drug–systems obeying an AB(2Φ) mechanism.

A wide range of important drugs and formulations undergo photoreversible reactions. A recent review (Ming, 2012) has listed a number of examples for drugs that degrade through E/Z photoisomerisation. Such drugs have varied therapeutic activities including but not limited to the treatment of depression (Tammilehto and Torniainen, 1989), Alzheimer desease (Azevedo Fihlo et al., 2010), neuroleptic disorders and psychosis (Stehfest et al., 2010; Maquille et al., 2010; Li Wan Po and Irwin, 1980), asthma (Al Omari et al., 2007; Radhakrishna et al., 2003) and infections (Lerner et al., 1988). In most cases, the produced photoisomer is much less or not biologically active compared to its counterpart, the initial drug isomer. Small photoisomerisable molecules have also been employed in neurobiology to target the $GABA_A$ receptor (Feliciano et al., 2010) for potential development of photo-nanomedicine and photodynamic materials. Another fast developing field is the incorporation of photoreversing systems in formulations and delivery systems such as photoresponsive hydogels for biomedical applications (Tomatsu et al., 2011), photoresponsive materials for

drug delivery (Wohl and Engebersen, 2012) and light-triggered release from nanocarriers (Fomina et al., 2012).

Therefore, rationalising the kinetics of such photoreversible reactions is of importance to quantitatively evaluate the reactivity of the systems studied and shed light on their performance. This can best be achieved by the development of adequate integrated rate–laws.

2. Materials and methods

The method used here of deriving integrated rate–law equation for photodegradation drug systems whose differential equations cannot be integrated in a closed–form, has been recently developed in our team (Maafi and Maafi, 2013), and is applied here for AB(2Φ) photodegradation reactions. It is based on the principle of using synthetically calculated data (representing the temporal variation of the species' concentrations or any other measurable variable such as absorbance), as model datasets to test, optimise and validate the proposed formula of the integrated rate–law and overall rate–constant. The RK–4 calculation is fed with plausible reaction parameters to produce the kinetic traces. The reliability of RK–4 in solving differential equation makes it a powerful tool to deliver photodegradation reaction traces with high accuracy. The theoretical numerical integration used in this study has been constructed on the basis of the fourth–order Runge–Kutta (RK–4) method (results obtained from a homemade programme).

Around 50 traces were fitted with the proposed template formula for the integrated rate–law in order to optimise the analytical expressions of the exponential and the pre-logarithmic factors (*vide infra* Eqs. 2 and 3). This procedure is also meant to provide good indications on the limits of applicability of the proposed integrated rate–law equation. Once the complete formula has been derived, it has been tested against *c.a.* 100 more RK–4 traces for validation and for application purposes.

The validation of the optimised integrated rate–law formula is achieved by not only recording a good fit of the RK–4 traces by the formula but also by ensuring that the values of reactions' overall rate–constants and initial velocities obtained from the fitting, differ by no more than 10 % of those values calculated using the theoretical equations.

A Levenberg–Marquardt iterative programme within the Origin 6.0 software package were used to run the non–linear fitting and the determination of the best fit curves.

3. Results

3.1. The semi-empirical model for AB(2Φ) kinetics

The differential equation expressing the time variation of the concentrations of species A and B (C_A(t) and C_B(t), respectively, Scheme 1), considering that the solution, subjected to a monochromatic and continuous irradiation, is homogeneously and continuously stirred, the concentration of the excited–state is assumed to be negligible, the medium temperature is constant, and at the (non–isosbestic) irradiation wavelength (λ_{irr}) species A and B absorb different amounts of light (P), i.e., the absorption coefficients (ε) of the species are different and have non-zero values ($\varepsilon_A^{\lambda_{irr}} \neq \varepsilon_B^{\lambda_{irr}} \neq 0$), is (Maafi, 2008; Maafi and Brown, 2008)

$$\frac{dC_A\ (t)}{dt} = -\frac{dC_B\ (t)}{dt} = \left(\Phi_{B\to A}^{\lambda_{irr}} \times \varepsilon_B^{\lambda_{irr}} \times C_B\ (t) - \Phi_{A\to B}^{\lambda_{irr}} \times \varepsilon_A^{\lambda_{irr}} \times C_A\ (t)\right) \times l_{\lambda_{irr}} \times P_{\lambda_{irr}} \times F_{\lambda_{irr}}(t) \quad (1)$$

where $\Phi^{\lambda_{irr}}$ are the forward and reverse quantum yields of the photochemical steps realised at the irradiation wavelength (λ_{irr}), $P_{\lambda_{irr}}$ is the radiant power, $l_{\lambda_{irr}}$ is the optical path length of the irradiation beam inside the sample, and $F_{\lambda_{irr}}$ the photokinetic factor.

Because $F_{\lambda_{irr}}$ is a time dependent function, Eq.1 is not possibly integrated in a closed-form (Maafi and Brown, 2008).

To circumvent this situation, the model equation previously developed for the unimolecular photoreaction AB(1Φ),(Maafi, 2010; Maafi and Brown, 2007) which has been obtained by a closed–form integration, can be used as a template to approach the model equation for AB(2Φ) kinetics. Provided that irradiation (λ_{irr}) and observation (λ_{obs}) wavelengths are clearly set (to define the specific $\lambda_{irr}/\lambda_{obs}$ condition), an expression (Eq.2) can be proposed as an integrated rate–law that describes the time evolution of the observed total absorbance of the medium, $A_{tot}^{\lambda_{irr}/\lambda_{obs}}(t)$, for an AB(2Φ) system.

$$A_{tot}^{\lambda_{irr}/\lambda_{obs}}(t) = A_{tot}^{\lambda_{irr}/\lambda_{obs}}(pss) + \frac{A_{tot}^{\lambda_{irr}/\lambda_{obs}}(0) - A_{tot}^{\lambda_{irr}/\lambda_{obs}}(pss)}{A_{tot}^{\lambda_{irr}/\lambda_{irr}}(0) - A_{tot}^{\lambda_{irr}/\lambda_{irr}}(pss)} \times \frac{l_{\lambda_{obs}}}{l_{\lambda_{irr}}}$$
$$\times Log\left[1 + \left(10^{\left[\left(A_{tot}^{\lambda_{irr}/\lambda_{irr}}(0) - A_{tot}^{\lambda_{irr}/\lambda_{irr}}(pss)\right) \times \frac{l_{\lambda_{irr}}}{l_{\lambda_{obs}}}\right]} - 1\right) \times e^{-k_{A \rightleftharpoons B}^{\lambda_{irr}} \times t}\right] \qquad (2)$$

In this mathematical description, it is assumed that experimental measurements (A_{tot}) of spectroscopic and kinetic data are achieved under the observation ($l_{\lambda_{obs}}$) and not the excitation ($l_{\lambda_{irr}}$) conditions (with $l_{\lambda_{obs}}$ being the optical path length of the monitoring light inside the sample). It is important to notice that these optical path lengths ($l_{\lambda_{irr}}$ and $l_{\lambda_{obs}}$)

may not be equal, and the absorbance of the medium in the excitation conditions (i.e measured along $l_{\lambda_{irr}}$) may not be directly accessible.

The coefficients $A_{tot}^{\lambda_{irr}/\lambda_{obs}}(t)$, $A_{tot}^{\lambda_{irr}/\lambda_{obs}}(0)$, $A_{tot}^{\lambda_{irr}/\lambda_{obs}}(pss)$, $A_{tot}^{\lambda_{irr}/\lambda_{irr}}(0)$ and $A_{tot}^{\lambda_{irr}/\lambda_{irr}}(pss)$ in Eq.2 are the measured total absorbances of the medium (along $l_{\lambda_{obs}}$) respectively recorded at reaction time t, at the initial time (t = 0) and at the photostationary state, *pss* (where t = ∞), when the reaction medium is irradiated at a given irradiation wavelength and simultaneously monitored at either a different observation wavelength ($\lambda_{irr}/\lambda_{obs}$) or at the same wavelength ($\lambda_{irr}/\lambda_{irr}$). It is assumed that the reaction is quantitative and proceeds without by-products.

Eq.2 takes into account the presence of a *pss* by the introduction of the coefficient $A_{tot}(pss)$ in the formula previously set for AB(1Φ) systems (Maafi and Maafi, 2013).

The analytical expression of the exponential factor, $k_{A\leftrightharpoons B}^{\lambda_{irr}}$ in Eq.2, which represents the overall reaction rate–constant, is given by

$$k_{A\leftrightharpoons B}^{\lambda_{irr}} = \left(\Phi_{A\to B}^{\lambda_{irr}} \times \varepsilon_A^{\lambda_{irr}} + \Phi_{B\to A}^{\lambda_{irr}} \times \varepsilon_B^{\lambda_{irr}}\right) \times l_{\lambda_{irr}} \times P_{\lambda_{irr}} \times F_{\lambda_{irr}}(pss) \qquad (3)$$

This expression of $k_{A\leftrightharpoons B}^{\lambda_{irr}}$ has been worked out from the denominator of the equations of the species concentrations at *pss* (where it is assumed that $(dC/dt)_{PSS} = 0$). This template flows from an analogy with the case of an AB(2Φ) system considered under an isosbestic irradiation (at λ_{isos}) (Maafi and Brown, 2008; 2005a).

It is worth noting that the parameters involved in the formula of the overall rate-constant correspond exclusively to the excitation conditions. This includes the photokinetic factor, $F_{\lambda_{irr}}(pss)$, measured at *pss* (i.e. the observed total *pss* absorbance at $\lambda_{irr}/\lambda_{irr}$ used in Eq.4 has been multiplied by the ratio of the optical path lengths in order to convert it to the total absorbance corresponding to the irradiation conditions, i.e. a measurement along the optical path length λ_{irr}).

$$F_{\lambda_{irr}}(pss) = \frac{1 - 10^{-\left(A_{tot}^{\lambda_{irr}/\lambda_{irr}}(pss) \times \frac{l_{\lambda_{irr}}}{l_{\lambda_{obs}}}\right)}}{A_{tot}^{\lambda_{irr}/\lambda_{irr}}(pss) \times \frac{l_{\lambda_{irr}}}{l_{\lambda_{obs}}}} \qquad (4)$$

3.2. Optimization of the parameters and validation of the semi–empirical model

The validation of the semi–empirical model (Eq.2) is achieved by checking the model's performance against independently–generated RK–4 synthetic datasets for AB(2Φ) kinetics.

This step is mandatory since the efficiency of the new model can objectively be evaluated if the proposed integrated rate–law (Eq.2) is not only successful in fitting the RK–4 – simulated kinetic traces but also able to deliver the values of the model's parameter ($k_{A \leftrightharpoons B}^{\lambda_{irr}}$) for a large number of simulated reactions involving a range of system and experimental specifications.

Selected sets of such specifications involved different values of (i) the absorption coefficients for the reactive species (i.e., $\varepsilon_A > \varepsilon_B$ and $\varepsilon_A < \varepsilon_B$), (ii) the reaction quantum yields including cases where $\Phi_{A \to B}^{\lambda_{irr}} = \Phi_{B \to A}^{\lambda_{irr}}$, (iii) the optical path lengths for irradiation and observation, and (iv) radiant power (Table 1). Examples of calculated plots are shown in Figure 1.

Table 1 : Examples of reaction parameters used to feed RK–4 calculation of traces.

Attributes Sample #	C_0 [a] / M	$l_{\lambda_{irr}}$ [b] / cm	$\varepsilon_A^{\lambda_{irr}}$ / M^{-1} cm^{-1}	$\varepsilon_B^{\lambda_{irr}}$ / M^{-1} cm^{-1}	$\Phi_{A\to B}^{\lambda_{irr}}$	$\Phi_{B\to A}^{\lambda_{irr}}$	$P_{\lambda_{irr}}$ / einstein s^{-1} dm^{-3}
1	2.0×10^{-5}	2	6748	32159	0.50	0.20	1.0×10^{-6}
2	2.0×10^{-5}	1	8587	30269	0.85	0.17	9.3×10^{-7}
3	2.0×10^{-5}	1	8587	30269	0.17	0.17	3.4×10^{-6}
4	7.5×10^{-6}	1	55984	10837	0.60	0.20	1.5×10^{-6}
5	1.0×10^{-5}	1.7	35984	10837	0.70	0.40	2.0×10^{-6}
6	6.0×10^{-5}	1	5231	30273	0.10	0.50	7.0×10^{-6}
7	1.0×10^{-5}	2	22231	71273	0.10	0.30	3.0×10^{-7}

[a]: $C_0 = C_A(0)$ and $C_B(0) = 0$. [b]: $l_{\lambda_{irr}}$ = 1cm.

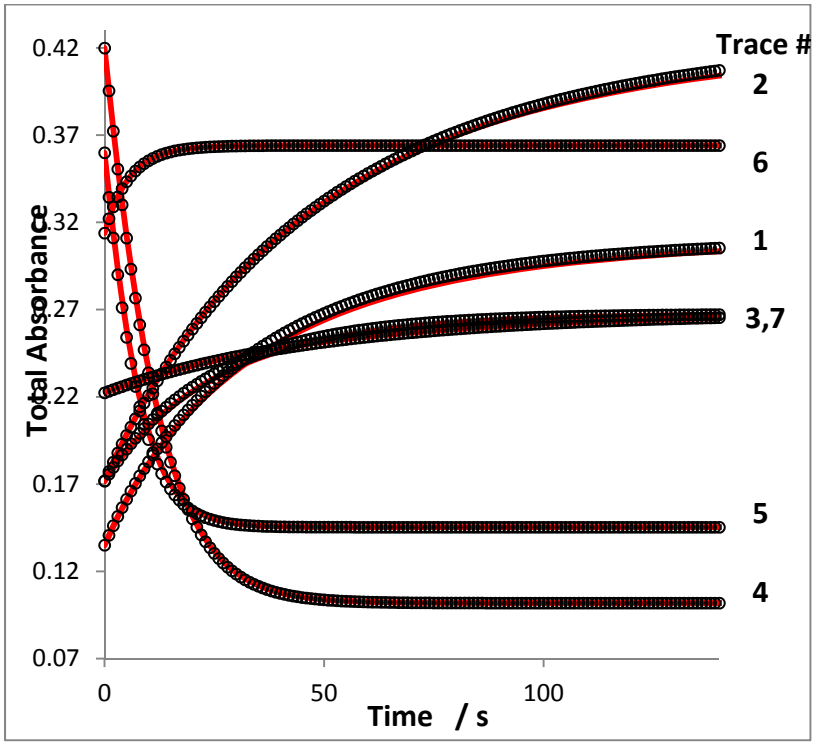


Fig. 1. Examples of the semi–empirical model, Eq.2 (lines), fitting of simulated RK–4 kinetic traces (circles), $A_{tot}^{\lambda_{irr}/\lambda_{irr}}$ *vs.* time, for AB(2Φ) photochemical reactions. The RK–4 calculations are based on the data of Table 1.

For the selected cases (> 150) of this study, the RK–4 data were all readily fitted by the semi–empirical model. The overall reaction rate–constants ($k_{A\leftrightharpoons B}^{\lambda_{irr}}$) values of this set spanned over more than three orders of magnitude ranging between 2×10^{-3} and 1.8 s^{-1}. A good agreement was found between $k_{A\leftrightharpoons B}^{\lambda_{irr}}$ values obtained from the fitting ($k_{A\leftrightharpoons B\ (mod.)}^{\lambda_{irr}}$) and those calculated ($k_{A\leftrightharpoons B\ (cld.)}^{\lambda_{irr}}$) using Eq.3 (Fig.2). It is also worth noting that a similar conclusion has been reached for cases with high radiant power values (up to 10^6 times higher than those used in Table 1).

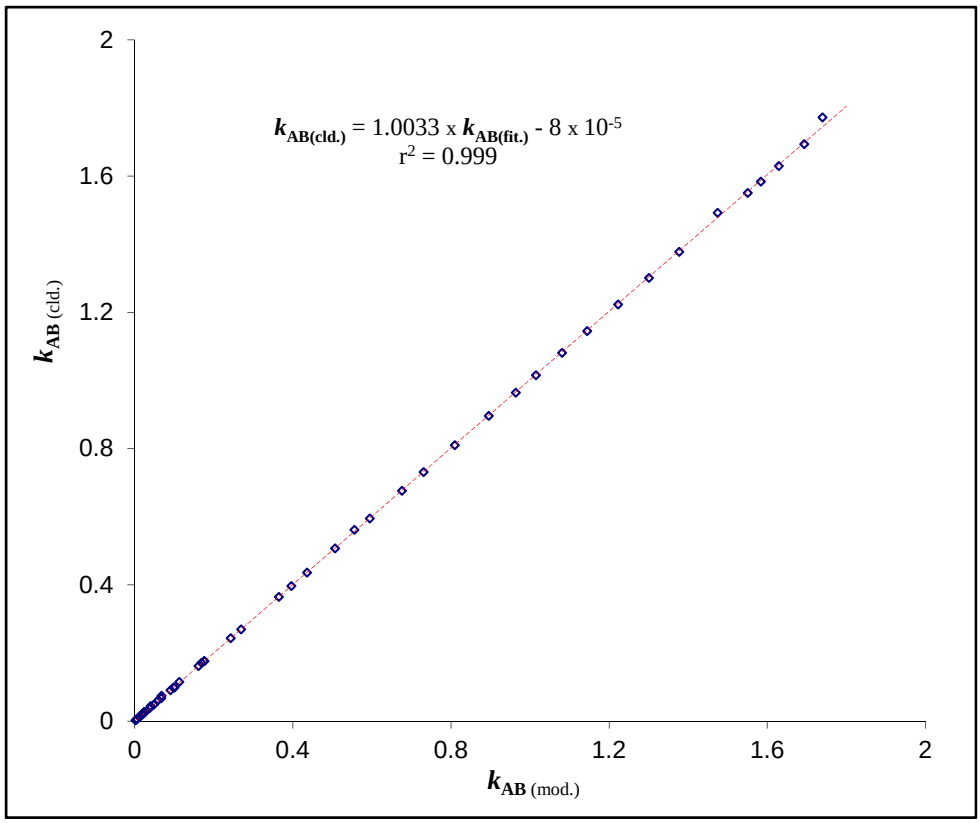


Fig. 2. Correlation between the calculated values of overall rate–constants of the reaction ($k_{A\leftrightharpoons B\ (cld.)}^{\lambda_{irr}}$) against those obtained from the fitting of RK–4 data with Eq.2 ($k_{A\leftrightharpoons B\ (mod.)}^{\lambda_{irr}}$). $k_{A\leftrightharpoons B}^{\lambda_{irr}}$ is expressed in s^{-1}.

Similarly, the initial velocities, $v_0^{\lambda_{irr}/\lambda_{obs}}$, of the photoreactions have also been calculated and compared.

The theoretical initial velocity equation is derived from Eq.1 (written here for the reaction medium absorbances) at t = 0, $(dA_{tot}/dt)_{t=0}$ (Maafi and Brown, 2008; 2005a), as

$$v_{0\ (cld.)}^{\lambda_{irr}/\lambda_{obs}} = \left(\varepsilon_B^{\lambda_{obs}} - \varepsilon_A^{\lambda_{obs}}\right) \times l_{\lambda_{obs}} \times \Phi_{A\rightarrow B}^{\lambda_{irr}} \times \varepsilon_A^{\lambda_{irr}} \times l_{\lambda_{irr}} \times P_{\lambda_{irr}} \times F_{\lambda_{irr}}(0) \times C_0 \qquad (5a)$$

where $F_{\lambda_{irr}}(0)$ is calculated using the initial absorbance, $A_{tot}^{\lambda_{irr}/\lambda_{irr}}(0)$ (i.e. replacing $A_{tot}^{\lambda_{irr}/\lambda_{irr}}(pss)$ in Eq.4). The values of the calculated initial velocity ($v_{0\ (cld.)}^{\lambda_{irr}/\lambda_{obs}}$) are obtained by using Eq.5a and the corresponding values of its parameters (as given in Table 1).

The initial velocity values can also be determined by differentiation of the model equation (Eq.2) at the initial time, $v_{0\ (mod.)}^{\lambda_{irr}/\lambda_{obs}}$, as

$$v_{0\ (mod.)}^{\lambda_{irr}/\lambda_{obs}} = \left(\frac{dA_{tot}^{\lambda_{irr}/\lambda_{obs}}}{dt}\right)_0 =$$

$$\frac{A_{tot}^{\lambda_{irr}/\lambda_{obs}}(0) - A_{tot}^{\lambda_{irr}/\lambda_{obs}}(pss)}{A_{tot}^{\lambda_{irr}/\lambda_{irr}}(0) - A_{tot}^{\lambda_{irr}/\lambda_{irr}}(pss)} \times \frac{k_{A\leftrightharpoons B\ (mod.)}^{\lambda_{irr}}}{\frac{l_{\lambda_{irr}}}{l_{\lambda_{obs}}} \times Ln(10)} \times \left(10^{\left(A_{tot}^{\lambda_{irr}/\lambda_{irr}}(pss) - A_{tot}^{\lambda_{irr}/\lambda_{irr}}(0)\right) \times \frac{l_{\lambda_{irr}}}{l_{\lambda_{obs}}}} - 1\right) \qquad (5b)$$

A good agreement is reached between pairs of $v_0^{\lambda_{irr}/\lambda_{irr}}$ (or $v_0^{\lambda_{irr}/\lambda_{obs}}$) values obtained from Eqs.5 (Fig.3). The straight line encompassing values ranging between 2.2 x 10^{-5} and 3.8 x 10^{-1} s^{-1} is characterized by a correlation coefficient close to unity and a small intercept value. Such range of v_0 is thought to span a wide number of experimental values.

The errors between the two sets of values in Figs. 2 and 3 do not exceed 5 % whenever the value of $F_{\lambda_{irr}}(pss)$ is higher than 1.2. This stands as a condition of reliability for the application of the semi–empirical model (Eq.2).

These findings strongly suggest that the semi–empirical model of the integrated rate–law is suitable to describe the kinetic behaviour of AB(2Φ) photochemical systems. Furthermore, it can provide reliable values for both overall reaction rate–constant and reaction initial velocity. This is achieved even before the reaction attributes (e.g. ε, Φ) have been determined.

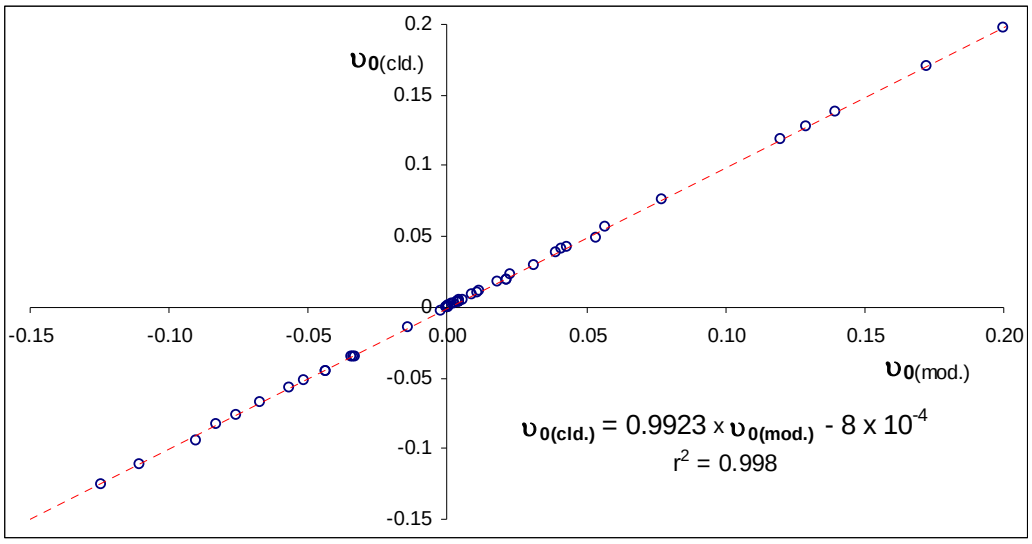


Fig. 3. A plot of initial velocity values obtained theoretically (Eq.5a and Table 1) against those generated by the fitting of the RK–4 trace with the semi-empirical model (Eq.5b). υ_0 are expressed in s^{-1}.

4. Discussion

The determination of integrated rate–law equations capable of faithfully describing photolabile drug reactions including photoreversible systems is an area of research that requires fundamental developments as there is number of drugs and/or technological applications, that obey an AB(2Φ) mechanism, already exist or in development. The common usage of the classical equations, set for 0^{th}–, 1^{st}– and 2^{nd}– order thermal reaction kinetics to treat photodegradation data of drugs, which has been thus far accepted as a *standardized* good approximation, cannot be conceptually justified since both the frequency and intensity of the light employed represent crucial parameters in the occurrence and

kinetic behaviour of the drug's reaction. This is mathematically conveyed by the presence of the time–dependent photokinetic factor that renders the differential equations and their solutions for photochemical reactions fundamentally different from those already established for the pure thermal processes (Maafi and Maafi, 2013; Maafi and Brown, 2007).

The application of thermal reaction kinetics to photodegradation reactions is not reliable as well from a practical viewpoint since most often only the data corresponding to the first section of the kinetic trace (reaching up to the half-life time) can effectively be utilized to define the reaction order (the rest of the data do not usually fit on the line). Caution has been raised about this approach as the data of a given reaction may well be fitted by the equations corresponding to two distinct thermal reaction-orders (Piechocki and Thoma, 2010). In this context, the ICH Q1b recommendations (ICH, 1996) could benefit from a revision regarding issues on kinetic data treatment and the new replacement approach proposed in the present work.

The strategy adopted in a previous study (Maafi and Maafi, 2013), consisting of using RK–4 simulated kinetic traces as background data for the generation of semi–empirical integrated rate–law equations for photochemical systems, as was readily applied to AB(1Φ) systems, has been successfully employed here for the photodegradation of drugs obeying AB(2Φ) reactions. This approach, based on combining synthetic RK data of photoreactions and a convenient mathematical model for their integrated rate–law, may well represent a tool to explore further its potential usefulness and applicability for more extended drug

photodegradation processes whose differential equations cannot be integrated in a closed–form. Attempts in this field are being undertaken in our team.

The proposed semi–empirical model (Eq.2) fitted with high accuracy RK–4 synthetic data (Figs. 2) of AB(2Φ) kinetic systems subjected to continuous, non–isosbestic and monochromatic irradiations. The variety of the selected reaction attributes and experimental conditions (over 100 exemplars, in addition to those used for the development of Eq.2 and the analytical definition of its parameters) was aimed at spanning a large set of plausible situations, has proven the usefulness of Eq.2 in describing the kinetic behaviour of AB(2Φ) photodrugs with good accuracy. The threshold value imposed on $F_{\lambda_{irr}}(\infty)$ (> 1.2) can easily be overcome experimentally by lowering the value of either the initial concentration of the drug or the optical path length of irradiation, $l_{\lambda_{irr}}$ (Maafi and Maafi, 2013).

Nevertheless, no limitations were found in terms of radiant power, absorption coefficients or quantum yield values. As a result, photoreversible drug degradation reactions are proven to obey Φ–order kinetics. Also, it is interesting to underline that the integrated rate–law for Φ–order AB(2Φ) reactions inherently depends on several parameters, namely $k_{AB}^{\lambda_{irr}}, t, \varepsilon_{A\ or\ B}^{\lambda_{irr}}, \Phi_{A\to B\ or\ B\to A}^{\lambda_{irr}}$, and $C_{A\ or\ B}(PSS)$, conversely to the thermally reversible AB(2Δ) reaction rate–law that is exclusively expressed by k_{AB} , t and $C_{A\ or\ B}(PSS)$ (Maafi and Brown, 2005a).

Since the model Eq.2 has been developed using as a template the formula of AB(1Φ) systems, and if one assumes that there is an analogy with thermal reaction kinetics (Maafi and Brown, 2005a), then it should be possible to derive a single general equation to describe the kinetic behaviour of any AB photoreaction performed at any observation/irradiation conditions (Eq.6).

$$A_{tot}^{\lambda_{irr}/\lambda_{obs}}(t) = A_{tot}^{\lambda_{irr}/\lambda_{obs}}(\infty) + \frac{A_A^{\lambda_{irr}/\lambda_{obs}}(0) - A_{tot}^{\lambda_{irr}/\lambda_{obs}}(\infty)}{A_A^{\lambda_{irr}/\lambda_{irr}}(0) - A_{tot}^{\lambda_{irr}/\lambda_{irr}}(\infty)} \times \frac{l_{\lambda_{obs}}}{l_{\lambda_{irr}}}$$
$$\times Log\left[1 + \left(10^{\left[\left(A_A^{\lambda_{irr}/\lambda_{irr}}(0) - A_{tot}^{\lambda_{irr}/\lambda_{irr}}(\infty)\right) \times \frac{l_{\lambda_{irr}}}{l_{\lambda_{obs}}}\right]} - 1\right) \times e^{-k_{A\leftrightharpoons B}^{\lambda_{irr}} \times t}\right] \qquad (6a)$$

with

$$k_{A\leftrightharpoons B}^{\lambda_{irr}} = \left(\Phi_{A\to B}^{\lambda_{irr}} \times \varepsilon_A^{\lambda_{irr}} + \Phi_{B\to A}^{\lambda_{irr}} \times \varepsilon_B^{\lambda_{irr}}\right) \times l_{\lambda_{irr}} \times P_{\lambda_{irr}} \times F_{\lambda_{irr}}(\infty) \qquad (6b)$$

Accordingly, for an AB(2Φ) system where both species (A and B) absorb at λ_{irr}, the quantities $A_{tot}^{\lambda_{irr}/\lambda_{obs}}(\infty)$ and $F_{\lambda_{irr}}(\infty)$ in Eqs.6 will represent respectively $A_{tot}^{\lambda_{irr}/\lambda_{obs}}(pss)$ and $F_{\lambda_{irr}}(\infty)$, which yields Eqs. 2 and 3. For a pure unimolecular AB(1Φ) reaction, where only the initial compound absorbs the irradiation light, $A_{tot}^{\lambda_{irr}/\lambda_{obs}}(\infty) = \Phi_{B\to A}^{\lambda_{irr}} = 0$ and $F_{\lambda_{irr}}(\infty) = 2.3 \cong Ln(10)$, Eqs.6 reduce to the model equations obtained through closed–form integration for this system (Maafi, 2010; Maafi and Brown, 2007). For AB(1Φ) cases

where both A and B absorb at the irradiation wavelength (characterised by $\varepsilon_{A\ or\ B}^{\lambda_{irr}} \neq 0$), then Eqs.6 derive the same equations previously obtained for this situation ($\Phi_{B\rightarrow A}^{\lambda_{irr}} = 0\ and\ F_{\lambda_{irr}}(\infty) = F_{\lambda_{irr}}(C_B\ (\infty))$ which is calculated using $A_{tot}^{\lambda_{irr}/\lambda_{obs}}(\infty) = \varepsilon_B^{\lambda_{irr}} \times l_{\lambda_{irr}} \times C_A\ (0)$) (Maafi and Maafi, 2013). Finally, if A and B individual traces can be observed separately for any photoreversible system, then $A_{tot}^{\lambda_{irr}/\lambda_{obs}}(\infty)$ would correspond to that of the particular observed species in all terms of Eqs.6 except for $F_{\lambda_{irr}}(\infty)$, which should be equal to that recorded for the medium at $\lambda_{irr}(i.e. A_{tot}^{\lambda_{irr}/\lambda_{obs}}(\infty) = A_{tot}^{\lambda_{irr}/\lambda_{irr}}(\infty)$, in Eq.6b).

Incidentally, the equations expressing the variations of either species concentration with reaction time can readily be also worked out from Eqs.6. It flows, from the above discussion, that Eqs.6 stand for the most general equations that are sufficient to fit the kinetic behaviour for AB photosystems as given in or part of Scheme 1.

It is also worthwhile noting that not only the overall reaction rate-constant but also the integrated rate–law (C(t)) equations of Φ–order systems, explicitly depend on the absorption coefficients (ε). This represents a major difference with the known expressions of classical reaction-orders.

In terms of elucidation of the kinetics based on spectral data there are two distinct situations. In the case where either the electronic spectrum of the photoproduct (or at least $\varepsilon_B^{\lambda_{irr}}$ is known) or the composition of the medium at the *pss* (i.e. the ratio, ρ =

$C_A\ (PSS)/C_B\ (PSS)$, of the species *pss* concentrations. With $\rho = 0$ for AB(1Φ) mechanisms) is available, the determination of the absolute values of the forward and reverse quantum yield values, are worked out using Eqs.7.

$$\Phi_{A\to B}^{\lambda_{irr}} = \frac{v_0^{\lambda_{irr}/\lambda_{obs}}}{\left(\varepsilon_B^{\lambda_{obs}} - \varepsilon_A^{\lambda_{obs}}\right)\times\varepsilon_A^{\lambda_{irr}}\times F_0^{\lambda_{irr}}\times P_{\lambda_{irr}}\times l_{\lambda_{irr}}\times l_{\lambda_{obs}}} = \frac{k_{AB}^{\lambda_{irr}}}{\varepsilon_A^{\lambda_{irr}}\times F_{pss}^{\lambda_{irr}}\times P_{\lambda_{irr}}\times l_{\lambda_{irr}}\times(1+\rho)} \qquad (7a)$$

$$\Phi_{B\to A}^{\lambda_{irr}} = \frac{k_{AB}^{\lambda_{irr}}}{\varepsilon_B^{\lambda_{irr}}\times F_{pss}^{\lambda_{irr}}\times P_{\lambda_{irr}}\times l_{\lambda_{irr}}} - \frac{\varepsilon_A^{\lambda_{irr}}\times\Phi_{A\to B}^{\lambda_{irr}}}{\varepsilon_B^{\lambda_{irr}}} = \frac{\varepsilon_A^{\lambda_{irr}}\times\Phi_{AB}^{\lambda_{irr}}\times\rho}{\varepsilon_B^{\lambda_{irr}}} \qquad (7b)$$

However, if only the spectroscopic data relative to reaction kinetics (e.g. UV-Vis traces) obtained when the medium is subjected to non–isosbestic irradiation are available for drugs where the electronic spectra of A and B totally overlap (this is the case for a majority of AB drugs (Piechocki and Thoma, 2010; Piechocki and Thoma, 2010; Tashtoush et al., 2008; Tonnesen, 2004), then the application of Eqs.6 would not be sufficient to determine the values of the unknown parameters ($\Phi_{A\to B}^{\lambda_{irr}}$, $\Phi_{B\to A}^{\lambda_{irr}}$ and $\varepsilon_B^{\lambda_{irr}}$) and/or ascertain whether the reaction obeys an AB(1Φ) or an AB(2Φ) mechanism. This is a distinguishability problem where the elucidation solution for the kinetics is degenerate (Maafi and Brown, 2005b). It is a direct consequence of the generalization provided by Eqs.6. This consideration must be taken into account in the treatment/interpretation of photodegradation reactions of drugs. Therefore, the elucidation of the true mechanism, for this case, can only be achieved using additional information that might be obtained by alternative means (until a pure spectrokinetic method is developed).

Nonetheless, a good fitting of the experimental data with Eqs.2 or 6a certainly proves that the reaction obeys AB Φ–order kinetics. As shown in Fig.4, a linear relationship is only obtained when the whole set of reaction data are treated according to Φ–order kinetics. It is also worth noticing that the data corresponding to the early stages of the reaction (*c.a.* the half–life time) fit relatively well the models corresponding to 0^{th}–, 1^{st}– and 2^{nd}–order reactions.

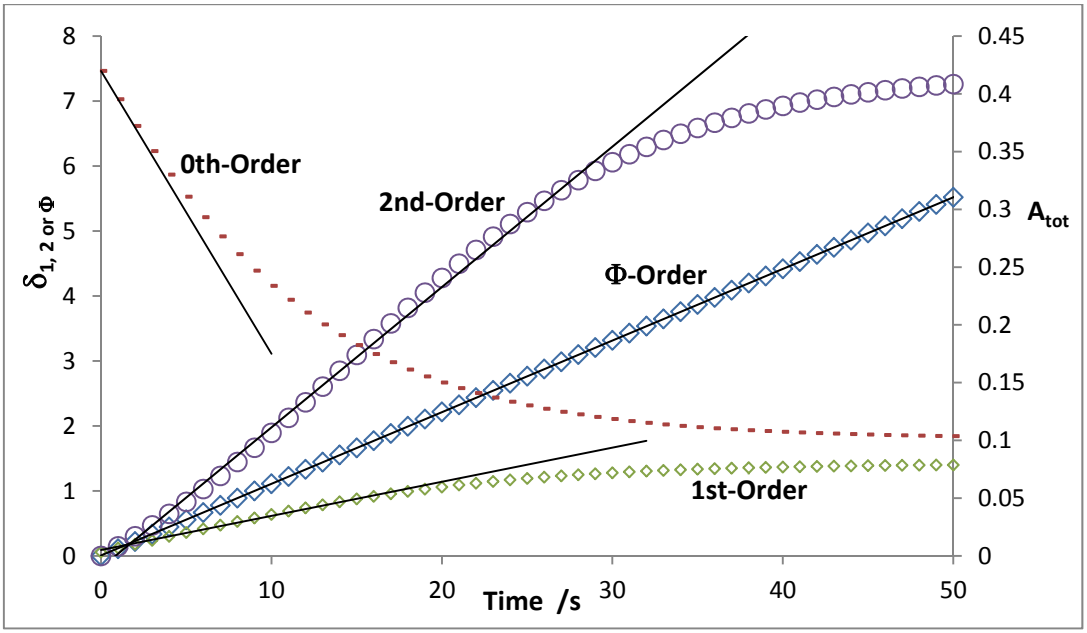


Fig. 4. Treatment of the data corresponding to example 4 of Table 1 by models corresponding to 0^{th}–, 1^{st}– , 2^{nd}– and Φ–order kinetics. The Y–axes are labelled either as $\delta_{1,2\ or\ \Phi} = k_{A \leftrightharpoons B}^{\lambda_{irr}} \times t$ (left–hand side), correspond to the first terms of linear equations describing 1^{st}– , 2^{nd}– or Φ–order reactions, or A_{tot} (right–hand side), the total absorbance assuming that the reaction obeys 0^{th}–order kinetics. Solid lines correspond to the lines of best fit.

The expression of $k_{A \leftrightharpoons B}^{\lambda_{irr}}$ (Eq.6b) indicates that the photodegradation overall rate–constant of AB(2Φ) photodrugs depends inherently on the irradiation wavelength, the absorption coefficients of mother compound and its photoproduct ($\varepsilon^{\lambda_{irr}}$), the forward and reverse

quantum yields ($\Phi^{\lambda_{irr}}$), the optical path length travelled by the irradiation light inside the sample ($l_{\lambda_{irr}}$), the radiant power ($P_{\lambda_{irr}}$) and the photokinetic factor ($F_{\lambda_{irr}}(\infty)$). This rationalises, for the first time, the set of factors affecting the overall rate–constant of such AB(2Φ) systems. It may contribute to a better interpretation of the literature data and reiterates the importance of using monochromatic irradiation for such photokinetic studies (Maafi and Maafi, 2013; Maafi, 2010). It is also worth noting that in the formula of $k_{A\leftrightharpoons B}^{\lambda_{irr}}$, the terms $\varepsilon^{\lambda_{irr}} \times \Phi^{\lambda_{irr}}$ relative to A and B add up in a similar way to that observed for both photoreactions performed with isosbestic irradiation, and thermal reactions (Maafi, 2008; Maafi and Brown, 2008; 2005a). Furthermore, it indicates that the contribution of the latter term is balanced, in the formula of $k_{A\leftrightharpoons B}^{\lambda_{irr}}$, by that of $F_{\lambda_{irr}}(\infty)$.

The analytical formula also strongly implies that $k_{A\leftrightharpoons B}^{\lambda_{irr}}$ directly depends on the initial concentration of the mother compound as implicitly stipulated in the expression of $F_{\lambda_{irr}}(\infty)$. Therefore, it is evident that, assuming that all other experimental parameters and conditions are kept identical, an increase of the initial concentration would lead to a slowdown of the photoreaction and a self–stabilising effect is expected to occur on the photodegradation of the drug (Fig.5). This corroborates and explains a number of experimental observations reported in the literature (Piechocki and Thoma, 2010; Tonnesen, 2004). The initial velocity of the photoreaction is expected to increase with initial concentration of the drug as it depends on the non–linear factor $\left(1 - 10^{-A_{tot}^{\lambda_{irr}/\lambda_{irr}}(0)}\right)$ as implicit in Eq.5a (Fig.5).

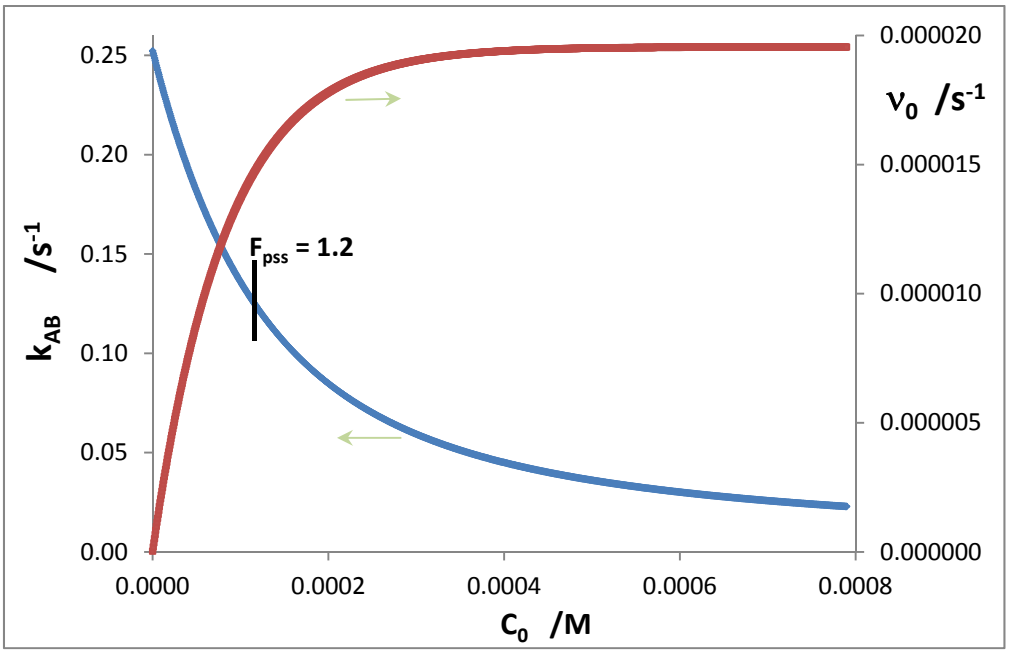


Fig. 5. Reduction of $k_{A\leftrightharpoons B}^{\lambda_{irr}}$ and increase of $\upsilon_0^{\lambda_{irr}/\lambda_{irr}}$ with increasing initial concentration of species A. Data corresponding to example 6 of Table 1. The limit of applicability of Eqs.2 and 6 is indicated by the vertical line ($F_{\infty}^{\lambda_{irr}}$ = 1.2); the curve of $k_{A\leftrightharpoons B}^{\lambda_{irr}}$ after the horizontal line corresponds to the assumption its formula applies.

Another effect of the variation of the drug's initial concentration is that of the half–life time to equilibrium (or completion) of the reaction ($t_{\frac{1}{2}\rightleftharpoons}$ corresponds to $A_{tot}^{\lambda_{irr}/\lambda_{obs}}\left(t_{\frac{1}{2}\rightleftharpoons}\right) = \pm\frac{A_{tot}^{\lambda_{irr}/\lambda_{obs}}(0)-A_{tot}^{\lambda_{irr}/\lambda_{obs}}(\infty)}{2}$). Indeed, for given reaction and set of $\lambda_{irr}/\lambda_{obs}$ wavelengths, Eq.8 suggests a non–linear evolution of $t_{\frac{1}{2}}(j)$ for *j* different initial concentrations, $C_{Aj}(0)$, as well as for $l_{\lambda_{irr(j)}}$ and $l_{\lambda_{obs(j)}}$.

Eq.8 makes $t_{\frac{1}{2}\rightleftharpoons}$ of Φ–order reactions very different from those concentration–independent half–life times worked out for 0th– and 1st–order thermal reactions. It is also different from

that of 2nd–order reactions even though they share this property of being concentration–dependent (but only $t_{\frac{1}{2}\rightleftharpoons}$ of Φ–order reactions depends on absorbance and optical path length values). It is then essential to use reliable experimental values of end–of–reaction ($A_{tot}^{\lambda_{irr}/\lambda_{obs}}(\infty)$) absorbances for more accuracy. $t_{\frac{1}{2}\rightleftharpoons}$ is found to vary quasi–linearly with initial concentration for $F_{pss}^{\lambda_{irr}} < 1.2$ for example 7 of Table 1 (Fig.5).

$$t_{\frac{1}{2}\leftrightharpoons} = \frac{-1}{k_{A\leftrightharpoons B}^{\lambda_{irr}}} \times Ln\left[\frac{10^{\left[\frac{\left(A_{tot}^{\lambda_{irr}/\lambda_{obs}}\left(t_{\frac{1}{2}\leftrightharpoons}\right)-A_{tot}^{\lambda_{irr}/\lambda_{obs}}(\infty)\right)\times\left(A_A^{\lambda_{irr}/\lambda_{irr}}(0)-A_{tot}^{\lambda_{irr}/\lambda_{irr}}(\infty)\right)\times l_{\lambda_{irr}}}{\left(A_A^{\lambda_{irr}/\lambda_{obs}}(0)-A_{tot}^{\lambda_{irr}/\lambda_{obs}}(\infty)\right)\times l_{\lambda_{obs}}}\right]}-1}{10^{\left[\left(A_A^{\lambda_{irr}/\lambda_{irr}}(0)-A_{tot}^{\lambda_{irr}/\lambda_{irr}}(\infty)\right)\times\frac{l_{\lambda_{irr}}}{l_{\lambda_{obs}}}\right]}-1}\right] \quad (8)$$

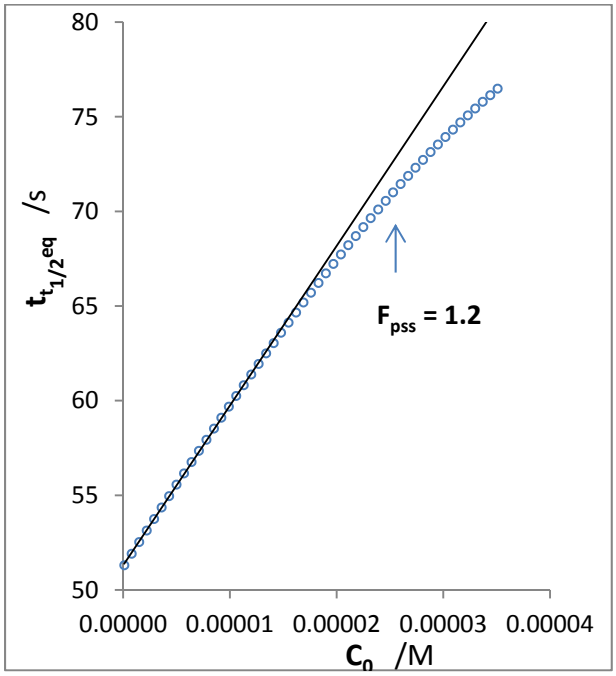


Fig. 5. Examples of the variation of the half–life time for an AB(2Φ) photodegradradation with initial drug concentration. The data points correspond to example 7 of Table 1.

In order to avoid non–linear fittings of the experimental traces, the overall rate–constant of an AB(2Φ) reactions can be obtained as the slope of a line. The linear relationships (Eq.9), obtained by rearranging Eq.6a to give the variation of $A_{tot}^{\lambda_{irr}/\lambda_{obs}}(t)$ *vs.* time, might be found much easier to handle and agrees with the classical pattern adopted for the treatment of reaction kinetic data.

$$Y_{tot}^{\lambda_{irr}/\lambda_{obs}} = Ln\left[\frac{10^{\left[\left(A_A^{\lambda_{irr}/\lambda_{irr}}(0)-A_{tot}^{\lambda_{irr}/\lambda_{irr}}(\infty)\right)\times\frac{l_{\lambda_{irr}}}{l_{\lambda_{obs}}}\right]}-1}{10^{\left[\frac{\left(A_{tot}^{\lambda_{irr}/\lambda_{obs}}(t)-A_{tot}^{\lambda_{irr}/\lambda_{obs}}(\infty)\right)\times\left(A_A^{\lambda_{irr}/\lambda_{irr}}(0)-A_{tot}^{\lambda_{irr}/\lambda_{irr}}(\infty)\right)\times l_{\lambda_{irr}}}{\left(A_A^{\lambda_{irr}/\lambda_{obs}}(0)-A_{tot}^{\lambda_{irr}/\lambda_{obs}}(\infty)\right)\times l_{\lambda_{obs}}}\right]}-1}\right] = k_{A\leftrightharpoons B}^{\lambda_{irr}} \times t \qquad (9)$$

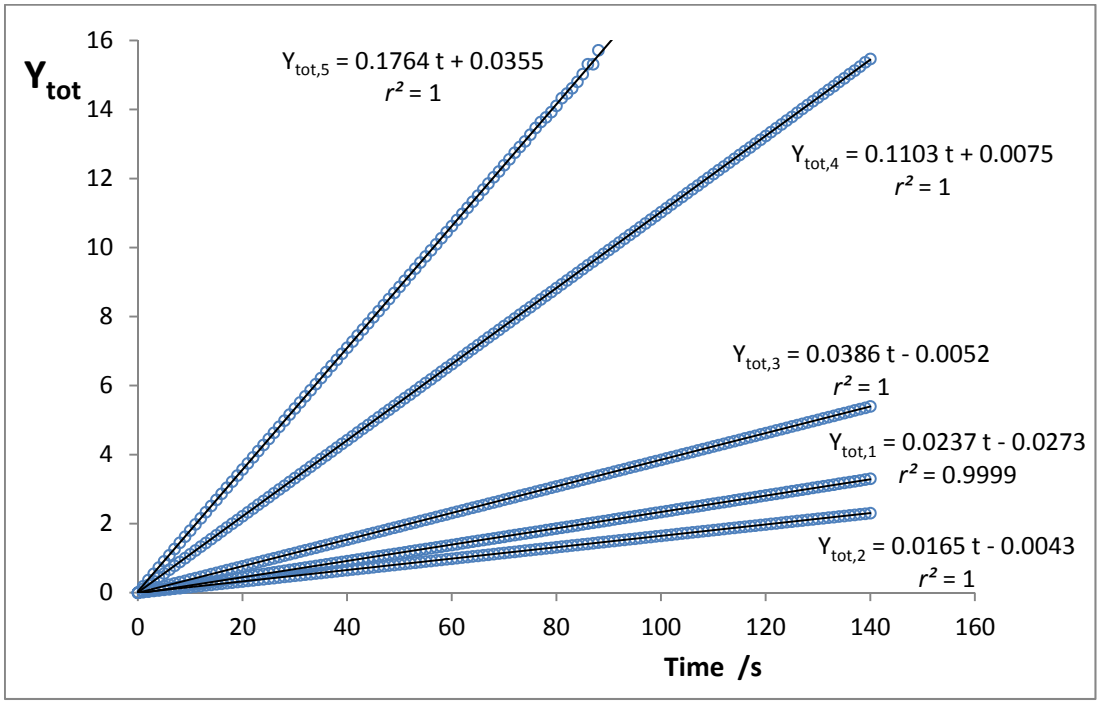


Fig. 6. Φ-order plots ($Y_{tot,n}^{\lambda_{irr}/\lambda_{obs}} = k_{A\leftrightharpoons B}^{\lambda_{irr}} \times t$, Eq.9) for *n* = 1 – 5 examples of Table 1.

Finally, the models presented in this study (Eqs.2 and 6a) would facilitate the development of new AB(2Φ) photodrug-based actinometers. For this purpose, the expected linear relationships between $k_{A \leftrightharpoons B}^{\lambda_{irr}}$ or $v_0^{\lambda_{irr}/\lambda_{obs}}$ with $P_{\lambda_{irr}}$ (Eqs.5a and 6b), offer the possibility to monitor the variation of either parameter with radiant power. The collected linear data on the relationships for a given photodrug will be used for the development of an actinometric method spanning the wavelength range covering the whole absorption spectrum of the drug. This actinometric data can be used later to determine the radiant power of an unknown light source at given wavelengths. Such an approach can palliate the lack of drug–actinometers (Montali et al., 2006) and put forward alternatives to the quinine hydrochloride as proposed by ICH guidelines (ICH, 1996). The fact that the actinometric method presented in this study can be developed and implemented without requiring prior knowledge of any of the unknown reaction parameters (i.e. $\varepsilon_B^{\lambda_{irr}}$, $\Phi_{A \to B}^{\lambda_{irr}}$ and $\Phi_{B \to A}^{\lambda_{irr}}$), as long as the reaction obeys an AB mechanism, represents an undeniably important advantage.

Work is ongoing in our team to applying the new mathematical strategy to the photodegradation of AB(2Φ) drugs and exploring their actinometric potential (Maafi and Maafi, 2014).

5. Conclusion

The particular subject of drug photodegradation as well as photokinetics in general, an area of research with important industrial implications, requires some crucial developments with relation to valid and reliable integration rate–law equations able to describe and rationalize the kinetic behaviour of photodegradation reactions. This is crucially evident in the ICH recommendations set out in section Q1b, as the latter document lacks precise protocols and/or procedures aimed at the treatment of kinetic data, the determination of reactions' overall rate-constants, and/or quantum yields. Besides, the approaches based on zeroth, first or second order kinetics, though ubiquitous in the pharmaceutical literature, are arguably not appropriate to assess kinetic data corresponding to Φ–order reactions.

The combination of a template equation and RK data, as has been proposed in the present investigation, has successfully led to establishing a useful equation that describes well the kinetics of drugs obeying AB(2Φ) mechanisms. It has also made possible a straightforward derivation of some fundamental parameters of the reaction including the photochemical quantum yields. This approach might contribute, as a new concept, to derive semi–empirical integrated rate–law equations suitable for drug photodegradations involving more extended mechanisms than that of the AB(2Φ) reaction.

Our results have also established that the magnitude of a photoreaction rate–constant is sensitive to all parameters related to AB reactions including the reactant and product

attributes ($C_A\ (0)$, $\varepsilon_A^{\lambda_{irr}}$, $\varepsilon_B^{\lambda_{irr}}$, $\Phi_{A\to B}^{\lambda_{irr}}$ and $\Phi_{B\to A}^{\lambda_{irr}}$) as well as the experimental conditions (λ_{irr}, $P_{\lambda_{irr}}$, $l_{\lambda_{irr}}$ and the irradiated volume of the solution). For the first time, a mathematical formulation allows to quantify the effect of each of the latter parameters. Furthermore, it offers an interesting tool for the development of new drug–actinometrs for either or both the UV and Visible ranges.

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