Figure 2—*Rectangular parallelepiped having the dissolution rate constants* k_i, αk_i, *and* βk_i.

average dissolution rate constant, k_{ia} ($M = 1.0$, $\sigma = 0.5$, $p = 1.5$, $\alpha = 1.0$, and $\beta = 10.0$), and with isotropic behavior are presented in Table III. Both profiles are almost the same. The ratio of the time necessary for 50% dissolution is 1:0.95. This result implies that the evaluation of the dissolution for the acicular or flaky particles with nonisotropic behavior is roughly possible by means of Eq. 6 using the mean dissolution rate constant, k_{ia}, which may be obtained experimentally as described.

The basic assumptions behind the theory are that the constituent particles are rectangular parallelepipeds that are similar in shape and dissolve isotropically under sink conditions. In actual situations, more factors may affect the overall dissolution profiles such as deviation from the log-normal law, irregularity in shape, and differences in the diffusion barrier for each particle, none of which is easily available. But these factors do not prevent an understanding of particle-shape effects on drug dissolution profiles, since they normally act independently of the effects.

In practical terms, the sizes of acicular or flaky particles measured microscopically or by an automated counter tend to be larger than those available for the evaluation of their dissolution profiles since the microscopic method does not always give the smallest side length but gives a larger one and the automated counter method gives volume diameter.

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Autoxidation of Polysorbates

M. DONBROW ˣ, E. AZAZ, and A. PILLERSDORF

Abstract ◻ Aqueous solutions of polysorbate 20 undergo autoxidation on storage, with the peroxide number increasing and subsequently decreasing again, the acidity increasing continuously, the pH and surface tension falling and tending to level off, and the cloud point dropping sharply until turbidity begins at room temperature. The changes are accelerated by light, elevation of temperature, and a copper sulfate catalyst. At the same time, hydrolysis occurs, liberating lauric acid. Analysis of the alterations in these properties leads to the conclusion that hydrolysis has the major influence near room temperature and that oxyethylene undergoes chain shortening at temperatures above 40°. However, evidence of degradation is detectable even in previously unopened commercial samples of polysorbates 20, 40, and 60, warranting attention to the stability of and standards for these surfactants as compared with the solid alkyl ether type of nonionic surfactant.

Keyphrases ◻ Polysorbates, various—autoxidation on storage, effect of light, temperature, and copper sulfate ◻ Oxidation—various polysorbates on storage, effect of light, temperature, and copper sulfate ◻ Stability—various polysorbates, autoxidation on storage, effect of light, temperature, and copper sulfate ◻ Degradation—various polysorbates, autoxidation on storage, effect of light, temperature, and copper sulfate ◻ Surfactants—various polysorbates, autoxidation on storage, effect of light, temperature, and copper sulfate

In view of accumulating evidence of the ease of autoxidation of polyethylene glycols and polyoxyethylene fatty alcohol ethers (1–4), it was suspected that other nonionic surfactants might undergo a similar process. Information about such reactions could increase the understanding of drug instability in aqueous solutions containing nonionic surfactants (1, 3).

The only systematic investigation of autoxidation in nonionic surfactants was carried out on cetomacrogol (1, 2). Peroxides were formed and decomposed spontaneously at rates increasing with temperature and decreasing with surfactant concentration. Furthermore, the induction period for peroxide chain propagation was shortened by an increase of temperature, a reduction of pH, a copper sulfate catalyst. The period was also reduced by the addition of chemical initiators, such as hydrogen peroxide or partially oxidized surfactant, and by free radical-initiating processes, such as exposure to light or thermal treatment as in sterilization by autoclaving.

During storage, the pH and cloud point fell and the acid content rose while the surface tension characteristics changed drastically. Polyglycols exhibited parallel changes in peroxide and acid content and in pH after autoclaving. These changes were interpreted as showing that degradation occurred in the hydrophilic chain with progressive reduction of the oxyethylene content until the hydrophilic–lipophilic balance fell below the critical value for solubility in water, when phase separation of the surfactant occurred at room temperature.
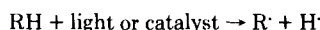
Since sorbitan derivatives are used widely, knowledge of their stability is important. Their behavior relative to the fatty alcohol ether type of surfactant may govern the choice between these two agents in a formulation. In the present work, the decomposition of polysorbate 20 (polyoxyethylene 20 sorbitan monolaurate) was studied systematically at controlled temperatures. The results are also

relevant to the stability of other polysorbates. Some data on the purity of polysorbates 40, 60, and 80 indicative of the state of commercial samples also are reported.

For comparison with cetomacrogol, the peroxide content, pH, and total acidity were measured as parameters of chemical decomposition; cloud point and surface tension were used as criteria of physical changes bearing on both the decomposition process and the possible failure of the surfactant as a solubilizer or emulsifier in a formulation.

THEORETICAL

Apart from peroxide formation, which might be expected to occur in all oxyethylene-containing materials under suitable conditions, the possibility of hydrolysis also must be considered in the polysorbate ester surfactants. The first process is a chain reaction analogous to the peroxidation of oils and ethers (5) and occurs by autoxidation reactions as shown in Schemes I and II:
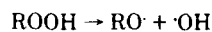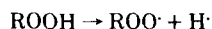
$$RH + light \text{ or } catalyst \rightarrow R\cdot + H\cdot$$
Scheme I—Initiation

$$R\cdot + O_2 \rightarrow ROO\cdot$$
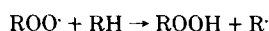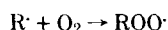
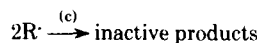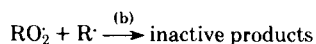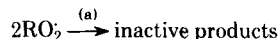$$ROO\cdot + RH \rightarrow ROOH + R\cdot$$
Scheme II—Propagation

Free radicals also may be formed by the processes in Scheme III and removed by those in Scheme IV:

$$ROOH \rightarrow ROO\cdot + H\cdot$$

$$ROOH \rightarrow RO\cdot + \cdot OH$$

$$2ROOH \rightarrow ROO\cdot + RO\cdot + H_2O$$
Scheme III

$$2RO_2\cdot \xrightarrow{(a)} inactive \text{ } products$$

$$RO_2\cdot + R\cdot \xrightarrow{(b)} inactive \text{ } products$$
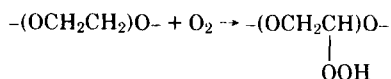
$$2R\cdot \xrightarrow{(c)} inactive \text{ } products$$
Scheme IV—Termination

On the basis that the peroxidation occurs in the hydrophilic chain in polyoxyethylene surfactants (1, 2), the initiation and propagation steps (Schemes I and II) yield hydroperoxides of the oxyethylene units according to Scheme V:

$$-(OCH_2CH_2)O- + O_2 \rightarrow -(OCH_2CH)O-$$
$$|$$
$$OOH$$
Scheme V

The hydroperoxide concentration is measured iodometrically in oils and polyglycol solutions, and results are expressed as the hydroperoxide equivalent to the iodine liberated in milliequivalents or millimoles per liter (5, 6). Recalculation with respect to the weight of material undergoing autoxidation gives the peroxide number (P.N.), expressed in milliequivalents per kilogram of surfactant (1, 5).

Peroxide Decomposition—Degradation of both hydroperoxides and peroxide free radicals may occur by a number of routes (7–10), as summarized elsewhere (11, 12). The peroxide formation rate during the initial stage of propagation is normally faster than that of its decomposition. The rates subsequently become equal, giving rise to a short plateau representing a temporary steady state, following which decomposition is the faster reaction. The analytical data give the residual peroxide content, which is determined by the rates of the various simultaneous reactions involved (8, 9); these reactions are temperature, concentration, and catalyst dependent in aqueous surfactant systems (1).

The typical kinetic pattern, showing the rise to the maximum P.N. value and then the fall, is a clear indication of autoxidation with degradation. The presence of more than minimal quantities of peroxide (P.N. > 5) signifies that autoxidation is underway and has probably passed the lag phase, but a low P.N. value may also be obtained if the decomposition
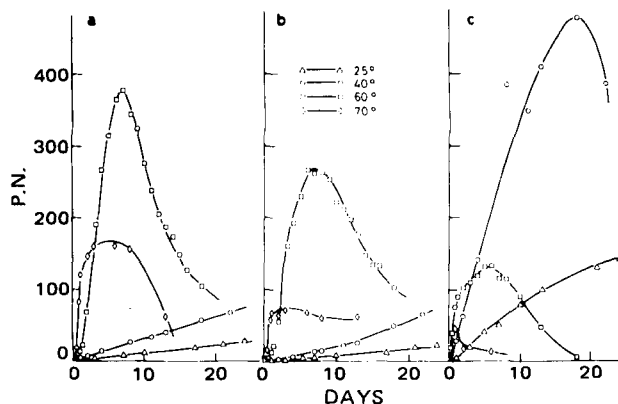

Figure 1—*Rate of peroxide formation in 3% aqueous polysorbate 20 at 70, 60, 40, and 25° in daylight (a), darkness (b), or daylight with 1 × 10^{-4} M copper sulfate catalyst (c). P.N. = peroxide number in milliequivalents per kilogram.*

rate is or has been high. Therefore, a low P.N. value is not in itself a criterion of nondegradation of the surfactant.

Surfactant Chain Degradation—Various chemical degradation products have been detected, including carbonyl compounds and acidic products (12), but no stoichiometric relationship with the degree of decomposition of the surfactant has been established. Acid formation is readily measured by the change in pH and the total acid content, and it is an important indicator of the extent of degradation and the quality of the surfactant (1, 12). Increased degradation leads to larger amounts of low molecular weight acids and, thus, a lower pH. The terminal hydroxyl groups are relatively stable compared with hydroperoxide and free radicals, requiring highly acidic conditions with strong oxidizing agents for their oxidation to terminal aldehydic and carboxylic groups.
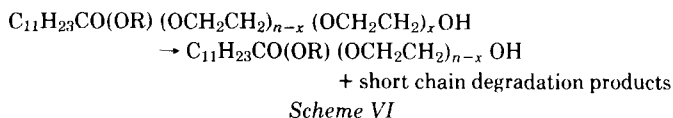
However, substitution of a hydroperoxide radical in the α- or β-position to the terminal hydroxyl leads to instability, which generally causes migration and/or C–C or C–O fission (9, 11, 12) with consequent formation of a two-carbon acid or formic acid, respectively. The latter has been identified as a degradation product (12).

In view of the complexity of the degradation reactions and the difficulty of performing separations quantitatively in dilute aqueous surfactant solutions, physical–chemical methods have particular importance. Surface tension–concentration curves enable measurement of changes in the critical micelle concentrations (CMC); furthermore, the sub-CMC slope is determined by the surfactant area per molecule at the air–liquid interface if the molecules are close packed. In the oxyethylene type of nonionic surfactant, the area per molecule at close packing is determined by the number of oxyethylene groups present in the molecule and is relatively independent of the hydrophobic group due to coiling of the polyglycol groups (13). The surface tension value above the CMC is relatively constant and is also a characteristic property, becoming progressively lower in a series based on the same hydrophobic group as the hydrophilic chain is shortened (2).

The cloud point of nonionic surfactants is the temperature at which turbidity appears on heating their aqueous solutions. It is related to the hydrophilic–lipophilic balance; in a series based on the same hydrophobic group, phase separation occurs at progressively lower temperature as the oxyethylene chain length is reduced (2), but the cloud point is also sensitive to the presence of additives (14).

Changes in surface tension and cloud point properties were used to establish that degradation occurred in the hydrophilic chain in cetomacrogol and to estimate the rate of loss of oxyethylene groups at 50° (2).

For polysorbate 20, chain breakdown may be represented as shown in Scheme VI:

$$C_{11}H_{23}CO(OR) (OCH_2CH_2)_{n-x} (OCH_2CH_2)_x OH$$
$$\rightarrow C_{11}H_{23}CO(OR) (OCH_2CH_2)_{n-x} OH$$
$$+ short \text{ } chain \text{ } degradation \text{ } products$$
Scheme VI

where R is the sorbitan ring, n is the number of oxyethylene groups originally present, and x is the number of oxyethylene groups peroxidized and subsequently degraded.

Hydrolysis of Polysorbate—Hydrolysis, which may be acid, base,

Table I—Peroxide Formation in Polysorbate 20 at Different Temperatures

Temper-ature	Conditions[a]	Induction Period[b], hr	Maximum[c] P.N., mEq/kg	Time of[c] Maximum P.N., days
70°	C + L	<2	50	1
	L	5.5	168	5
	D	—	75	2.5
60°	C + L	<2	130	5.5
	L	10	368	7
	D	—	268	7
40°	C + L	<5	440	17
	L	~50	(>70)	(>20)
	D	—	(>70)	(>20)
25°	C + L	<24	(>140)	(>25)
	L	144	(>70)	(>50)
	D	—	(>50)	(>50)

[a] C = catalyst (1 × 10⁻⁴ M CuSO₄), L = light, and D = dark. [b] Based on P.N. of 5 (1). [c] Numbers in parentheses indicate values at end of experiment before termination was reached.

or solvent catalyzed (15), would be expected to proceed at an increasing rate as the pH falls on formation of acidic degradation products, following the reaction in Scheme VII:

$C_{11}H_{23}CO(OR) (OCH_2CH_2)_n OH$

$\rightarrow C_{11}H_{23}COOH + H(OR) (OCH_2CH_2)_n OH$

Scheme VII
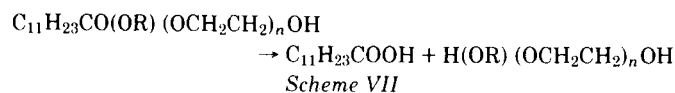
Of the products, lauric acid is stable and micelle soluble. The micelle saturation point would be determined by the increasing quantity of lauric acid and decreasing quantity of micelles, both functions of the hydrolysis rate, and also by changes in the micelle-solubilizing capacity as a result of chain shortening. The sorbitan polyglycol would pass out of the micellar phase, raising the aqueous concentration of hydrophilic solute progressively and possibly reducing the cloud point of the surfactant. It would be expected to undergo peroxidation and degradation by the reactions outlined for the parent surfactant; but since the process would occur outside the micellar phase, the rate constants and mechanism might not be identical with those of the polysorbate.

Turbidity in the solution could be the result of either lauric acid separation or reduction of the cloud point.

EXPERIMENTAL

Polysorbate 20 was neutralized before use to pH 6.00 with sodium hydroxide.

Autoxidation was effected under the same conditions as used previously in studies on cetomacrogol (1, 2). The method was designed to ensure adequate agitation and free access of air during storage, without loss of solvent by evaporation. Therefore, the oxygen concentration remained constant and was not rate limiting.

The acid content, pH, cloud point (1), and surface tension (2) were determined as described previously.

The peroxide number was determined using the spectrophotometric method developed for determining hydroperoxide in micellar solutions (6). Final readings were made at a concentration level of 1% polysorbate containing pH 6.00 buffer and potassium iodide at the same concentrations as described for cetomacrogol. Readings were taken at 360 nm (ε = 11,400) and were time independent in this system. Dilutions, when necessary, were made with solutions of 1% polysorbate 20; readings were corrected by deducting the amount of iodine liberated by the polysorbate content of the diluent. The polysorbate used as the diluent was stored under nitrogen and refrigerated.

RESULTS AND DISCUSSION

Development of Peroxides—The three stages of autoxidation—*viz.*, induction, propagation, and termination, were observed (Fig. 1). The peroxide number (P.N.) values at each stage varied with conditions but were comparable with those of cetomacrogol under parallel conditions (1).

Elevation of temperature from 25 to 70° reduced the induction period and raised the peroxide formation rate under all conditions. Copper sulfate and light had the expected catalytic effects, shortening induction and raising the peroxide formation rate relative to the dark uncatalyzed reaction. Pronounced catalysis of peroxide breakdown by the metal ions at 60 and 70° occurred (1, 3, 11), with a shorter time required to reach the
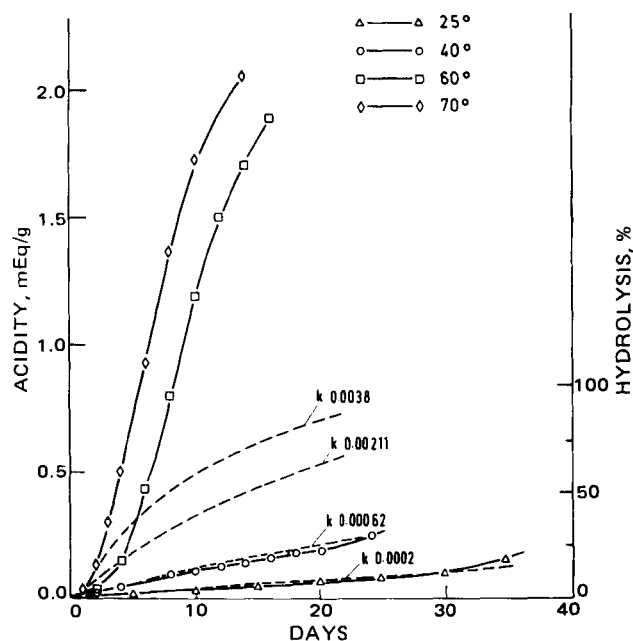

Figure 2—*Rate of acid formation in 3% aqueous polysorbate 20 at 70, 60, 40, and 25° in daylight with no catalyst. Broken lines represent lauric acid produced by hydrolysis and were calculated using the indicated values of* k *(hour⁻¹), the first-order hydrolysis constant, on both acidity and percent hydrolysis scales.*

maximum P.N. value and a lower value of P.N. obtained (Table I). Elevation of temperature also catalyzed the decomposition of peroxide.

Generally speaking, the greater the peroxide decomposition rate, the lower was the P.N. value at the termination stage, in which the degradation rate of the peroxides equaled or exceeded their formation rate. The enhancement of formation and decomposition rates by the temperature–catalyst combinations was such that termination was reached even at 40°; yet at this temperature, the rate balance brought about the highest P.N. value. Even at 25° with the catalyst, the P.N. rose to 150 within 25 days, and there was virtually no induction period (Fig. 1c).

pH and Acidity—As observed with cetomacrogol (1), the increase in acidity (Fig. 2) continued after the P.N. fell and was, therefore, the most reliable factor for following the degree of deterioration. The phenomenon of incessant increase in acidity in short chain polyglycols also was described by McKenzie (11). The rate of development of acidity had an inverse relation to the time of onset of propagation (Fig. 1a) and also to the initial rate of formation of peroxides.

The pH value approached 4.0 at 25 and 40°, whereas at 60 and 70° it fell rapidly and continuously to 2.5 (Fig. 3a). The relation between pH and acid concentration, c (Fig. 3b), indicated that the acids developed at the lower temperatures contained weaker functions. Log acid concentration–pH plots were linear at 40, 60, and 70° and tended to converge at high acidity. By use of the equation $pH = \frac{1}{2}(pKa + \log c)$, the intercepts at $\log c = 0$ enabled estimation of apparent pKa values[1], which were 3.6 ± 0.5 at 60 and 70° and 4.9 ± 0.8 at 40°.

These results suggest the presence of a larger fraction of stronger acids at the higher temperatures, which is consistent with greater rupture of the oxyethylene chains (Scheme VI). Indeed, in cetomacrogol, an ether for which hydrolysis is not to be expected, formic acid (pKa 3.75) constituted 50% or more of the acid formed during the initial stages of autoxidation under drastic conditions (12). The weaker acids present at 25° could be constituted of micelle-solubilized lauric acid (Scheme VII), carboxylated surfactant, or acetic acid (12).

The hydrolysis rate of polysorbate 80 was reported to be relatively constant and lowest between pH 3 and 7.6, increasing rapidly as a function of pH below 3 and above 7.6 (15). There was little difference between the hydrolysis rates of different polysorbate esters. To estimate the degree
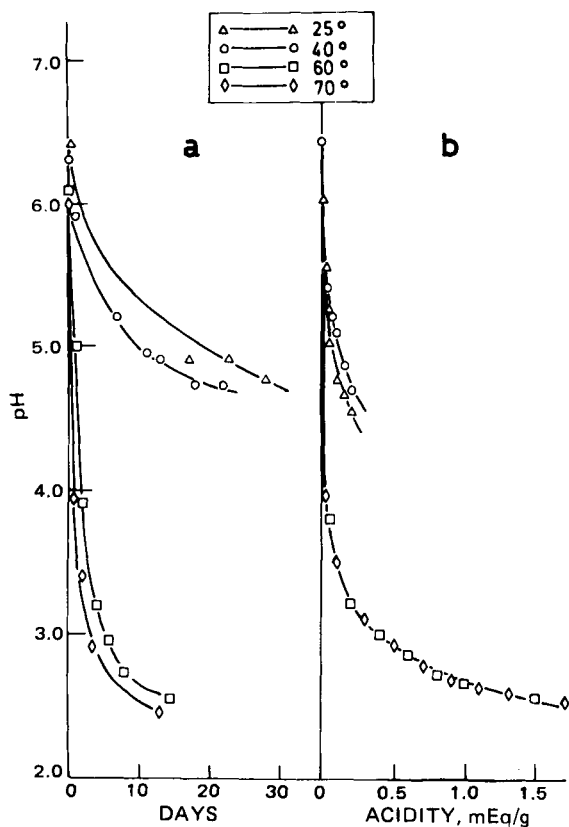
Figure 3—*The pH change of 3% aqueous polysorbate 20 at 70, 60, 40, and 25° in daylight with no catalyst, with time* (a), *and as a function of total acidity at the corresponding time* (b).

Figure 4—*Rate of change of surface tension, γ, of 3% aqueous polysorbate 20 at 70, 60, 40, and 25° in daylight with no catalyst. (Cetomacrogol, 3% aqueous solution at 50°, is shown for comparison.)*

of hydrolysis expected at the temperatures used in the present work, approximate rate constants, k, were calculated based on the rate constant reported for 0.02% polysorbate 80 at pH 3.95 and 80°, utilizing the reported energy of activation (15). This calculation gave k values of 3.80, 2.65, 1.21, and 0.62×10^{-3} hr^{-1} at 70, 60, 40, and 25°, respectively, and these values were used to calculate the respective quantities of lauric acid that would be yielded at various times.

Some of these results have been included in Fig. 2 for comparison. The values are of the same order as the observed acidities at 25 and 40°, although somewhat overestimated[2]; the curves are also similar in form. However, at 70 and 60°, the quantity of acid formed on storage after 3 and 6 days, respectively, greatly exceeded that expected theoretically from hydrolysis. Again, the upward curvature indicates a rate rising with time, as in cetomacrogol (1), characteristic of degradation processes of the chain-reaction type[3].

Surface Tension (γ) Changes—The surface tension above the CMC decreased on storage and ultimately reached a constant value (Fig. 4). The rate of fall of γ increased systematically with a temperature rise; the minimum values for $\gamma_{3\%}$ developed at 60 and 70° were lower than at 40 and 25° (about 28 and 30 dynes/cm, respectively). The rate was much greater than observed under parallel conditions in cetomacrogol (1); a typical result is included in Fig. 4. There was a rank correlation among the rates of fall of γ, increase of acidity, and fall in pH suggestive of an acidic reaction product increasing in quantity with temperature and influencing surface tension.

For the consideration of the hydrolysis of the fatty acid ester, temperature acceleration has already been discussed. The increasing quantity
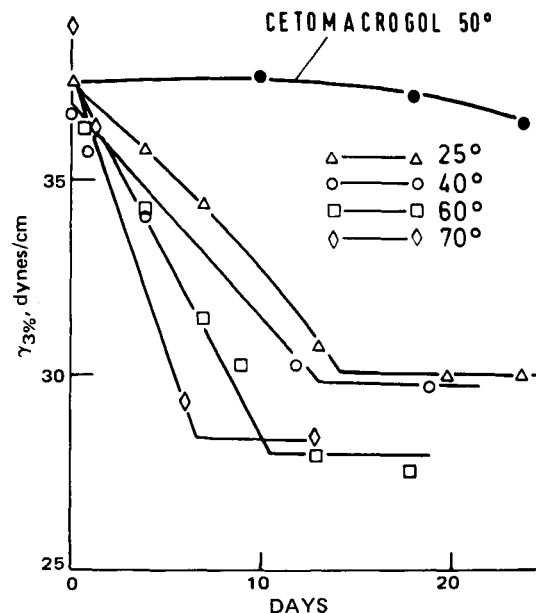
of hydrophobic lauric acid formed would be largely solubilized in the micelles. However, being in equilibrium with the surface, some acid would tend to be adsorbed there, forming a mixed surface film with the more hydrophilic surface-active monomers of the polysorbate. Mixed films are closer packed and are expected to give lower surface tension values than the separate amphiphiles (13). Confirmation that this was the probable explanation was obtained by measurement of the surface tensions of mixtures of lauric acid and polysorbate 20 (Fig. 5).

The $\gamma_{1\%}$ value of the polysorbate fell steeply and almost linearly as the lauric acid concentration was raised to about 2.2% (w/w) in polysorbate $[\Delta\gamma/\Delta c: \sim -3.1$ dynes/cm/1% (w/w) lauric acid in polysorbate or -61 dynes/cm/mEq of lauric acid/g of polysorbate]. Above 2.2% lauric acid (equivalent to about 10% hydrolysis of the polysorbate), the rate of fall decreased greatly to 0.32 dyne/cm/1% but remained approximately linear up to saturation concentration [9% (w/w) lauric acid, 0.45 mEq/g,
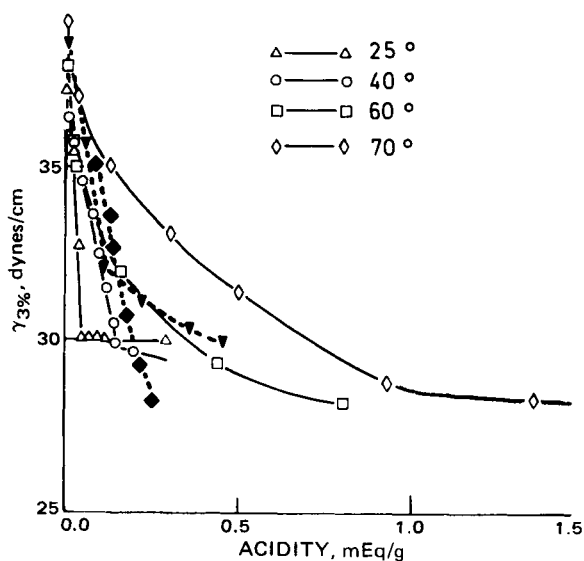

Figure 5—*Surface tension of 3% aqueous polysorbate 20 at 70, 60, 40, and 25° as a function of total acidity at the corresponding time. Broken lines represent surface tension of lauric acid solutions in polysorbate 20 (1% w/v), expressed as milliequivalents of lauric acid per gram of polysorbate (▼); and experimental surface tensions at 70° "corrected" for acidity due to autoxidation by plotting against hydrolyzed polysorbate at the corresponding time using k = 0.00211 hr^{-1} (♦).*

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[2] Hydrolysis rates are concentration dependent in acid solution, with the rate constant falling by some 60% at high surfactant concentration (15). This fact is the probable reason for the discrepancy; the 40 and 25° experimental acidities accord better when the estimated k values are reduced by some 60%, as do the acidities at 60 and 70° during the first 2 days (Fig. 2). A similar reduction of the rate constant at a high surfactant concentration also was observed for peroxide formation in cetomacrogol (1).

[3] The general picture and conclusions drawn would not be altered by the errors inherent in this treatment due to the approximated k values or to the possibility that the hydrolysis data on which they are based (15) are uncorrected for acids formed by autoxidation, which could be a serious source of error at 80°, particularly at low pH values.

Table II—Phase Separation Time as Measured by Surface Tension, γ, and Cloud Point

Temperature	Phase Separation Time, days	
	γ Constant	Cloud Point 59°
25°	14.5	12.5
40°	12–13	15.5
60°	10.5	11
70°	6.5	6

equivalent to about 50% hydrolysis; $\Delta\gamma$(total) = −9 dynes/cm approximately to saturation][4].

The γ–time curves of Fig. 4 are closely predictable by using selected values of the hydrolysis constants and estimating surface tensions from the data for the prepared mixtures corresponding to the amount of lauric acid formed at the time intervals, but they are highly sensitive to the k values selected. There was reasonable agreement on a γ–acidity scale (Fig. 5) between the lauric acid solubilizate curve and the experimental curves at the three lower temperatures initially, but the 70° curve deviated almost from the start and the 60° curve deviated at a later stage toward increased acidity at corresponding γ values; both fell ultimately to lower γ values than were accounted for by the lauric acid–polysorbate mixtures.

Degradation of the oxyethylene chains (Scheme VI) also would be expected to be temperature accelerated and, as noted, to give rise to short chain acids. The residual surfactant would have a lower hydrophilic–lipophilic balance and, hence, be preferentially adsorbed on the surface or from a mixed surface film, as described for lauric acid. Consequently, lowering of surface tension should also occur during degradation and was, in fact, demonstrated in cetomacrogol where a series of hexadecyl polyoxyethylene ethers was used to determine the degree of degradation (2, 13). One must assume that the γ values at 70 and 60° in particular reflect the added effects of hydrolysis and chain shortening in view of the pattern of acid formation noted earlier.
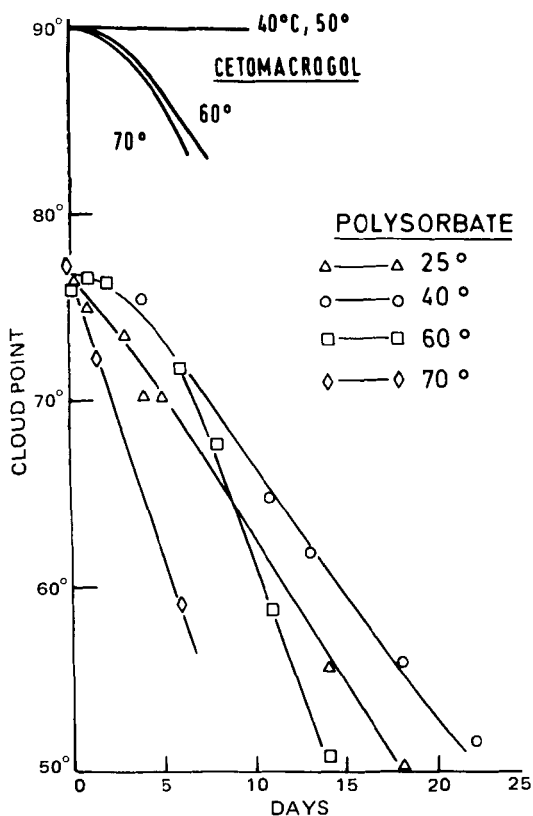

Figure 6—*Rate of change of cloud point of 3% aqueous polysorbate 20 at 70, 60, 40, and 25° in daylight with no catalyst, measured after addition of 1 M NaCl. (Cetomacrogol is shown for comparison.)*

This hypothesis was borne out by the γ–total acid plot (Fig. 5). At the higher temperatures, the acid content was greatly in excess of the amount of lauric acid that could be solubilized in the micelles, this excess acid being constituted of short chain autoxidation products that were probably not very surface active. To test this proposition, the total acid formed at 70° was "corrected," with γ being replotted against the amount of lauric acid formed hypothetically by hydrolysis on the basis that k was about 0.0021 hr^{-1}. This approach brought the curve more closely into line with the data for the lower temperatures and with the curve for the lauric acid–polysorbate mixtures. Thus, at low acid concentration, most of the acid formed at 25, 40, and 60° was accounted for by lauric acid; at 70° and at the higher acidities at 60°, the acids formed by autoxidation became predominant. At the same time, the sharper fall than expected of γ at the lowest temperatures may indicate that oxyethylene chain degradation occurs here as well.

The region of time independence of γ (Fig. 4) is explained by phase separation at room temperature, as evidenced by the appearance of cloudiness, with the nature and concentration of water-soluble surface-active species at the surface remaining virtually constant. Phase separations occurred earlier as the temperature was raised because of the accumulation of larger quantities of the hydrophobic products. At the same time, the higher terminal γ values at 40 and 25°, close to the lauric acid saturation γ value, imply that the main reaction was that of lauric acid formation. The greater surface activity at 60 and 70° was compatible with the summated effect of the two reactions.

Cloud Point—As in cetomacrogol (1, 2), the cloud point of polysorbate 20 solutions (3% containing 1 M NaCl) decreased during autoxidation (Fig. 6); but unlike in cetomacrogol, the rates of fall were not in rank order of temperature change. Results could not be determined accurately below 60° because of cloudiness appearing at room temperature (the cloudy phase partially dissolved on heating but interfered with observations). The turbidity stage corresponded fairly well to the time at which $\gamma_{3\%}$ reached a constant value at 70 and 60° but less closely at 40 and 25° (Table II).

The cloud point dropped unexpectedly rapidly at 25 and 40°, and room temperature turbidity appeared well within 15–20 days. Under comparable conditions, cetomacrogol exhibited little change in the cloud point at 50°, phase separation being evident only after 60 days of storage; even catalyzed solutions remained optically clear for some 30 days or more (2). At 60 and 70°, cetomacrogol ultimately exhibited a similar rate of fall of the cloud point to that of polysorbate, but there was a longer induction period (Fig. 6). These differences again point to the hydrolysis reaction as a probable explanation. Lauric acid will be taken almost entirely into the micelles up to saturation concentration, above which turbidity will appear at room temperature; warming will clarify the solution due to a solubility increase.

The phenomenon was studied in some depth for benzoic acid and a series of substituted phenols (14). Except for certain aliphatic hydrocarbons, most solubilizates lower the cloud point. The effect is not straightforward, however, being dependent on factors such as concentration, type of polar group present, and site of solubilization in the micelle (see references in 14). In the present work, saturation with lauric acid (90 mg/g of polysorbate) lowered the cloud point of 3% polysorbate to 59° and that of 3% cetomacrogol to 64° (150 mg of lauric acid/g of cetomacrogol).

The form of the 60° curve was deviant, showing a lag during the first 6 days and then falling more steeply; *i.e.*, the initial stage resembled 40°, and the later stage resembled 70°. To the extent that the cloud point fall in polysorbate is a function of polyglycol chain shortening, as demonstrated in cetomacrogol (2), the chain breakdown is presumed to occur *via* reactions of the hydroperoxides formed in the initial stages (Scheme V) and modified by acid catalysis (Figs. 7 and 8 in Ref. 1). The P.N. data (Fig. 1 and Table I) show that the peroxide stability was enhanced at 60° relative to 70°, which could explain the initial lag in chain breakdown at 60°. However, the absolute peroxide concentration increased greatly by the 7th day (P.N. 368), which would enhance the rate of reactions involving the peroxide species, and, indeed, the slope of the cloud point–time relation increased at the time corresponding to the peak P.N. value[5].

This time was also close to the time at which the pH drops below the critical value of 3 (15). Therefore, autocatalytic effects would also operate[5] here, as well as at 70°.

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[4] Cetomacrogol 1000 gave a similar picture [$\Delta\gamma/\Delta c$: ~ −1.9 dynes/cm/1% lauric acid up to 6% (w/w) lauric acid, after which the rate fell to −0.44 dyne/cm]. The total fall was about 12 dynes/cm because of higher lauric acid solubility [15% (w/w)].

[5] For example, with the assumption of a first-order dependence on the hydroperoxide concentration in decomposition reactions, the rate will follow equations of the type $dx/dt = k_t[H^+][P.N.]$, where k_t is the temperature-dependent rate constant and $k_{70} > k_{60} \gg k_{40} > k_{25}$.

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