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Non-steroidal anti-psoriatic prodrugs. II. Citric acid stabilization of lonapalene in various alcohol media and an ointment formulation

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Summary

Stability of the anti-psoriatic naphthyl diester, 1,4-diacetoxy-6-chloro-2,3-dimethoxynaphthalene, **1** (lonapalene) was studied in various alcohols and in propylene carbonate (PC) at 50°–100°C. For comparison, lonapalene was also incorporated into a propylene glycol-based ointment formulation and the drug reactivity was monitored from 40° to 80°C. In several of the alcohols, biphasic kinetics were observed where a slower phase occurred after the initial 20–60% of reaction. This second, slower phase is due to a lowering of the solution acidity by acetic acid, one of the degradation products. When 0.1 mg/ml citric acid was added to the reaction solution, the initial 'pH' dropped from ca. 6–7 to ca. 4–5 resulting in an approximate order of magnitude increase in drug stability. A good linear correlation between log k_{CA} (when 0.1 mg/ml citric acid was present) and the solvent hydroxyl group concentration was observed for the degradation of **1** at 80°C. This diester also degraded slowly in pure PC showing apparent first-order kinetics. In the ointment formulation, lonapalene degradation closely paralleled the reactivity observed in alcohol solutions with respect to kinetic order, Arrhenius behavior, and influence of citric acid on stability. Taken together, these results were interpreted as follows: (i) a change in mechanism occurs from specific base catalysis in neutral 'unbuffered' alcohols to one involving reaction of the alcohol with ester directly in solutions containing citric acid (where specific base catalysis is suppressed), (ii) lonapalene degrades in PC at a rate comparable to the rate of reaction in some alcohols, even though the hydroxyl group concentration (due to traces of water present) in propylene carbonate is negligible, and (iii) lonapalene reactivity in alcohols closely models drug degradation in a glycol-based ointment indicating common reaction pathways for these solution-phase and semisolid media.

Introduction

The thermal and enzymatic stability of various ester prodrugs continues to be a topic of great interest (see, for example: Roche, 1976; Smith et al., 1983). Since many ester prodrugs are formulated in alcohol-based solution and semisolid vehicles, it is important to understand the factors governing ester stability in these vehicles. Although it is known that esters may degrade by both hydrolysis and transesterification (Irwin et al., 1984; Wyatt et al., 1979), little work has been

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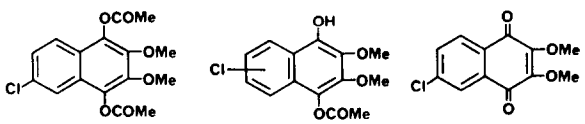
done to understand the effects of different alcohols and alcohol concentration on ester stability. Because most ester hydrolysis and transesterification studies have been carried out at relatively high pH, the dominant reaction is specific base catalysis, a reaction which does not reflect ester reactivity at the pH of maximum stability. Finally, the preponderance of the published literature deals with solution reactivity only, and largely ignores the important subject of ester reactivity in more complex pharmaceutical formulations.

To shed some light on the mechanism(s) of ester degradation in alcohol media in the absence of strong bases, we studied the degradation of the anti-psoriatic compound 1,4-diacetoxy-6-chloro-2,3-dimethoxynaphthalene (**1**) (Jones et al., 1984, 1986; Simpson et al., 1984; Young et al., 1988) in various alcohol solvents with and without added citric acid. Because lonapalene is intended for topical application, we also extended our investigation to include the effects of temperature and citric acid on lonapalene incorporated into a glycol-based ointment formulation.



1 **2** **3**

Scheme 1

In our previous paper (Powell et al., 1987), we have demonstrated that **1** hydrolyzes in aqueous solution to give a pair of isomeric monoesters (named collectively as **2**) which react further to give (eventually) 6-chloro-2,3-dimethoxy-1,4-naphthoquinone (**3**). The hydrolysis of **1** was characterized by a log(rate)–pH profile defined by 3 rate constants, k_{H^+}, k_0 and k_{HO^-}. Below pH 3 specific acid catalysis dominated whereas, above pH 5, specific base catalysis made the greatest contribution to the observed rate. At the pH of maximum stability, however, the spontaneous (or water-catalyzed) reaction overwhelmed the acid- and base-catalyzed reactions. For example, neglecting the k_0 term, the room temperature (RT) shelf-life for **1** at pH 4 was calculated to be > 3 years. In contrast, the observed RT shelf-life for **1** at pH 4 was found to be ~ 1 month.

In an attempt to suppress this spontaneous reaction, we have studied the influence of various solvents, primarily alcohols, on the reaction of **1** at (or near) the 'pH' * of maximum drug stability. Citric acid (CA) was used to reduce the 'pH' of the various alcohol solutions and the alcohol-based ointment to a final 'pH' of approximately 3–4, reasonably close to the pH of maximum stability for **1** in aqueous solution.

Materials and Methods

Materials

Compounds **1**, **2** and **3** were prepared in the Institute of Organic Chemistry at Syntex (Palo Alto, CA); the synthetic details of these and other anti-psoriatic compounds are described elsewhere (Jones et al., 1986). Radiolabeled 1,2,3,4,4a,8a-[^{14}C]**1** was also prepared at Syntex in $> 98\%$ radiochemical purity (Parnes, personal communication). The 1- and 2-acetoxy monoesters of propylene glycol (**4** and **5**, respectively) were prepared by reaction of acetic anhydride/acetic acid with a large excess of propylene glycol at 80 °C. After reaction for 48 h, the esters were purified by semi-preparative reversed-phase (RP) HPLC and identified by ^{1}H-NMR and GC-MS. Propylene glycol (PG), propylene carbonate (PC), polyethylene glycol-400 (Peg-400), ethylene glycol (EG), diethylene glycol (DEG), and CA were either USP or NF grade. Methanol (MeOH), ethanol (EtOH), and isopropanol (IPA) were HPLC grade and were not further purified or dried. Typically solvents contained only residual amounts ($<$ 0.05%) of water. The ointment formulation contained PC, PG, glycerol monostearate, white wax,

* Since the term pH refers to hydronium ion concentration in totally aqueous solution, we have adopted the term 'pH' for the apparent pH of alcohol solutions. It is emphasized that these observed pHs (denoted 'pH') are not really true pHs because they contain a sizable activity contribution due to the mixed solvent system (Bates, 1973). They are useful, however, for determining a relative change in solution acidity, say during the course of the degradation reaction, or an increase in acidity when adding citric acid to the reaction solution.

white petrolatum, lonapalene, and CA. The inorganic compounds KH_2PO_4, H_3PO_4, D_2O, DCl and NaCl were reagent grade (Aldrich or Mallinckrodt) and were also used without further purification. Mobile phase was prepared from HPLC-grade acetonitrile (Burdick and Jackson) and distilled deionized water.

Apparatus

The kinetic analysis of **1**, **2** and **3** in solution samples was carried out using an HPLC system consisting of a Micromeritics Model 725 autoinjector, Model 110A Altex pump, Model 770 Spectra Physics spectrophotometric detector and an SP 4000 computing integrator. The following RP-HPLC conditions provided a linear response throughout the range of 0.04–40 μg injected: column, Alltech Spherisorb S5-C6 (150 × 4 mm, 5 μm); mobile phase, acetonitrile–0.01 M potassium dihydrogen phosphate (adjusted to pH 4 with phosphoric acid before mixing with CH_3CN) (45 : 55, v/v); flow rate, 1 ml/min; detection, 242 nm; typical retention times, **3**, 7 min; **2**, 8 min; **1**, 12 min. The 1- and 2-acetoxy monoesters of propylene glycol were separated and collected by RP-HPLC using the following conditions: column, Altex Ultrasphere ODS (250 × 4.1 mm, 5 μm); mobile phase, acetonitrile–water (10 : 90, v/v); flow rate, 1 ml/min; retention times, 1-acetoxy monoester **4**, 6 min; 2-acetoxy monoester **5**, 8 min. The ointment samples were assayed by HPLC using a previously described method (Kenley et al., 1985).

Collection and assay of the radioactive HPLC fractions were carried out using an LKB Multi-Rac fraction collector and a Beckman LS 860 liquid scintillation counter. All sample activities were corrected for background counts and traces (~ 2%) of radioimpurities in [^{14}C]**1**. Electron impact mass spectra were obtained using a Varian MAT 1125 or 311A direct inlet mass spectrometer. NMR spectra were determined using a Bruker WM 300 FT-NMR spectrometer. pHs were determined prior to the reaction using a Radiometer PHM 64 pH meter and Model GK2401C combination electrode. The pH measurement of mixed solvents was carried out by standardizing the pH meter using aqueous buffers of known pH, and then reading the apparent 'pH' of the mixed aqueous solvent at the same temperature. When the 'pH' of a non-aqueous solvent such as pure propylene glycol was desired, a 1 : 4 (PG : H_2O) dilution with distilled deionized water was made prior to the pH measurement.

Kinetics

In all solution phase experiments, the initial drug concentration (~ 5 μg/ml) was significantly lower than the concentration of added citric acid (0.01 → 1 mg/ml) or alcohol concentration. A stock solution of **1** was prepared using acetonitrile and stored in the dark at 4° C when not in use. In a typical kinetic run, 100 ml of reaction solution and a small amount (ca. 0.1–0.5 ml) of the stock solution of **1** were mixed and 5 ml aliquots of the solution were transferred to pretreated amber ampoules, flame-sealed, and temperature-equilibrated (±1° C). At known time intervals, the ampoule contents were either assayed immediately against a freshly prepared reference solution of **1**, or were stored in a refrigerator until all samples were collected, and then all samples were analyzed on the same day. Typically, 8–12 samples were analyzed, and the peak area integration values were converted to concentrations or % remaining values by use of linear response calibration curves determined earlier for **1**, **2**, and **3**.

Ointment samples were stored in glass scintillation vials with plastic screw caps. Each vial contained 0.5 g sample, and the entire contents of a vial were used for each determination. The vials were stored in constant temperature (±2° C) ovens and withdrawn for assay (at least in triplicate) at timed intervals.

Product identification

UV spectra of the major RP-HPLC peaks were obtained by monitoring the HPLC effluent using an HP-8450A spectrophotometer equipped with an 8 μl flow cell. Large scale separation and collection of the major peaks using acetonitrile–water (45 : 55, v/v) as the HPLC mobile phase afforded **2** and **3**. Product identification was made by spectral (UV, NMR and MS) and chromatographic (reversed-phase and normal-phase HPLC) comparison of isolated degradation products with

authentic samples of both isomers of **2**, and **3** (Powell et al., 1987). The 1- and 2-acetoxy monoesters, **4** and **5**, were separated by RP-HPLC and identified by GC-MS and ^{1}H-NMR. The identities of the radiolabeled peaks in the HPLC chromatograms of [^{14}C]**1** were assigned by chromatographic retention time comparisons with authentic materials.

Results and Discussion

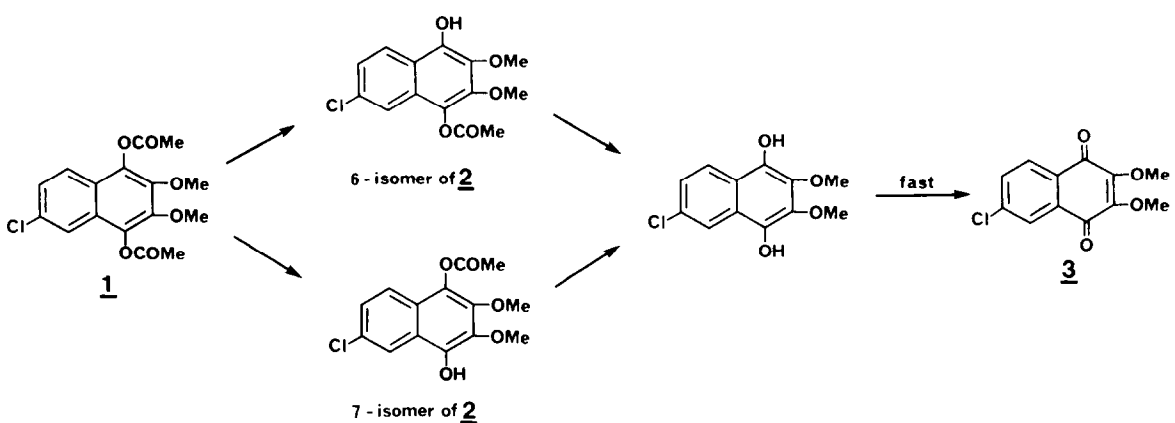
Reaction products

In alcohol solutions, the degradation of **1** initially gave an approximate 1 : 1 mixture of the 6- and 7-chloro monoesters (designated collectively as **2**) *. As an example, the degradation of **1** in propylene glycol is shown in Eqn. 1 (Scheme 2). The pseudo-first-order rate constants k_{CA} and k are used to denote the reactivity of **1** in solvents with and without added citric acid, respectively. Although subsequent reaction of **2** must afford the dihydroquinone (**6**), this intermediate was not observed in kinetic experiments because of rapid oxidation to give primarily 6-chloro-2,3-dimethoxy-1,4-naphthoquinone (**3**). Compound **6**, however, has been synthesized by others using preparative methods (Jones et al., 1986).

The degradation product formed from the acetate moiety was dependent upon the solvent used. For example, in aqueous solution, acetic acid was the complimentary product (Powell et al., 1987) whereas in propylene glycol, acetic acid and the 1- and 2-acetoxy monoesters of PG (**4** and **5**) were found; the latter two compounds in an approximate 1 : 1 product ratio.

Mass balance using [^{14}C]**1** was also carried out to ensure that all the degradation products of **1** were detected and accounted for. The use of radiolabeled compound for detection and mass balance is superior to spectrophotometric methods (such as UV detection) because it does not require a knowledge of their products or their molar absorbtivities. Mass balance for the reaction of [^{14}C]**1** in various alcohol solvents was obtained from reactions carried out to at least one half-life. Results obtained using [^{14}C]**1** agreed with the data obtained from the cold assay. Pseudo first-order rate constants determined from the loss of [^{14}C]**1** were in close agreement with rate constants determined by the UV-spectrophotometric assay method. In propylene carbonate, mass balance for the reaction of [^{14}C]**1** was also obtained, although in this case the primary degradation products were not **2** or **3**. The reaction products of **1** in PC have

* Earlier studies have shown that the formation and degradation rates of the 6- and 7-isomers of 2 in aqueous solution are nearly identical (Powell et al., 1987), and so these isomers are treated collectively herein.



(1)

Scheme 2

not been identified but are probably polar in nature as indicated by their short reversed-phase HPLC retention times.

Reaction kinetics in solution — effect of added citric acid

The degradation of **1** in various alcohols containing 0.1 mg/ml added citric acid followed first-order kinetics. In solvents without citric acid, however, biphasic kinetics were usually observed; an initial rapid drug loss was followed by a much slower reaction (Fig. 1). When such biphasic kinetics were observed, the rate of drug loss was calculated using only the initial part of the reaction. The pseudo-first-order rate constants determined from the first phase of the reaction accurately reflect the initial rate of drug degradation because the reaction remains first order for the first 10% of reaction (no lag phase observed until past t_{90}). Rate constants obtained from reactions in PG without added CA showed some variability, especially when different lots of PG were used. It was noted that the higher the "pH", the faster was the rate of drug degradation. Typically, rate constants in PG varied no more than by a factor of 3; the value for PG in Table 1 is the average of rate constants from several PG lots.

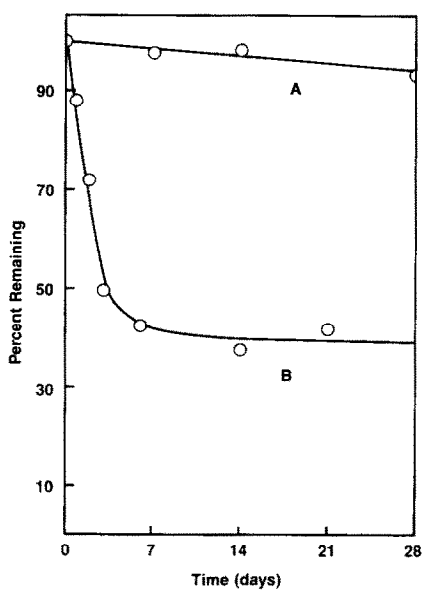


Fig. 1. Degradation of **1** in propylene glycol at 80 °C showing: (A) slow pseudo first-order kinetics with 0.1 mg/ml added CA and, (B) biphasic kinetics with no CA present. The pH in reaction solutions without added CA dropped from ~ 6.5 to 5.0–5.5 after 14 days reaction.

The addition of 0.1 mg/ml CA to alcohol solutions of **1** resulted in an approximate 10-fold increase in drug stability. Inspection of Table 1 shows that this behavior is observed for nearly all alcohols and alcohol/PC mixtures, the exceptions being PC and Peg-400, which are discussed below. The degradation of **1** also depended on the amount of CA added up to approximately 0.1 mg/ml; above this concentration drug stability did not increase noticeably and so the k_{CA} values of Table 1 reflect close to maximal stabilization by citric acid.

The mechanism of CA stabilization was investigated by determining the values of k and k_{CA}, and by correlating these rate constants with the 'pH' of the reaction solution. The 'pH' of all alcohol solutions (except for Peg-400) dropped from ca. 6–7 to ca. 4–5 when 0.1 mg/ml citric acid was added. This drop in 'pH' accounts for the observed increase in drug stability ($k_{CA} < k$) inasmuch as ester group cleavage, even in neutral pH solution, is strongly base-catalyzed. The lowering of the 'pH' with added CA effectively retards the base catalyzed reaction. CA did not stabilize **1** in Peg-400 solutions ($k \simeq k_{CA}$); in this case the initial 'pH' was already fairly low (ca. 4.1–4.3) and so was not altered by added CA.

Further evidence that citric acid stabilized **1** by neutralizing traces of specific base (i.e., formed by solvent autoprotolysis) was obtained by noting that biphasic degradation kinetics were usually observed when CA was not added (Fig. 1). In this case, the initial rate of drug loss was rapid to 40–80% drug remaining but then slowed down by a factor of 5–10, close to the rate observed when CA was present (k_{CA}). In propylene glycol, for example, biphasic kinetics are due to the generation of acetic acid, possibly formed by hydrolysis of the PG-ester product (Eqn. 2) or, more likely, by the reaction of **1** with traces of water present (Eqn. 3).

$$CH_3CH(OH)CH_2OOCCH_3 + H_2O \rightarrow CH_3CH(OH)CH_2OH + CH_3COOH \quad (2)$$

$$\mathbf{1} + H_2O \rightarrow \mathbf{2} + CH_3COOH \quad (3)$$

TABLE 1

Effect of solvent and 0.1 mg/ml added CA on the degradation of **1** *at 80 °C*

Solvent (v : v)	Solvent hydroxyl group concentration (M)	$10^7\ k\ (s^{-1})$ [a]	$10^7 k_{CA}\ (s^{-1})$
Water	111	330	170 [b]
PG/H_2O (30 : 70)	85	320	45 [b]
PG/H_2O (70 : 30)	52	92	2.0 [c]
PG	27	3.6	0.29
MeOH	25	5.2	0.54
EtOH	17	3.9	0.29
PC	0	0.053	0.20
PG/PC (10 : 90)	2.7	0.32	0.19
PG/PC (50 : 50)	14	0.32	0.19
PG/PC (90 : 10)	24	0.79	0.13
MeOH/PC (10 : 90)	2.5	11	0.14
EtOH/PC (10 : 90)	1.7	7.9	0.091
IPA/PC (10 : 90)	1.3	1.4	0.13
DEG/PC (10 : 90)	2.1	17	0.052
EG/PC (10 : 90)	3.6	21	0.13
Peg-400	5.6	1.1	0.76
Peg-400/PC (10 : 90)	0.56	2.7	1.0
Peg-400/PC (75 : 25)	4.2	0.43	0.74
Ointment (PG/PC = 64 : 36)	16 [d]	1.58	0.83 [e]

[a] Several reactions became non first-order after 40–80% of reaction. In these cases, the pseudo-first-order rate constants (k) were calculated from the initial phase (< 10%) of the reaction.

[b] pH 4.0 acetate buffer instead of CA.

[c] When run in pH 4.0 acetate buffer, the $k_{obs} = 3.4 \times 10^{-7}\ s^{-1}$.

[d] Calculated on the basis of an internal phase containing drug, PC, and PG.

[e] Citric acid = 0.005% w/w (0.05 mg/ml).

For the reaction of **1** in neat PG at 80 °C, the 'pH' dropped from approximately 6.5 (initial) to 5.0–5.5 (2 weeks later), where the different pH's were observed in different lots of PG, indicating an increase in $[H^+]$ and a decrease in the specific base concentration. It is this decrease in base concentration with time that results in the observed biphasic kinetics. A similar explanation has also been proposed to explain the biphasic kinetics for the degradation of aspirin in mixed protic–aprotic solvents (Chang et al., 1984). Thus, when critic acid is added to alcohol solutions of **1** the mechanism shifts away from specific base catalysis, to one involving a spontaneous reaction of the ester and alcohol directly. This latter mechanism for ester cleavage in alcohols is supported by the correlation of solvent hydroxyl group concentration with k_{CA} (next section), and by comparison of the activation parameters for k_{CA} and the water-catalyzed reaction k_0. We have shown previously (Powell et al., 1987) that the water-catalyzed reaction of **1** is characterized by a large E_a and a fairly sizable $-\Delta S^{\ddagger}$. Table 2 shows that the activation parameters for k_{CA} (obtained in alcohol solutions with added CA) are of comparable magnitude with those for k_0. Similar activation parameters have also been observed for the spontaneous reaction of methyl acetate and ethanol (Rao et al., 1972).

Reaction kinetics in solution — effect of solvent composition

The effect of PG solvent composition is shown clearly by plotting log k and log k_{CA} for drug loss vs the percent composition of PG in PC, and propylene glycol in water (Fig. 2). In the absence of added CA the degradation rate constant k increased with increasing solvent polarity from

TABLE 2

Activation parameters for the degradation of **1** *in various solvents* [a]

Rate constant	Solvent	E_a (kcal mol^{-1}) [b]	log A	$\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta S^{\ddagger}$ (cal K^{-1} mol^{-1})
k	H_2O	11 ± 1 [c]	8.0 + 0.3	10	−24
	PG/PC (90 : 10)	13 + 1	1.0 ± 0.7	12	−56
	PG/PC (50 : 50)	15 ± 1	2.0 ± 0.7	14	−51
	PG/PC (10 : 90)	17 ± 1	3.0 ± 0.4	16	−47
	Ointment (64 : 36)	22 ± 2	7.0 ± 1.3	22	−29
k_{CA}	H_2O	15 ± 1 [d]	3.7 + 0.5	14	−44
	PG	22 ± 6	6.0 ± 4	22	−32
	PG/PC (90 : 10)	26 ± 4	8.0 ± 3	25	−22
	PG/PC (50 : 50)	24 ± 5	6.0 ± 3	23	−29
	PG/PC (10 : 90)	21 ± 5	5.0 ± 3	20	−38
	Ointment (64 : 36)	22 ± 0.4	6.3 ± 0.2	21	−32

[a] For water and the PG/PC solvents, the temperatures studied were 50°, 60°, 80° and 100°C (< ±1°C).
[b] Means ± S.D.
[c] For the reaction of **1** and HO^- in aqueous media (k_{HO-}) (Powell et al., 1987).
[d] For the reaction of **1** and H_2O in aqueous media (k_0) (Powell et al., 1987).

5.3×10^{-9} s^{-1} in PC to 3.3×10^{-5} s^{-1} in distilled unbuffered water. In contrast, k_{CA} remained nearly constant from neat PC to PG, but then increased rapidly upon changing the reaction media from neat PG to pH ~ 4 aqueous buffer. If the reaction of **1** in alcohols containing citric acid resembles the k_0 reaction of **1** in aqueous media (vide supra), then the observed reaction rate should increase as the solvent hydroxyl group concentration ([OH]) increases. The reaction of **1** in water ([OH] = 111 M) is much faster than it is in pure PG ([OH] = 27 M), but it is not readily apparent why k_{CA} remains nearly constant throughout the PG–PC region, or why **1** reacts at all in neat propylene carbonate when [OH] for this solvent (due to trace impurities of water) is negligible.

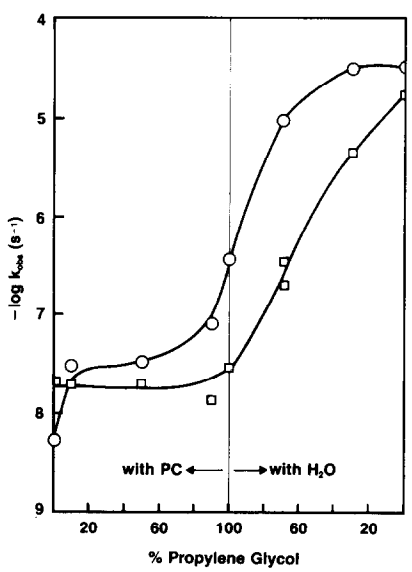


Fig. 2. Log k (○) and log k_{CA} (□) for the degradation of **1** in PG/PC and PG/H_2O mixtures (v : v) at 80°C. The solvent composition (from left to right) changes from PC to PG and then from PG to H_2O.

These unusual observations suggest that the degradation of **1** is governed not only by the [OH], but also by a large solvent effect. This solvent effect may be due to a change in the hydroxyl group nucleophilicity for the different solvents, or possibly due to other factors such as solvent viscosity or solvent polarity. In PG, for example, [OH] is comparable with PG/H_2O (70 : 30), yet the k_{CA} values differ by almost an order of magnitude. The rate of degradation of **1** in strongly polar alcohols such as Peg-400 is also faster than predicted by [OH] alone. Large rate accelerations have often been observed for reactions carried out in polyethers and are attributed to the polar nature of the solvent, presumably because of the highly electronegative ether oxygens (Eckert et al., 1977). In neat PC however, the degradation of **1** may occur by a different reaction pathway, as

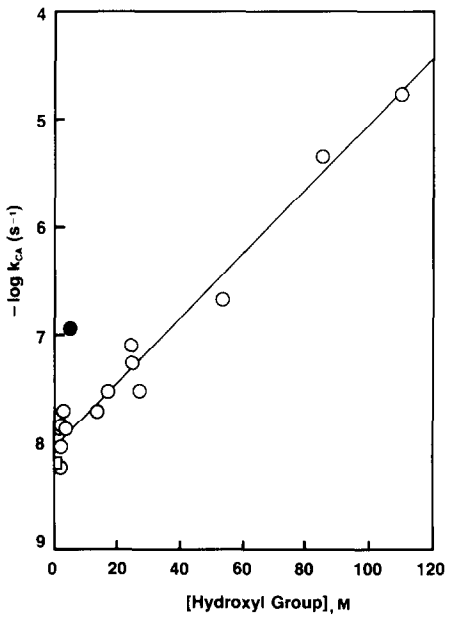


Fig. 3. Correlation of log k_{CA} for the degradation of **1** at 80 °C in various alcohol solutions containing 0.1 mg/ml CA with the hydroxyl group concentration [OH]. Log k_{CA} for reaction of **1** in neat PC (□) has been included to show evidence for a degradation pathway independent of hydroxyl species. The rate constant for reaction of **1** in Peg-400 (●) has also been included to show the positive deviation from the other alcohols used.

shown by the lack of **2** and **3** as degradation products in this solvent. Such a change in reaction mechanism with solvent type has been noted previously, for example, in the degradation of *t*-butyl heptafluoroperoxy-butyrate in methanol and in toluene (Sawada et al., 1984).

A linear plot of log k_{CA} vs [OH] also supports the notion of a large solvent effect (Fig. 3). If the reaction rate obeyed a first-order dependence on [OH], then a linear plot of k_{CA} vs [OH] (not log k_{CA} vs [OH]) would be expected. Although the linear correlation of log k_{CA} vs [OH] is purely empirical, it suffices to show that: (i) it is possible to estimate the degradation rate of **1** in other alcohol solvents by interpolation of Fig. 3 and (ii) **1** degrades in PC (the intercept of Fig. 3) even though the solvent hydroxyl group concentration is negligible.

Reaction kinetics in ointment samples — the effect of CA

Microscopic examination revealed that the PG/PC-based ointment consisted of two discrete phases wherein the internal phase was made up of mostly PG/PC globules, and the external phase largely comprised of petrolatum. Furthermore, lonapalene crystals were absent, indicating complete drug dissolution within the ointment. On the basis of these observations and known lonapalene solubility behavior, it is reasonable to infer that the lonapalene is found in the globules of PG/PC co-solvent, i.e., in the internal phase. Given this inference, it is possible (as a first approximation) to treat the neat PG/PC solution as a model system for the ointment. If PG/PC solutions accurately model the semisolid formulation, then the lonapalene degradation kinetics should be similar in both reaction media.

Our observations demonstrate that PG/PC solutions *do* provide a reasonable model for lonapalene ointment, both qualitatively and quantitatively. First, lonapalene degradation adhered strictly to pseudo-first-order kinetics in ointment with added CA but showed biphasic kinetics when citric acid was absent. Second, the influence of citric acid on lonapalene ointment stability was also similar to effects seen in PG/PC solutions. Table 1 shows that 0.05 mg/ml CA stabilized lonapalene by the factor $k/k_{CA} = 1.90$. By comparison, the PG/PC 50 : 50 solution gave $k/k_{CA} = 1.68$. Lonapalene was found to be slightly less stable in the ointment than in PG/PC solution, where the k and k_{CA} values in PG/PC solution vs ointment samples agreed to within a factor of approximately 5. Considering the differences in reaction medium, physical properties, and the errors inherent in the kinetic determinations, the agreement between solution and ointment samples is satisfactory.

Additional parallels are also evident, for example, in the Arrhenius data for ointment and PG/PC samples. Because lonapalene degradation adheres to the Arrhenius expression over a wide temperature range that extends above and below the ointment congealing point (approximately 55 °C), the ointment physical state is probably not a strong determinant of lonapalene reactivity (Fig.

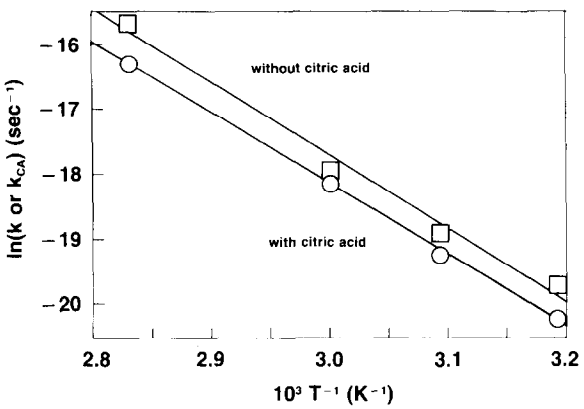


Fig. 4. Arrhenius plot for the degradation of lonapalene in a PG-based ointment formulation.

4). Rather, the ointment chemical composition must be the controlling factor.

Table 2 shows activation parameters for lonapalene degradation in ointments with and without added CA. It is mechanistically significant that both the E_a and log A values for the ointment with citric acid and for the PG/PC solutions containing CA are close in value. The good agreement between these activation parameters observed over a broad temperature range requires that ointment and PG/PC solution samples containing CA share a common reaction pathway, namely, transesterification of lonapalene with PG.

Reaction kinetics in ointment samples — effect of solvent composition

The hydroxyl group concentration in ointment samples is approximately 16 M, assuming a discrete phase containing only PC, PG, and lonapalene (vide supra). From the least-squares regression line shown in Fig. 3, [OH] = 16 M corresponds to a k_{CA} value of 0.30×10^{-7} s^{-1}, fairly close to the k_{CA} value of 0.83×10^{-7} s^{-1} for lonapalene ointment containing CA (Table 1). Thus, the observed ointment k_{CA} values agreed within a factor of 3 with values predicted on the basis of solution-phase data. This agreement seems reasonable and well within the limits of experimental uncertainty. The good agreement between k_{CA} values therefore constitutes additional evidence that PG/PC solutions adequately model the ointment formulation and that (in the presence of added citric acid) lonapalene reacts in both cases by transesterification with PG.

Conclusions

The room temperature shelf-life of **1** in neutral aqueous solution has previously been determined to be approximately 4 days whereas, at the pH of maximum stability (pH ~ 4), the shelf-life was 1 month (Powell et al., 1987). A comparable difference in reactivity was also observed for the reaction of **1** mixed in PG/PC solutions when the 'pH' was lowered by adding CA. In 10 : 90, 50 : 50 and 90 : 10 PG/PC without added CA the estimated shelf-lives are 8.4, 4.6 and 1.3 years, respectively. When 0.1 mg/ml CA was added, drug stability was increased approximately 2–5-fold resulting in calculated room temperature shelf-lives of 10–20 years. These results demonstrate that esters in alcohol solutions can be stabilized by the addition of CA. Significantly, CA also stabilizes lonapalene in PG-based ointments. The predicted room temperature shelf-lives for ointments with and without added CA are 11 and 66 years, respectively.

Comparisons between mixed PG/PC solution data and PG-based ointment data establish that lonapalene degrades by a common pathway (i.e., reaction with PG) in both reaction media. It is frequently the case that formulation development relies on kinetic data derived from model systems to design dosage forms with optimal drug stability. A well designed model system can often precisely and quantitatively predict drug stability in complex pharmaceutical formulations, as occurs for lonapalene. For this compound, model kinetic studies provided the insight needed to significantly improve the performance (in this case, the shelf-life) of the finished drug product.

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