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Solubility and Complexation Behavior of Griseofulvin in Fatty Acid–Isooctane Mixtures

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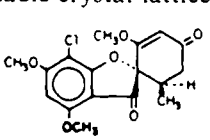
Abstract □ The influence of complex formation on the solubility behavior of griseofulvin in the straight-chain fatty acids was investigated by using phase solubility analysis in isooctane (2,2,4-trimethylpentane) at 25°C. The apparent molar solubility of the proton acceptor griseofulvin ($[A]_t$) was determined spectrophotometrically in the presence of various total molar concentrations ($[D]_t$) of each of the proton donors (acetic, propanoic, butanoic, hexanoic, and octanoic acids). Increasing $[D]_t$ caused a pronounced increase in $[A]_t$ according to a biphasic log-log relationship, suggesting the formation of two complexes, AD_m and AD_n. The data are in close agreement with a simple mathematical model which assumes that two complexes, AD_m and AD_n, are formed and that $[D]_t \approx 2[D_2]$, where D_2 refers to the fatty acid dimer. Linear regression analysis showed that the data best fit the complexation models with $n = 5$ or 6 and $m = 0$, 1, or 2, depending on the fatty acid. Assuming values of the dimerization constants of the fatty acids as reported in the literature, the stability constants of the complexes, K_n and K_m, were calculated and found to decrease with increasing chain length of the fatty acids. The proposed model was critically appraised. An alternative model, which takes into full account the fatty acid monomer while assuming that only one complex is formed, leads to unacceptable conclusions.

Keyphrases □ Molecular complexes—griseofulvin and straight-chain alkanoic acids, isooctane solution, solubility □ Carboxylic acid dimerization—influence on molecular complexation, griseofulvin and straight-chain fatty acids, isooctane solution □ Griseofulvin—solubility in isoocatane solution, straight-chain fatty acids

Complex formation, a valuable method for increasing the solubility, dissolution rate, and bioavailability of sparingly soluble drugs (1), also leads to a modification of the rate of transfer of certain drugs through lipid barriers (2). Griseofulvin (I) exhibits a poor bioavailability due to its low aqueous solubility (3). The stable crystal lattice of griseofulvin can, however, be broken down by proton-donating solvents, such as chloroform (4) and the fatty acids (5), which presumably form hydrogen-bonded complexes. Some of these complexes appear to exist in the solid state as solvates or inclusion compounds (6–8). Phenobarbital, a weak acid, also forms a solid complex with griseofulvin (9). Soluble complexes are formed between griseofulvin and phenols in carbon tetrachloride (10) and between certain steroidal drugs and organic solvents (11).



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The purpose of the present work is to investigate further the complexation of griseofulvin with the straight-chain alkanoic acids. The solubility method of Kostenbauder and Higuchi (12) was employed, and isooctane (2,2,4-trimethylpentane) was used as the inert solvent.

EXPERIMENTAL SECTION

Materials—Griseofulvin[1] was >99% pure, as described previously (5). Chloroform[2], acetic acid[3], *n*-butanoic acid[3], and *n*-octanoic acid[3] were reported to be >99% pure. Propanoic acid[4] and *n*-hexanoic acid[3] were distilled by using a glass apparatus. Isooctane (2,2,4-trimethylpentane)[4] was ≥99% pure.

Solubility Determinations—A mixture of griseofulvin (in excess of its solubility) and 5 mL of isooctane–fatty acid was shaken at 25.0 ± 0.05°C. Aliquots of 0.1–1.0 mL were diluted with chloroform, and the concentration of griseofulvin was determined (in duplicate) spectrophotometrically[5] at λ_{max} = 289.5 nm[6]. Saturation equilibrium was attained in <24 h. Each value (*e.g.*, $[A]_t$) is the mean of three separate determinations.

Analysis of the Solid Phases—A sample of the solid was removed from the equilibrated saturated solution, and the crystals were immediately placed on filter paper. The following methods of analysis were applied to all samples: X-ray diffraction (9), hot-stage microscopy (9), thermogravimetry (8), and

[1] ICI Ltd., Pharmaceuticals Division, Macclesfield, Cheshire, U.K.
[2] J.T. Baker Chemical Co.
[3] BDH Chemicals Ltd.
[4] Fisher Scientific Co. Ltd.
[5] Model PMQ II UV-visible spectrophotometer; Zeiss.
[6] Model 118 UV-visible spectrophotometer; Cary.

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Table I—UV Spectral Data of Griseofulvin in Various Solvents at 25°C

Solvent	$\lambda_{max,1}$, nm	ϵ_1, 10^3 M^{-1} cm^{-1}	$\lambda_{max,2}$, nm	ϵ_2, 10^3 M^{-1} cm^{-1}
Isooctane	248.5	13.3	317	2.71
Chloroform in isooctane (50% v/v)	289.0	16.5	321	5.03
Chloroform	289.5	23.8	321	5.30
Acetic acid	288.5	23.3	320	5.17
Propanoic acid	287.5	24.1	320	5.45
Butanoic acid	287.2	23.0	320	5.23
Hexanoic acid	287.0	19.4	319	5.07
Methanol[a]	291.0	24.1	324	5.47
Ethanol[b]	292.0	24.9	325	5.53

[a] From Ref. 13. [b] From Ref. 14.

Table II—Apparent Molar Solubility of Griseofulvin ($[A]_t$) in Isooctane Containing Various Total Molar Concentrations of Fatty Acids ($[D]_t$) at 25°C

Donor, % (v/v)	Acetic Acid		Propanoic Acid		Butanoic Acid		Hexanoic Acid		Octanoic Acid	
	$[D]_t$, M	$[A]_t$, M × 10^5	$[D]_t$, M	$[A]_t$, M × 10^5	$[D]_t$, M	$[A]_t$, M × 10^5	$[D]_t$, M	$[A]_t$, M × 10^5	$[D]_t$, M	$[A]_t$, M × 10^5
0	0	0.9358[a]	0	0.9358[a]	0	0.9358[a]	0	0.9358[a]	0	0.9358[a]
2	0.3476	2.7580	0.2605	2.6187	0.2095	1.5217	0.1632	2.3173	0.1271	2.7170
4	0.6952	6.2499	0.5146	4.5701	0.4168	2.8545	0.3121	3.2021	0.2533	3.6332
6	1.0428	9.6369	0.7708	7.2094	0.6191	4.5350	0.4648	4.1777	0.3794	4.8125
8	1.3904	17.922	1.0189	10.256	0.8241	7.0268	0.6297	6.2423	0.5062	5.5706
10	1.7380	26.807	1.2778	12.418	1.0211	9.4026	0.7839	7.7623	0.6280	7.1758
20	3.4759	185.35	2.6771	66.812	2.1798	29.339	1.5594	20.902	1.2338	12.631
30	5.2139	540.76	4.0173	117.21	3.2608	88.639	2.3478	43.084	1.8670	25.186
40	6.9519	1209.0	5.3612	302.02	4.3523	145.56	3.1179	77.581	2.4724	34.941
50	8.6898	2170.7	6.712	505.91	5.4329	249.86	3.9043	128.39	3.1073	53.863
60	10.428	3697.9	8.052	905.49	6.4994	424.78	4.6932	207.16	3.7195	80.505
70	12.166	5261.5	9.357	1491.1	7.5687	644.98	5.5410	319.74	4.3491	110.40
80	13.904	7675.9	10.658	2017.5	8.6098	976.96	6.3159	435.18	4.7815	138.99
90	15.642	10,349	12.023	3002.6	9.6715	1349.8	7.1204	622.85	5.5349	185.35
100	17.380	13,034	13.381	4160.5	10.826	1855.8	7.8545	858.98	6.1604	254.89

[a] The molar solubility of griseofulvin in pure isooctane ($[A]_0$) is 9.358 μM.

differential scanning calorimetry[7] (DSC). For DSC, a 2–3-mg sample was encapsulated and heated at a rate of 10 mcal·s^{-1}, with alumina as the reference material, helium as the gas phase, and indium as the calibrating standard. The data indicated that the samples removed from the saturated solutions were essentially unsolvated crystals of griseofulvin.

THEORETICAL SECTION

Griseofulvin (I) contains two keto groups, four ether oxygen atoms, and an aromatic ring, each of which can accept protons to form a hydrogen bond. Since griseofulvin has no proton-donating groups, it acts only as a proton acceptor, A.

Fatty acids act as proton donors, D. Since each acid molecule has only one proton, whereas griseofulvin has multiple acceptor sites, the total molar concentration of acid ($[D]_t$) and griseofulvin ($[A]_t$) in solution can be expressed by the following mass balance equations:

$$[A]_t = [A]_0 + [AD] + [AD_2] + [AD_3] + \ldots + [AD_z] \quad \text{(Eq. 1)}$$

$$[D]_t = [D] + 2[D]_2 + [AD] + 2[AD_2] + 3[AD_3] + \ldots + z[AD_z] \quad \text{(Eq. 2)}$$

where $[A]_0$ is the molar concentration of uncomplexed griseofulvin and is equal to the solubility in isooctane, $[AD_n]$ is the molar concentration of a complex of stoichiometric number n, $[D]$ is the molar concentration of fatty acid monomers, and $[D_2]$ is the molar concentration of fatty acid dimers.

If the standard state of each dissolved species (X) is assumed to be a hypothetical 1 M solution, which is assumed to behave as if it were infinitely dilute, then the activity of X, $\{X\}$, is given by:

$$\{X\} = \gamma_x[X] \quad \text{(Eq. 3)}$$

where γ_x is the molarity-based activity coefficient.

The formation of each complex can be represented as follows:

$$A + nD \rightleftharpoons AD_n \quad \text{(Eq. 4)}$$

$$\{AD_n\} = K_{1:n}\{A\}\{D\}^n \quad \text{(Eq. 5)}$$

$$[AD_n] = (K_{1:n}\{A\}\gamma_D^n/\gamma_{AD_n})[D]^n \quad \text{(Eq. 6)}$$

$$[AD_n] = K_n[D]^n \quad \text{(Eq. 7)}$$

where $K_{1:n}$ is the thermodynamic stability constant (based on activity), and K_n is the apparent stability constant (based on concentration), such that:

$$K_n = K_{1:n}\{A\}\gamma_D^n/\gamma_{AD_n} \quad \text{(Eq. 8)}$$

Dimerization of the fatty acid donor may be represented as:

$$2D \rightleftharpoons D_2 \quad \text{(Eq. 9)}$$

$$\{D_2\} = K_D\{D\}^2 \quad \text{(Eq. 10)}$$

$$[D_2] = (K_D\gamma_D^2/\gamma_{D_2})[D]^2 \quad \text{(Eq. 11)}$$

$$[D_2] = K_d[D]^2 \quad \text{(Eq. 12)}$$

where K_D is the thermodynamic dimerization constant (based on activity) and K_d is the apparent dimerization constant (based on concentration), such that:

$$K_d = K_D\gamma_D^2/\gamma_{D_2} \quad \text{(Eq. 13)}$$

Equations 7 and 12 can be combined as follows:

$$[AD_n] = (K_n/K_d^{n/2})[D_2]^{n/2} \quad \text{(Eq. 14)}$$

Two-Complex Model—If the two complexes, AD_m and AD_n, are present, Eq. 1 becomes:

$$[A]_t - [A]_0 = [AD_m] + [AD_n] \quad \text{(Eq. 15)}$$

$$= (K_m \cdot K_d^{-m/2})[D_2]^{m/2} + (K_n \cdot K_d^{-n/2})[D_2]^{n/2} \quad \text{(Eq. 16)}$$

whereas Eq. 2 becomes:

$$[D]_t = [D] + 2[D_2] + m[AD_m] + n[AD_n] \quad \text{(Eq. 17)}$$

Expressing $[D]$, $[AD_m]$, and $[AD_n]$ in terms of $[D_2]$ using Eqs. 12 and 14 affords:

$$[D]_t = K_d^{-1/2}[D_2]^{1/2} + 2[D_2] + (m \cdot K_m \cdot K_d^{-m/2})[D_2]^{m/2} + (n \cdot K_n \cdot K_d^{-n/2})[D_2]^{n/2} \quad \text{(Eq. 18)}$$

Two-Complex Model with Predominance of the Fatty Acid Dimer—In the presence of all but the lowest concentrations of fatty acid in a hydrocarbon

[7] DSC-2C differential scanning calorimeter; Perkin-Elmer.

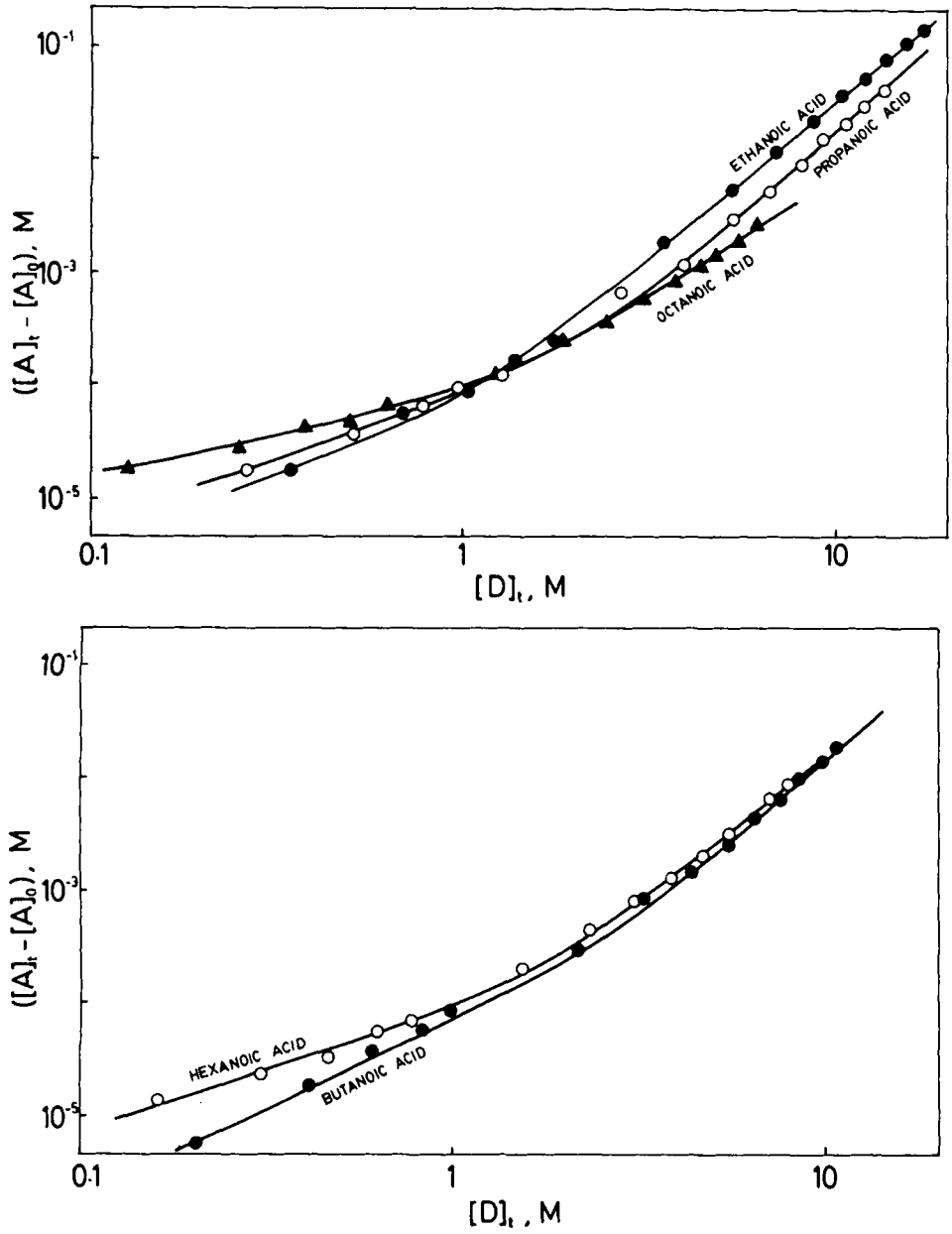

Figure 1—*Plots of log ([A]$_t$ − [A]$_0$) against log [D]$_t$, where ([A]$_t$ − [A]$_0$) is the increase in the apparent molar solubility of griseofulvin brought about by the presence of the following straight-chain alkanoic acids of total molar concentration, [D]$_t$, in isooctane at 25°C.*

solvent, $[D] \ll [D_2]$, because K_d in Eq. 12 has values of the order of 10^4 M^{-1}. Since the solubility of griseofulvin is always much smaller than the concentration of the fatty acid, $[AD_m] \ll [D_2]$ and $[AD_n] \ll [D_2]$. Equation 17 then simplifies to:

$$[D]_t \approx 2[D_2] \qquad \text{(Eq. 19)}$$

and Eq. 16 then becomes:

$$[A]_t - [A]_0 \approx (K_m \cdot K_d^{-m/2} \cdot 2^{-m/2})[D]_t^{m/2} + (K_n \cdot K_d^{-n/2} \cdot 2^{-n/2})[D]_t^{n/2} \qquad \text{(Eq. 20)}$$

Therefore:

$$[A]_t - [A]_0 \approx p[D]_t^{m/2} + q[D]_t^{n/2} \qquad \text{(Eq. 21)}$$

where:

$$p = K_m \cdot K_d^{-m/2} \cdot 2^{-m/2},\ q = K_n \cdot K_n^{-n/2} \cdot 2^{-n/2} \qquad \text{(Eq. 22)}$$

Therefore:

$$([A]_t - [A]_0)/[D]_t^{m/2} \approx p + q[D]_t^{(n-m)/2} \qquad \text{(Eq. 23)}$$

Thus, if two donor–acceptor complexes are present, $([A]_t - [A]_0)/[D]_t^{m/2}$ is expected to be a linear function of $[D]_t^{(n-m)/2}$. The slope q and intercept p afford the apparent stability constants, K_n and K_m, of the respective complexes, provided that the apparent dimerization constant, K_d, is known.

Single-Complex Model with Predominance of the Fatty Acid Dimer—If only one complex species, AD_m, is considered, Eqs. 1, 15, 20, and 21 reduce to:

$$[A]_t - [A]_0 = [AD_m] = (K_m \cdot K_d^{-m/2})[D_2]^{m/2} \qquad \text{(Eq. 24)}$$

$$\approx (K_m \cdot K_d^{-m/2} \cdot 2^{-m/2})[D]_t^{m/2} \qquad \text{(Eq. 25)}$$

$$[A]_t - [A]_0 \approx p[D]_t^{m/2} \qquad \text{(Eq. 26)}$$

The increase in solubility of the acceptor ($[A]_t - [A]_0$) is then expected to be proportional to the $m/2$ power of the total concentration of donor, $[D]_t^{m/2}$. The proportionality constant affords the apparent stability constant K_m of the complex if the apparent dimerization constant K_d is known. By taking logarithms, Eq. 26 yields:

$$\log([A]_t - [A]_0) \approx \log(K_m \cdot K_d^{-m/2} \cdot 2^{-m/2}) + (m/2) \cdot \log [D]_t \qquad \text{(Eq. 27)}$$

The linear regression of $\log([A]_t - [A]_0)$ against $\log [D]_t$ enables the stoichiometric number m of the complex to be determined from the regression coefficient (slope) and K_m to be determined from the intercept.

Single-Complex Model Allowing for all Donor Species Including the Monomer—Alternative models may be constructed which take into full account all species containing the fatty acid, including the monomer D. The approximate equation (Eq. 19) is clearly inappropriate here. For simplicity,

Table III—Linear Regression Analyses [a]

Donor	m	n	r [a]	$100s$ [b]	$10^5 p$	$10^5 q$
Acetic acid	0	4	0.9949	14.35	−385.3	42.49
	0	5	0.9997	3.52	−43.45	10.52
	0	6	0.9966	11.79	230.0	2.578
	1	5	0.9996	3.79	−19.16	10.55
	1	6	0.9957	12.04	72.56	28.88
	2	5	0.9992	4.45	−8.587	10.59
	2	6	0.9944	12.03	25.53	2.590
	3	5	0.9975	6.62	−3.732	10.63
	3	6	0.9932	10.84	11.57	2.540
	4	6	0.9806	11.27	8.597	2.166
Propanoic acid	0	5	0.9964	12.93	−67.64	6.127
	0	6	0.9997	3.75	9.529	1.723
	0	7	0.9976	10.54	74.26	0.4807
	1	5	0.9947	14.16	−21.82	6.070
	1	6	0.9996	4.14	10.78	1.724
	2	5	0.9906	16.18	−5.493	5.938
	2	6	0.9991	4.92	6.195	1.679
	3	5	0.9696	21.02	1.782	5.431
	3	6	0.9936	9.73	7.022	1.525
	4	6	0.5166	37.30	10.43	0.6557
Butanoic acid	0	5	0.9977	10.05	−21.91	4.695
	0	6	0.9997	3.44	13.51	1.470
	0	7	0.9964	12.60	43.25	0.4545
	1	5	0.9964	11.27	6.771	4.645
	1	6	0.9996	3.96	7.897	1.457
	2	5	0.9932	13.02	−0.6602	4.520
	2	6	0.9992	4.49	5.927	1.419
	3	5	0.9778	16.37	2.786	4.055
	3	6	0.9966	6.43	6.020	1.261
	4	6	0.5874	23.21	8.430	0.4527
Hexanoic acid	0	5	0.9976	9.99	−4.015	4.727
	0	6	0.9992	5.92	11.88	1.730
	0	7	0.9960	12.88	25.01	0.6289
	1	5	0.9968	10.17	0.7631	4.639
	1	6	0.9989	6.06	8.542	1.702
	2	5	0.9927	11.84	4.040	4.354
	2	6	0.9991	4.16	7.996	1.599
	3	5	0.8724	25.34	9.091	2.981
	3	6	0.9241	19.81	10.55	1.125
	4	6	−0.3866	15.91	19.78	−1.637
Octanoic acid	0	4	0.9963	10.97	−0.3622	6.254
	0	5	0.9988	6.32	6.168	2.597
	0	6	0.9941	13.79	11.38	1.068
	1	5	0.9988	5.03	6.301	2.468
	1	6	0.9940	11.13	9.047	1.017
	2	5	0.9781	12.01	8.879	1.906
	2	6	0.9905	7.92	10.04	0.7977
	3	5	−0.3132	53.17	17.64	−1.175
	3	6	−0.2141	54.69	16.30	−0.3239
	4	6	−0.5381	129.36	37.30	−7.222

[a] Linear regression analysis of $([A]_t - [A]_0)/[D]^{m/2} = p + q[D]_t^{(n-m)/2}$ corresponding to the formation of two complexes of stoichiometry AD_m and AD_n, where $[D]_t$ is the total molar concentration of donor fatty acid in isooctane and $([A]_t - [A]_0)$ is the increase in the apparent molar solubility of the acceptor, griseofulvin, brought about by the presence of the donor in isooctane solution. It is assumed here that $[D_2] \approx 2[D]_t$. [b] Residual standard deviation per mean value of $([A]_t - [A]_0)[D]_t^{-m/2}$.

only one complex, AD_n, may be assumed, in which case the third term on the right in each equation (Eqs. 17 and 18) is ignored, so that:

$$[D]_t = K_d^{-1/2}[D_2]^{1/2} + 2[D_2] + (n \cdot K_n \cdot K_d^{-n/2})[D_2]^{n/2} \quad \text{(Eq. 28)}$$

Equation 24 is applied to AD_n instead of AD_m; thus:

$$[A]_t - [A]_0 = (K_n \cdot K_d^{-n/2})[D_2]^{n/2} \quad \text{(Eq. 29)}$$

Eliminating $[D_2]$ from Eqs. 28 and 29 affords:

$$[D]_t = c_1([A]_t - [A]_0)^{1/n} + c_2([A]_t - [A]_0)^{2/n} + n([A]_t - [A]_0) \quad \text{(Eq. 30)}$$

where:

$$c_1 = K_n^{-1/n} \text{ and } c_2 = 2K_n^{-1/n} \cdot K_d^{1/2} \quad \text{(Eq. 31)}$$

Rearranging Eq. 30 into a form suitable for linear regression analysis, we obtain:

$$\frac{[D]_t - n([A]_t - [A]_0)}{([A]_t - [A]_0)^{1/n}} = c_1 + c_2([A]_t - [A]_0)^{1/n} \quad \text{(Eq. 32)}$$

where c_1 is the intercept, and c_2 is the slope. This model, if valid, enables both the stability constant (K_n) and the dimerization constant (K_d) to be calculated directly from the intercept and the slope. Thus, from Eq. 31, we obtain:

$$K_n = (c_1)^{-n}, \quad K_d = (c_2/2c_1)^2 \quad \text{(Eq. 33)}$$

RESULTS AND DISCUSSION

UV Spectra and the Nature of the Griseofulvin–Fatty Acid Interactions—The choice of chloroform as the spectrophotometric solvent for the determination of dissolved griseofulvin was based on the UV absorption[6] data presented in Table I. Griseofulvin gave a high molar absorptivity which was unaffected by the presence of small amounts of fatty acids or isooctane. However, to measure the very low solubility of griseofulvin in isooctane alone, dilution with an equal volume of chloroform was preferable to optimize sensitivity and accuracy. In each determination, the linear (Beer's law) region of the appropriate absorbance–concentration calibration was employed.

Proton-donating solvents cause small but consistent red shifts to the UV spectrum of griseofulvin and increase the molar absorptivities about twofold, as compared with the noninteractive solvent, isooctane (Table I). These transitions are therefore $\pi \rightarrow \pi^*$ (15) and suggest that each protic solvent forms a hydrogen-bonded complex with the lone pair of electrons on the ether oxygen atom and/or the carbonyl oxygen atom, all of which are conjugated with the π electrons in an unsaturated or aromatic center in the griseofulvin molecule (I).

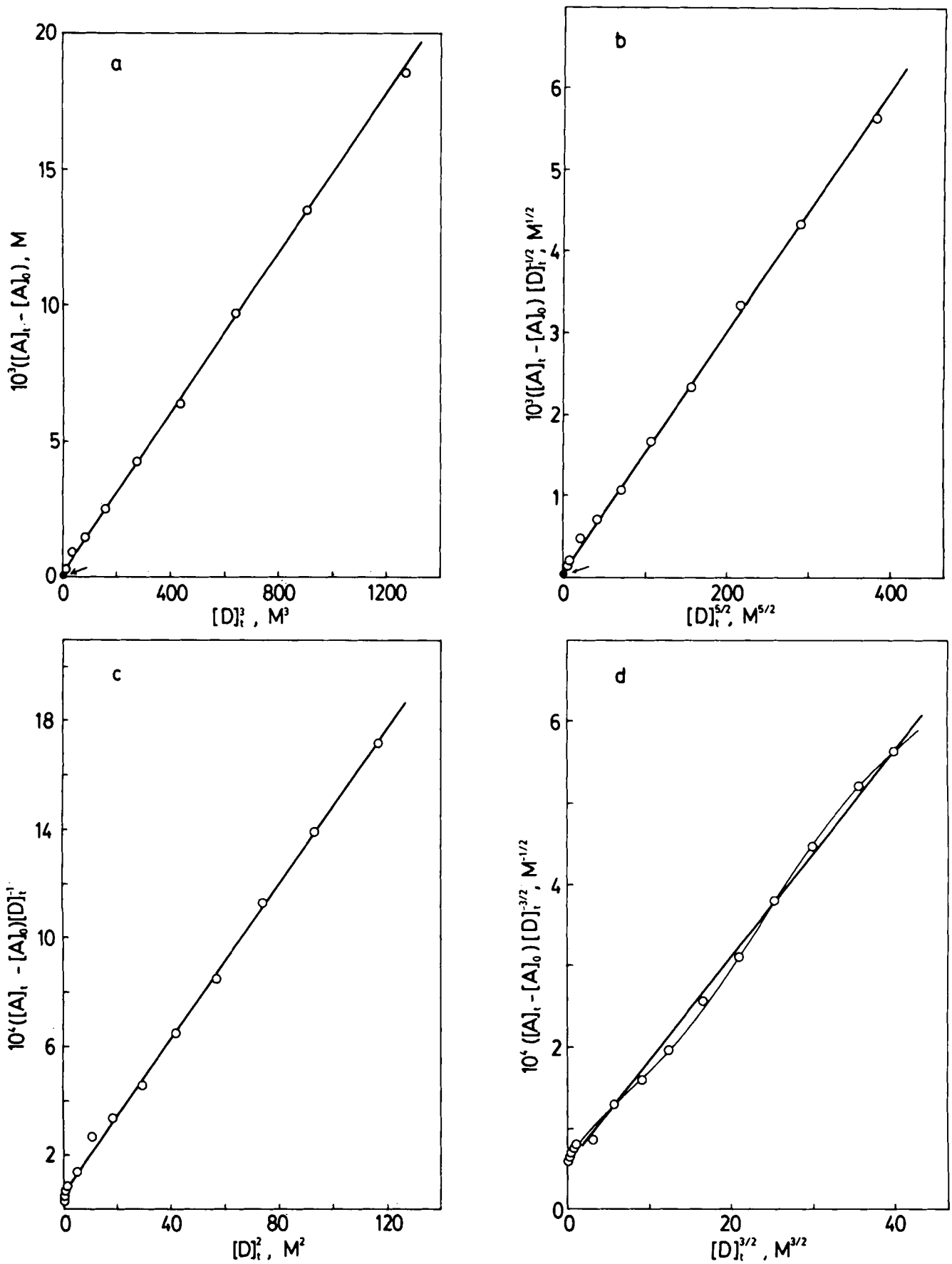

Figure 2—*Plots of various functions of* $([A]_t - [A]_0)$ *and* $[D]_t$, *where* $([A]_t - [A]_0)$ *is the increase in the apparent molar solubility of griseofulvin brought about by the presence of butanoic acid of total molar concentration* $[D]_t$, *in isooctane at 25°C. These plots correspond to linear regressions assuming the formation of the following complexes: (a)* AD_6 *alone; (b)* AD *and* AD_6; *(c)* AD_2 *and* AD_6; *(d)* AD_3 *and* AD_6.

Table IV—Stability Constants of Each of the Two Complexes Whose Stoichiometries Provide the Best Fit to the Solubility Data of Griseofulvin (A)[a]

Fatty Acid	K_d, M^{-1}	AD_m	K_m (Molarity Based)	AD_n	K_n (Molarity Based)
Acetic acid	37000[c]	AD	Very small[d]	AD_5	1.57×10^8
Propanoic acid	12000[b]	AD	0.0167	AD_6	2.38×10^8
Butanoic acid	9000[e]	AD	0.0106	AD_6	8.49×10^7
Hexanoic acid	6000[e]	AD_2	0.959	AD_6	2.76×10^7
Octanoic acid	5800[c]	AD	0.0068	AD_5	3.58×10^5

[a] In isooctane containing various concentrations of several fatty acids at 25°C. [b] Dimerization constant in cyclohexane at 25°C (from Ref. 19) is assumed to represent the corresponding value in isooctane at 25°C. [c] Dimerization constant in heptane at 23°C and 30°C (from Refs. 17 and 18) are assumed to represent the corresponding values in isooctane at 25°C. [d] Cannot be estimated from the negative intercept. [e] Determined by interpolation of the K_d values from Refs. 17–20.

Determination of the Stoichiometry of the Complexes—Table II presents the solubility data. The apparent molar solubility of griseofulvin in isooctane ($[A]_t$) increases rapidly with increasing molar concentrations of each acidic donor ($[D]_t$) from the value in isooctane, $[A]_0 = 9.358\ \mu M$. Plots of the logarithm of the increase in molar solubility, $\log([A]_t - [A]_0)$, against $\log [D]_t$ in Fig. 1 show two approximately linear regions: at $[D]_t < \sim 1$ M and at $[D]_t > \sim 2$ M. Each of these linear regions may be attributed to a complex between A and D, *e.g.*, AD_m or AD_n, according to Eq. 27. Regression analysis of the linear regions in Fig. 1 indicates high correlation coefficients ($r \geq 0.99$) and small residual standard deviations ($s < 1\%$). From each slope in Fig. 1, approximate values of the stoichiometric number, m or n, of fatty acid (D) molecules in each complex were calculated. Reference to Eq. 21 suggests that this is possible if m and n differ sufficiently such that at low $[D]_t$, the $[D]_t^{n/2}$ term is relatively small, whereas at high $[D]_t$, the $[D]_t^{m/2}$ term is relatively insignificant. Estimated stoichiometries are $m \simeq 1.7$–3.3 and $n \simeq 4.5$–5.9, depending on the fatty acid. However, the approximate nature of this treatment should be emphasized, especially with regard to the estimates of m for the lower-order complexes.

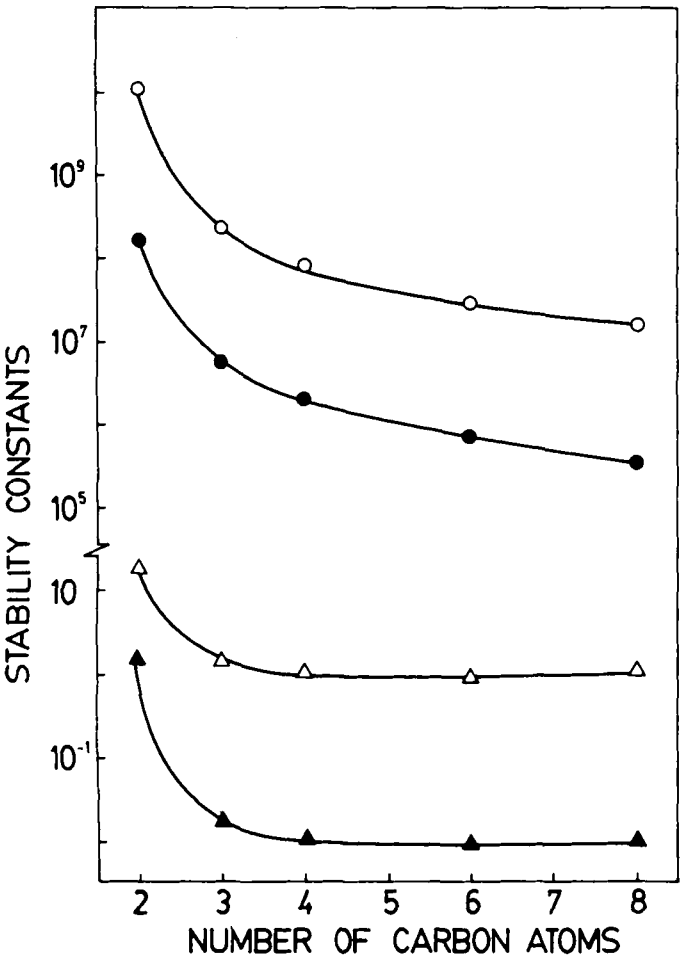

Figure 3—*Influence of the chain length of various straight-chain alkanoic acids on the molarity-based stability constants* K *of their complexes with griseofulvin. Key: (▲)* K_1 *for* AD *with* AD_6; *(△)* K_2 *for* AD_2 *with* AD_6; *(●)* K_5 *for* AD_5 *with* AD; *(○)* K_6 *for* AD_6 *with* AD.

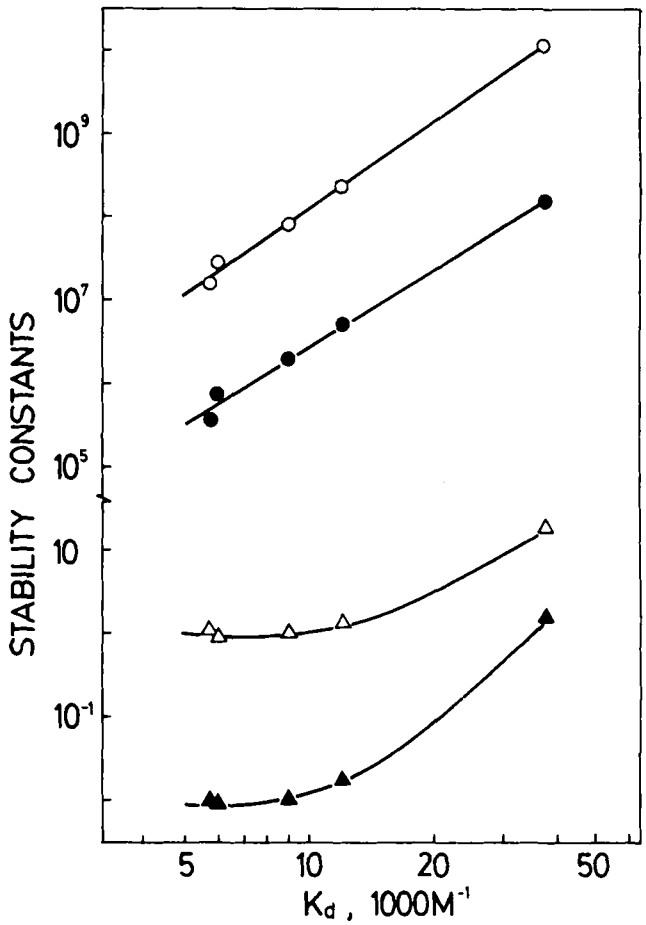

Figure 4—*Logarithmic relationships between the molarity-based dimerization constants* K_d *of various straight-chain alkanoic acids and the molarity-based stability constants* K *of their complexes* AD_n *with griseofulvin. Key: (▲)* K_1 *for* AD *with* AD_6; *(△)* K_2 *for* AD_2 *with* AD_6; *(●)* K_5 *for* AD_5 *with* AD; *(○)* K_6 *for* AD_6 *with* AD.

By using the approximate values of m and n as a guide, the solubility data were reanalyzed in terms of two stoichiometric complexes, AD_m and AD_n, by means of linear regressions represented by Eq. 23 (Table III). For this purpose, various probable and possible complexation models were assumed, with each corresponding to a certain pair of integral m and n values of greater or smaller magnitude than the approximate quantities, and the fatty acid dimers were generally assumed to predominate over all other species. For each acidic donor, the statistically most probable model (or pair of m and n values) corresponds to the linear regression with the highest correlation coefficient and the lowest residual standard deviation. Table III shows that these models are (m, n) 0,5 for acetic acid; 0,6 for propanoic and butanoic acids; 0,6 or 2,6 for hexanoic acid; and 1,5 for octanoic acid. When, however, the linear regressions were plotted (Fig. 2) for butanoic acid, the models for which $m = 0$ gave points that were crowded together at low $[D]_t$ and widely separated at high $[D]_t$ (Fig. 2a), whereas the models for which $m = 1$ or 2 gave points which were better separated (Fig. 2b–d). Therefore, the statistics of linear regression may be misleading at low $[D]_t$. Furthermore, the log-log plots in Fig. 1 clearly show two approximately linear regions, indicating $m > 0$. If, however, a value of m is selected that is too high, the correlation deteriorates (as shown by r and s in Table III), and the experimental points follow a sigmoidal curve on either side of the regression line. This is apparent in the case of the 3,6 model for butanoic acid (Fig. 2d) and is beginning to show in the 2,6 model (Fig. 2c). Bearing in mind all of these considerations, the preferred models (AD_m, AD_n) for each fatty acid donor with griseofulvin are summarized in Table IV.

To calculate the stability constants K_m and K_n of the complexes (Table IV) from the intercept (p) and slope (q) of each linear regression (Eqs. 20–22), the dimerization constant (K_d) of the fatty acid donor must be known.

Table V—Linear Regression Analyses [a]

Donor	n	r	$100s$ [b]	c_1	c_2	c_1^{-n} [c]	$c_2/2c_1^2$ [d]
Acetic acid	4	0.9702	10.08	7.12	36.97	3.9×10^{-4}	6.7
	5	0.9938	5.85	0.845	37.04	2.3	480
	6	0.9987	3.01	−3.06	36.58	1.2×10^{-3}	36
	7	0.9985	3.45	−6.00	36.46	-3.6×10^{-6}	9.2
	8	0.9967	5.37	−8.46	36.69	3.8×10^{-8}	4.7
	9	0.9945	7.19	−10.64	37.18	-5.7×10^{-10}	3.1
Propanoic acid	5	0.9808	11.28	−1.52	54.01	-1.2×10^{-1}	314
	6	0.9933	7.29	−5.36	49.01	4.2×10^{-5}	21
	7	0.9977	4.54	−8.21	46.26	-4.0×10^{-7}	8.5
	8	0.9988	3.41	−10.59	44.81	6.3×10^{-9}	4.9
	9	0.9985	3.89	−12.70	44.18	-1.2×10^{-10}	3.3
Butanoic acid	5	0.9892	8.71	−2.51	62.31	-1.0×10^{-2}	153
	6	0.9966	5.32	−5.85	53.32	2.5×10^{-5}	20
	7	0.9980	4.28	−8.26	48.33	-3.8×10^{-7}	8.5
	8	0.9972	5.29	−10.25	45.44	8.2×10^{-9}	4.9
	9	0.9956	6.87	−11.99	43.79	-1.9×10^{-10}	3.3
Hexanoic acid	5	0.9901	8.81	−4.73	69.30	-4.2×10^{-4}	54
	6	0.9973	4.96	−7.38	56.49	6.2×10^{-6}	14
	7	0.9993	2.63	−9.33	49.62	-1.6×10^{-7}	7.1
	8	0.9993	2.69	−10.95	45.66	4.8×10^{-9}	4.3
	9	0.9985	4.08	−12.41	43.30	-1.4×10^{-10}	3.0
Octanoic acid	4	0.9840	11.21	−7.26	168.08	3.6×10^{-4}	134
	5	0.9951	6.72	−10.47	106.26	-8.0×10^{-6}	26
	6	0.9983	4.13	−12.38	80.23	2.8×10^{-7}	11
	7	0.9988	3.58	−13.88	66.97	-1.0×10^{-8}	5.8
	8	0.9983	4.43	−15.22	59.42	3.5×10^{-10}	3.8
	9	0.9975	5.58	−16.48	54.83	-1.1×10^{-10}	2.8

[a] Linear regression analysis of $\{[D]_t - n([A]_t - [A]_0)\}([A]_t - [A]_0)^{-1/n} = c_1 + c_2([A]_t - [A]_0)^{1/n}$ corresponding to the single complex model allowing for all donor species, including the monomer, where $[D]_t$ is the total molar concentration of donor fatty acid in isooctane, and $[A]_t - [A]_0$ is the increase in the apparent molar solubility of the acceptor, griseofulvin, brought about by the presence of the donor in isooctane solution at 25°C. The single complex is represented by AD_n, where n corresponds to the stoichiometric number. [b] Residual standard deviation per mean value of ordinate. [c] $c_1^{-n} = K_n$, the stability constant of AD_n, if the model is correct. [d] $c_2/2c_1^2 = K_d$, the dimerization constant of D, if the model is correct.

Dimerization Constants of the Fatty Acid Donors—Equilibrium constants for hydrogen bonding, such as K_d, are usually largest in solvents of the saturated hydrocarbon type and do not differ much from one solvent to another within this group (16). They are not very dependent on temperature within a few degrees, because the negative enthalpies of hydrogen bonding are relatively small (<40 kJ·mol^{-1}, *i.e.*, <10 kcal·mol^{-1}). Consequently, the values of K_d for acetic, propanoic, and octanoic acids were taken to be the corresponding values in heptane and cyclohexane (17–19), whereas those for butanoic and hexanoic acids were obtained by interpolating the available data for six *n*-alkanoic acids (17–20) in these hydrocarbons (Table IV).

Although these values of K_d and the stability constants K_m and K_n (which are calculated from K_d and from the respective experimental quantities p and q) are only approximate (Table IV), the approximations will not affect the stoichiometry of complexation, since they are applied after the statistically favored complexation model has been selected from Table III.

Stability Constants of the Complexes—The stability constants of the various complexes plotted on a $\log_{10}$ scale against the chain length of the fatty acids are presented in Fig. 3. For the lower-order complexes AD and AD_2, the stability constants K_1 and K_2 are influenced by the stoichiometry of the accompanying higher-order complex and, for the purposes of comparison in Fig. 3, were calculated for the 1,6 and 2,6 models to form a self-consistent series. The values of K_1 and K_2 are, respectively, of the order 10^{-2}–10^{-1} M^{-1} and 1–10 M^{-2}, which are so small as to be accounted for by nonspecific, nonhydrogen-bonding interactions between D and A (21, 22). Values of $K_1 < \sim 1$ M^{-1} may be expected in nonbonding situations on a purely statistical analysis of the nearest neighbors (23, 24). K_1 and K_2 are preferably regarded as empirical quantities, reflecting an enhancement of the solubility of griseofulvin in isooctane by the presence of low concentrations of fatty acids interacting nonspecifically.

K_1 and K_2 are relatively independent of the chain length of the donor from propanoic to octanoic acid. The relatively high values of K_1 and K_2 for acetic acid may arise from deficiencies in the model, as reflected by the negative values of p, which have no physical meaning. The dimerization constants (K_d) also show relatively little dependence on the alkyl chain length (Table IV). Evidently, the flexible hydrocarbon chain has little effect on the stability of the smaller species (D_2, AD, or AD_2) derived from the fatty acids.

For the higher-order complexes AD_5 and AD_6, the values of the constants K_5 and K_6 are insensitive to the stoichiometry of the accompanying lower-order complex (AD_2, AD, or none) and are large, indicating powerful interactions between the fatty acids and griseofulvin. This reflects the strength of the donor and acceptor species and perhaps also the cooperative nature of hydrogen bonding. Griseofulvin has six obvious acceptor sites. The favored stoichiometries of the higher-order complexes suggest that these sites are saturated in AD_6 and not fully saturated in AD_5. Saturation of acceptor sites is probably accompanied by steric crowding, since K_6 decreases markedly with an increasing number of carbon atoms of the donor. This also reflects the increasing disruptive effect of the flexible hydrocarbon chain on the stability of the complex. The effect on K_5 is less pronounced, probably because one fewer acceptor site is occupied, thereby reducing the crowding and disruptive influences of the longer chains of the donor.

The concepts described above also explain why the relationships between $\log_{10} K_m$ or $\log_{10} K_n$ and the number of carbon atoms are not linear, as might be expected if a linear free energy relationship were obeyed (25). The gradient of the tangent to the curves in Fig. 3 represents the methylene-group contribution of the donor to the standard free energy of complexation; thus:

$$\Delta G_n^\theta = -RT \cdot \ln K_n \qquad \text{(Eq. 34)}$$

This contribution is not constant but decreases with increasing number of carbon atoms, reflecting the increasing disturbance to the griseofulvin–carboxyl group interactions by the longer hydrocarbon chains and perhaps the partial replacement of these interactions by weaker dispersion forces between the hydrocarbon chains and griseofulvin (5).

The statistically favored stoichiometry of the higher-order complex (Tables III and IV) for propanoic, butanoic, and hexanoic acids is AD_6; for octanoic acid it is AD_5, reflecting the steric crowding resulting from the larger size of the donor molecule in the latter case. The favored AD_5 stoichiometry for acetic acid is unexpected and is attributed tentatively to variations in the activity coefficients (γ in Eqs. 6, 8, 11, and 13), which are assumed to be constant.

In Fig. 4 are shown distinct linear free energy relationships between $\log_{10} K_5$ and $\log_{10} K_d$ and between $\log_{10} K_6$ and $\log_{10} K_d$. The linearity of these plots might result from the fact that the stability constants were calculated from K_d by Eq. 22. However, K_1 and K_2 were also calculated from K_d, but nonlinear relationships are found between their logarithms and $\log_{10} K_d$. Therefore, we suggest that the linear relationships between $\log_{10} K_6$ and $\log_{10} K_d$ and between $\log_{10} K_5$ and $\log_{10} K_d$ arise from the similarities of the intermolecular interactions, namely, hydrogen bonding, between D and A in the complexes AD_5 and AD_6 and between two fatty acid molecules in the dimer D_2. On the other hand, the nonlinearity of the relationships involving $\log_{10} K_1$, $\log_{10} K_2$, and $\log_{10} K_d$ probably reflect nonspecific interactions between A and D, in contrast to the specific interactions in the dimer.

Poor correlations are, however, found between $\log_{10} K_5$, $\log_{10} K_6$, $\log_{10} K_2$, $\log_{10} K_1$, and $\log_{10} K_d$, on the one hand, and the pK_a of the fatty acids (26) on the other hand. This is not unexpected, since ionization involves different intermolecular effects than interactions of the donor–acceptor type between D and A and two D molecules.

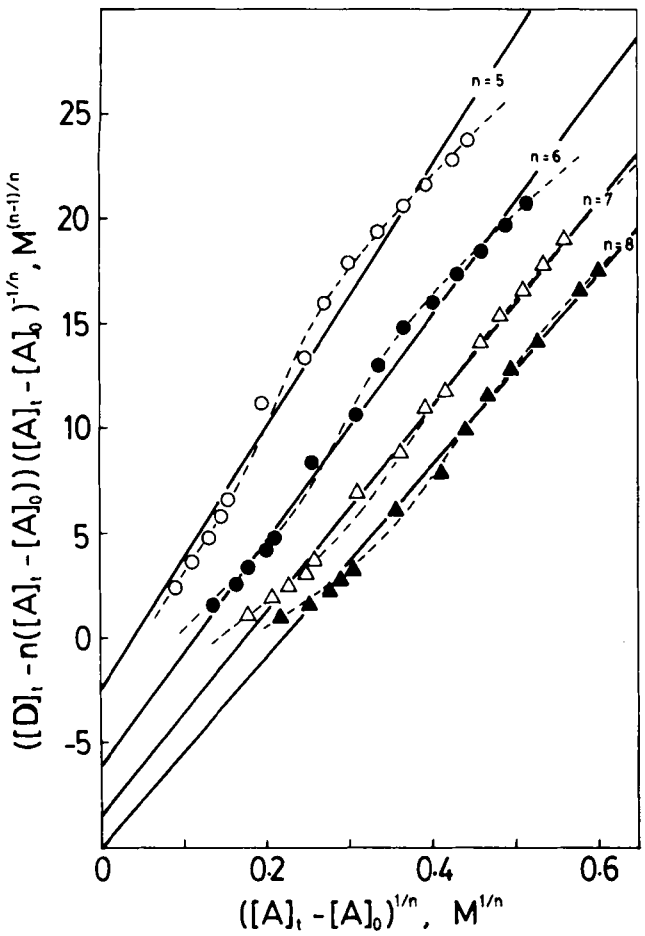

Figure 5—*Plots of* $\{[D]_t - n([A]_t - [A]_0)\}\{[A]_t - [A]_0\}^{-1/n}$ *against* $([A]_t - [A]_0)^{1/n}$, *corresponding to the single complex model allowing for all donor species, including the monomer. The stoichiometric number,* n, *of the single complex,* AD_n, *is as follows:* (○) n = 5; (●) n = 6; (△) n = 7; (▲) n = 8.

Critical Appraisal of the Proposed Models—The solubility behavior of griseofulvin in fatty acid–isooctane mixtures appears to conform to simple donor-acceptor models involving one or two complexes, AD_m and AD_n, which are summarized by Eqs. 20–27. These models are based on the following major assumptions: (*a*) the activity coefficient (γ) of each dissolved species (*e.g.*, in Eqs. 6, 8, 11, and 13) is constant and independent of the concentration terms, particularly $[D]_t$; (*b*) the activity of the solid which is in equilibrium with every saturated solution consisting of each fatty acid and isooctane (*e.g.*, in Eqs. 5, 6, and 8) is a constant equal to the activity of pure griseofulvin $\{A\}$; (*c*) the total amount of fatty acid is present almost exclusively as the dimer according to Eq. 19.

The assumption of constant activity coefficients becomes less reliable with increasing $[D]_t$, and the deviations become increasingly positive. In other words, with increasing concentrations of the highly polar fatty acid molecules in nonpolar isooctane solution, their activity or escaping tendency probably increases more rapidly than their concentration increases. Thus, although AD_6 is probably, for structural reasons, the real activity-based stoichiometry for the lower straight-chain alkanoic acids (C_2–C_6) as donors, the concentration-based stoichiometric number of D derived from the statistical treatment may be slightly less than the integral values of 6, as seen in Table III. When, however, acetic acid is present as the donor at volume fractions >60%, its molar concentration (>10 M; Table II) is so high that very large positive deviations from the ideal laws are expected, and the concentration-based stoichiometry which emerges from the statistical treatment is apparently AD_5 (Table III). The positive deviations, corresponding to $\gamma > 1$, may simply account for the negative values of p, which occur most commonly with acetic acid (Table III).

The activity of solid griseofulvin ($\{A\}$) depends on the nature of the solid phase which is in equilibrium with the saturated solution. When griseofulvin is allowed to crystallize from supersaturated solutions in each of the straight-chain alkanoic acids (except propanoic acid), new solid phases are obtained which contain both griseofulvin and the fatty acid (7, 8). Analysis of the excess of solid griseofulvin which stood in contact with each saturated solution in the solubility measurements, however, corresponded to that of the original griseofulvin crystals whose surface was moistened with liquid solution. The techniques used were DSC of five samples, which had previously been equilibrated with different mixtures of each fatty acid and isooctane, and differential thermal analysis and X-ray powder diffraction of one sample after equilibration with each neat fatty acid. This was confirmed by the inclusion of propanoic acid as a negative control which did not form solvates and which gave solubility data that were qualitatively no different from those of the other acids. We therefore conclude that $\{A\}$ was essentially constant in all the solubility measurements in the presence of each fatty acid and that solvates or inclusion compounds are not formed by allowing griseofulvin merely to stand in contact with each fatty acid.

The assumption that $[D]_t \approx 2[D_2]$ by Eq. 19 agrees with the experimental data. An alternative single-complex model in which $[D]_t$ accounts for the monomer, dimer, and complex leads to Eq. 32. The experimental data fit this equation also (Table V, Fig. 5 for butanoic acid), and it would appear that the statistically favored complexes correspond to $n = 6$, 7, or 8, depending on the fatty acid donor. However, except for statistically disfavored values of n for acetic acid, the data give negative values of c_1, which correspond to unacceptable negative values of the stability constant K_n (Eq. 33, Table V). In theory, this model should yield values of the dimerization constant K_d, but unacceptably small values are derived from the experimental data (*cf.* Table IV and V). Thus, this model, which accounts for the fatty acid monomer and a single complex, is totally unsatisfactory. Nevertheless, fatty acid monomers are undoubtedly present when fatty acids are dissolved in isooctane, and their relative concentration and influence increase as $[D]_t$ decreases. There is also evidence (27) that fatty acids in nonpolar solvents can form trimers, and perhaps also higher oligomers, in which the concentration is likely to increase with increasing $[D]_t$. If, however, all fatty acid species, with the exception of the dimer, are ignored, the solubility of griseofulvin in isooctane containing low concentrations of fatty acid can be explained by the presence of the lower-order complex, AD_m (in which $m = 1$ or 2). No doubt the most comprehensive model would involve a range or spectrum of AD_n complexes (Eq. 1) together with monomers, dimers, and perhaps even higher-order-associated species of fatty acids. Such a model would be algebraically complicated and would involve so many adjustable constants that it would be capable of fitting virtually any experimental data.

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pH–Solubility Profile of Papaverine Hydrochloride and Its Relationship to the Dissolution Rate of Sustained-Release Pellets

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Abstract □ The pH–solubility profile of papaverine hydrochloride (I) was determined using the phase-solubility technique and equilibrium solubilities in buffers. The release of I from sustained-release pellets consisting of a shellac-based matrix was determined by the USP basket technique and was found to exhibit zero-order kinetics. Release rates at various pH values of the permeating solvent were compared with the pH–solubility profile and were directly proportional to the solubility below, but not above, the apparent pH_{max} (3.9). This lack of proportionality was also shown by the intrinsic dissolution rates. The effect was attributed to the self-buffering action of I and the metastability of the papaverine salt–base system in the vicinity of pH_{max}. It is postulated that the outer layer of polymer and filler on the surface of the pellets forms a barrier which determines the rate of release. The inner matrix serves as a drug reservoir in which the internal pH may not be the same as the bulk pH.

Keyphrases □ Papaverine hydrochloride—pH–solubility profile, supersaturation effect, common-ion effect, solubility–dissolution rate ratio, self-buffering effect □ Shellac-based matrix—sustained-release dosage forms, solubility–dissolution rate ratios, internal self-buffering effect □ Mechanism of release—matrix model, effect of filler

The solubility of a hydrochloride salt and its base may vary greatly in the GI pH range, depending on the solubilities of ionized and un-ionized forms and the pK_a of the compound (1). Kramer and Flynn (2) have investigated the solubility interrelationships of hydrochloride salts and their bases. They observed that instead of giving a smooth curve, the solubility curves of a salt and its base intersect at a sharp angle at the pH of maximum solubility (pH_{max}) of both forms. Chowhan (3) has also noticed a similar relationship between organic acids and their salts.

The release of papaverine hydrochloride (I) from commercial sustained-release preparations has been reported to be significantly affected by pH (1). A partial pH–solubility profile showed that the drug solubility reached a maximum at pH ~4.5, and a common-ion effect owing to the addition of excess chloride ion was noticed at low pH.

In the present investigation, the pH–solubility profile of I and the interrelationships betwen the solubility of its salt and base forms were studied. Experiments were then conducted to study the dissolution of I from sustained-release pellets[1] in relation to the pH–solubility profile.

EXPERIMENTAL SECTION

Materials—Papaverine hydrochloride[2] (I) was used as received. The papaverine base (II) was prepared by increasing the pH of an aqueous solution of I to at least 12.0, washing the resultant precipitate four to five times with water, and drying under reduced pressure over phosphorus pentoxide. The identity of II was established by elemental analysis.

Commercial sustained-release papaverine hydrochloride capsules were used as the dosage forms. Each capsule contained ~500 pellets. The diameter of each individual pellet was 0.9 ± 0.1 mm. The diameter of sugar granules around which I was embedded in a shellac-based matrix by a coating process in a conventional rotating pan (4) was ~0.6 mm. The outermost layers of pellets were formed by the addition of drug-free shellac and filler.

The citric acid–phosphate buffers (pH 2.2–7.8) were prepared by mixing 0.1 M citric acid and 0.2 M disodium phosphate. All other reagents used were of analytical grade.

pH–Solubility Profile—The solubility profile of I and its base was determined by the phase-solubility technique of Dittert *et al.* (5). The pH of I in saturated aqueous solution was 3.0. The solubilities at pH <3.0 were determined by titrating dropwise with 1 M HCl, stirring with an overhead stirrer for 1 h at 37°C in a water bath, recording the pH, and then collecting a suitable aliquot. To attain a higher pH, 1 M NaOH was similarly added. Throughout the titration, care was taken to maintain an excess of solid in equilibrium with the solution. The aliquots were filtered[3] immediately, diluted with 0.1 M HCl, and analyzed spectrophotometrically[4] at 310 nm. The solubility was calculated in terms of the hydrochloride salt. A preliminary study showed that the solubility did not change significantly if the equilibration of solution was continued for more than 1 h after each addition of titrant.

The solubility in a citric acid–phosphate buffer was determined by adding an excess of I to ~15 mL of the buffer in a 50-mL volumetric flask, shaking overnight with a wrist-action shaker[5] in a water bath at 37°C, and analyzing the aliquot as described above. The saturation solubility in 0.01 and 0.1 M HCl was determined in the same manner.

[1] Cerespan, (lot no. 56370; 150 mg); USV Pharmaceutical Corp., Tuckahoe, N.Y.
[2] USVP no. 29745; USV Pharmaceutical Corp., Tuckahoe, N.Y.
[3] Millipore filter, Type HA; Millipore Corp., Bedford, Mass.
[4] Model 25; Beckman Instruments, Fullerton, Calif.
[5] Burrell Corp., Pittsburgh, Pa.

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