Complexation of Organic Substances in Aqueous Solution by Hydroxyaromatic Acids and Their Salts II

Influence of Halogen, Nitro, and Other Substituents and Correlation of Binding Tendencies Toward Prednisolone, Theophylline, and Phenacetin

By TAKERU HIGUCHI and FRANCIS D. PISANO*

Complexing tendencies of (*a*) variously substituted halo, methyl, nitro, and amino benzoates, (*b*) several phthalates, (*c*) dihydroxyphthalates, (*d*) dihydroxy and halohydroxy-2-naphthoates, and (*e*) pamoate have been evaluated by the solubility technique. The rather generalized binding effects observed earlier were again observed. Of all the salts studied, sodium pamoate exhibited the strongest tendency with a stability constant of 160 L./mole for prednisolone.

THE GENERAL APPROACH, techniques, and objectives of these studies have already been reported (1). In this paper the authors present additional data on hitherto uninvestigated systems which were selected to elicit further information on factors which control the intensity of these type interactions. The present studies were concerned specifically with the effects of alkyl, halo, nitro, carboxyl, and amino substituents and of enlargement of the size of the aromatic anionic group.

EXPERIMENTAL

Reagents

The following reagents were recrystallized from water, ethanol, methanol, or mixtures of these: isophthalic acid, m.p. 338–343°; terphthalic acid, m.p. >340°; 2,3-naphthalenedicarboxylic acid,[1] m.p. 238–239°; 3,4-dimethylbenzoic acid,[1] m.p. 165–167°; 3,4-dichlorobenzoic acid,[2] m.p. 205–206°; 5-iodosalicylic acid,[1] m.p. 194–197°; 4-aminosalicylic acid,[2] m.p. 147–148°; 2-chlorobenzoic acid,[3] m.p. 139–140°; 4-chlorobenzoic acid,[3] m.p. 235–236°; 4-bromobenzoic acid,[3] m.p. 254–256°; 4-iodobenzoic acid,[3] m.p. 271–273°; 4-nitrobenzoic acid,[3] m.p. 232–237°; *p*-toluic acid,[3] m.p. 178–180°; 5,5-methylenedisalicylic acid,[3] m.p. 215–220° with decomposition; 3,6-dihydroxy, 2-naphthoic acid,[4] m.p. 256–260°; theophylline U.S.P., m.p. 270–272°; phenacetin U.S.P., m.p. 134–136°; prednisolone alcohol,[5] m.p. 240–242°; sodium pamoate,[6] m.p. >330°.

Dowex 1-X4 anion exchange resin,[7] 50–100 mesh as the chloride form, was washed with water and methanol prior to use.

The following were used without further purification: potassium acid phthalate, sodium bicarbonate, potassium bicarbonate, bromine, iodine, hydrochloric acid, methanol, chloroform, *n*-propanol, all analytical reagent grade, and ethanol U.S.P.

2,3-Dihydroxyterphthalic Acid.—This was prepared from catechol using the Marasse modification of the Kolbe-Schmidt reaction described by Cameron, *et al.* (2). The reaction was carried out in a model MBT 250 high pressure magne dash autoclave.[8] The isolated product, recrystallized from aqueous methanol, melted at 315–317° with decomposition. Neutralization equivalent: found, 108.4; calcd. for the monohydrate, 108.1.

4,6-Dihydroxyisophthalic Acid.—This was prepared from resorcinol using the above procedure. The product, recrystallized from aqueous ethanol, melted at 332–333°. Neutralization equivalent: calcd.: 99.1; found: 99.8.

2,5-Dihydroxyterphthalic Acid.—This was prepared using the Kolbe-Schmidt synthesis on the dipotassium salt of gentisic acid (2, 3). The reaction was run for 6 hours at 160° and 1500 p.s.i. CO_2 pressure. The isolation was carried out as above and the product recrystallized from aqueous methanol. The crystals darkened but did not melt at 330°. Neutralization equivalent: calcd., 99.1; found, 99.2.

3,6-Dihydroxy-2-naphthoic Acid.—This was prepared from the potassium salt of 2,7-naphthalenediol using the Kolbe-Schmidt synthesis (2, 3). The reaction was run for 4 hours at 130° under CO_2 pressure of 1100 p.s.i. The product, recrystallized from aqueous ethanol, melted at 256–258°. Neutralization equivalent: calcd., 204.2; found, 207.0;

4-Iodo-3-hydroxy-2-naphthoic acid. This was prepared by dropwise introduction of an iodine-potassium solution into a stoichiometric amount of 3-hydroxy-2-naphthoic acid dissolved in sodium bicarbonate solution. The product was precipitated with dilute phosphoric acid and recrystallized from

Received August 15, 1963, from the School of Pharmacy, University of Wisconsin, Madison.
Accepted for publication September 19, 1963.
This study was supported in part by the Research Committee, Graduate School, University of Wisconsin, from funds supplied by the Wisconsin Alumni Research Foundation, Grant RG-5830 C3, C4 from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md., and Lederle Laboratories, Pearl River, N. Y.

* Present address: Lederle Laboratories, Pearl River, N. Y.

[1] Aldrich Chemical Co., Inc.
[2] Matheson Coleman and Bell, Division of the Matheson Co., Inc.
[3] Eastman Organic Chemicals.
[4] Pfister Chemical Works.
[5] Courtesy of The Upjohn Co., Kalamazoo, Mich.
[6] Courtesy of Parke, Davis and Co., Detroit, Mich.
[7] J. T. Baker Chemical Co.
[8] Autoclave Engineer, Inc., Erie, Pa.

aqueous methanol. The crystals decomposed with the liberation of iodine vapor at 210°. Neutralization equivalent: calcd., 314.1; found, 317.5.

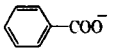
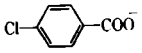
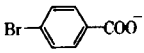
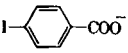
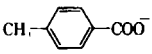
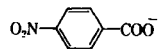
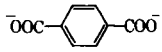
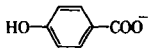
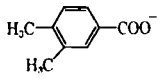
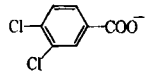
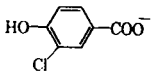
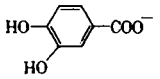
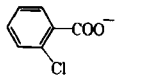
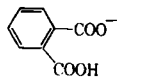
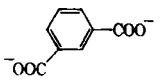
4-Bromo-1-hydroxy-2-naphthoic Acid.—This was prepared by the dropwise addition of a methanolic bromine solution to a stoichiometric quantity of 1-hydroxy-2-naphthoic acid in methanol. The product which was precipitated by the addition of cold water and recrystallized from dilute ethanol melted at 250–251° with decomposition. Neutralization equivalent: calcd., 267.1; found, 268.1.

PROCEDURE

Solubility Studies.—Except for potassium acid phthalate, sodium pamoate, and sodium 3,5-diiodosalicylate, the salt forms of the acids were prepared *in situ*. Stock solutions of the salts were prepared by dissolving and bringing to volume an accurately weighed quantity of acid and enough sodium bicarbonate so that the acid was completely converted to the salt, and the resulting solution was 0.1 *M* with respect to the bicarbonate. Increments of the stock solution were bureted or pipeted into 15-ml. screw cap vials containing a constant excess of the substrate, usually three to 10 times the solubility in water. The solution was brought to a constant final volume (generally 10 ml.) with the required amount of 0.1 *M* sodium bicarbonate solution.

Equilibration was effected by rotation of the vials in a water bath thermostated at 30.0 ± 0.1°. The time necessary for equilibration was determined to be less than 24 hours when phenacetin and theophylline were the substrates and less than 72 hours for prednisolone. After equilibration, an

TABLE I.—APPARENT STABILITY CONSTANTS[a] (L./MOLE) FOR THE INTERACTION OF SOME SUBSTITUTED BENZOATE SALTS

Compd.	Theophylline	Phenacetin
1  Benzoate	5.3[b]	1.0[b]
2  4-Chlorobenzoate	14	2.1
3  4-Bromobenzoate	16	2.7
4  4-Iodobenzoate	23	3.4
5  4-Methylbenzoate	7.7	1.3
6  4-Nitrobenzoate	9.0	3.3
7  Terphthalate	3.9	0.42
8  4-Hydroxybenzoate	12[b]	1.2
9  3,4-Dimethylbenzoate	16	2.6
10  3,4-Dichlorobenzoate	52	4.3
11  4-Hydroxy-3-chlorobenzoate	34	2.7
12  3,4-Dihydroxybenzoate	14[b]	1.5[b]
13  2-Chlorobenzoate	1.6	0.85
14  Acid phthalate	12	1.4
15  Isophthalate	1.9	0.27

[a] Calculated from the mass action equation assuming a 1:1 stoichiometry. [b] Data from Higuchi and Drubulis (1) included for comparison.

aliquot of the supernatent liquid was withdrawn and analyzed for total substrate.

Analysis.—Theophylline was separated from the complexing agent by one of two extraction procedures, depending on the partition coefficient of the acid form of the complexing agent. In most cases the theophylline was partitioned into an organic phase of 10% by volume of propanol in chloroform from an aqueous 0.5 *M* sodium bicarbonate solution. In those cases in which the acid form of the complexing agent was particularly water insoluble, the separation was effected by extraction with 1.0 *M* hydrochloric acid from an organic phase of 10% by volume diethylether in chloroform.

Prednisolone was isolated with an ion exchange column of Dowex 1-X4 resin. The aliquots were placed on the column and eluted slowly with methanol. Retention of the complexing agent was verified by prior elution of a solution containing only complexing agent.

Phenacetin was similarly isolated, except that 50% methanol in water was used as the eluent. In some cases an extraction procedure was employed in which the phenacetin was partitioned into chloroform from an aqueous 0.5 *M* bicarbonate solution.

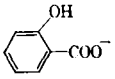
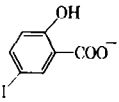
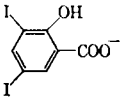
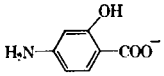
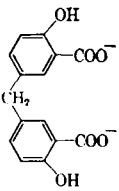
The solutions containing the substrate were appropriately diluted and the absorbance read on the Cary model 11MS spectrophotometer at the wavelength of maximum absorbance. Beer's law determinations of the substrate in each of the corresponding solvents were previously made, and the concentrations of the substrates were calculated from these.

RESULTS AND DISCUSSION

Results of these studies together with some of the pertinent data from the earlier study are shown in Tables I–IV expressed generally as apparent stability constants at the saturation concentration of the three solubilized compounds. For details of calculation and treatment reference should be made to the previous work (1).

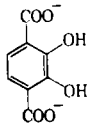
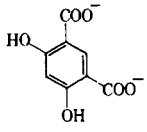
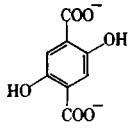
It is apparent from the tables that in every instance the intensities of interaction are in the order theophylline > prednisolone > phenacetin. The interactions with the xanthine were quite strong, often so strong that more than one molecule

Table II.—Apparent Stability Constants[a] (L./Mole) for the Interactions of Some Substituted Salicylates

Compd.	Theophylline	Phenacetin	Prednisolone
16  Salicylate	20[b]	1.9[b]	7.3[b]
17  5-Iodosalicylate	1:1.0[c]	5.8	27
18  3,5-Diiodosalicylate	1:1.3[c]	12	58
19  4-Aminosalicylate	20	1.9=	...
20  5,5′-Methylenedisalicylate	1:1.0[c]	12	62

[a] Calculated from the mass action equation assuming a 1:1 stoichiometry. [b] Data of Higuchi and Drubulis (1) included for comparison. [c] Stoichiometric ratios (salt:theophylline).

TABLE III.—APPARENT STABILITY CONSTANTS[a] (L./MOLE) FOR THE INTERACTION OF SOME DIHYDROXYPHTHALATES

Compd.	Theophylline	Phenacetin	Prednisolone
21  2,3-Dihydroxyterphthalate	107	3.9	18
22  4,6-Dihydroxyisophthalate	110	5.3	22
23  2,5-Dihydroxyterphthalate	166	5.3	...

[a] Calculated from the mass action equation assuming a 1:1 stoichiometry.

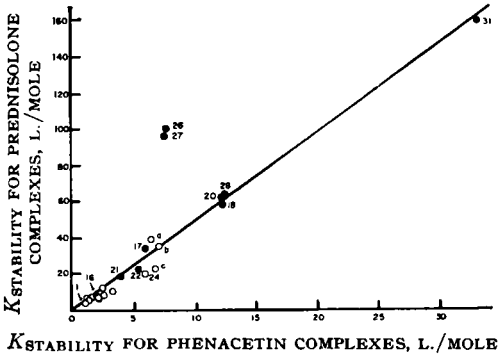
of theophylline was brought into solution for each molecule of salt added. In these instances the molar ratios are given since stability constants calculated on a 1 to 1 basis are meaningless.

The trend observed by Higuchi and Drubulis (1) which suggested that these interactions are extremely generalized seems to be confirmed by the present study. The nature of this relationship is readily evident in the plot, shown in Fig. 1, of the stability constants of prednisolone against the stability constants of phenacetin for each of the several complexing agents. The data of Higuchi and Drubulis have been included for comparison purposes. Figure 1 shows that the majority of the compounds fall essentially on a straight line going through the origin. Thus, the ratio of stability constants for prednisolone and phenacetin is essentially for the weakest complexing pairs the same as for the strongest complexing combinations. Such a correlation is interesting, particularly since prednisolone and phenacetin are structurally quite dissimilar, and the complexing agents involved represent a variety of substituted benzoates, naphthoates, phthalates, and substances such as the methylene derivatives, sodium pamoate and 5,5′-methylenedisalicylate—the group as a whole consisting of a spectrum of differently oriented substituents.

With such systems, if the behavior depended significantly on localized interactions, one may well expect a fair degree of "lock and key" effect, in which case certain orientations of the functional groups would particularly tend to favor formation with one of the drugs rather than the other. Since it is unlikely that prednisolone and phenacetin have similarly oriented sites of interaction, the absence of a lock and key effect must mean that the interaction with these substrates is largely of a nonspecific nature.

As indicated by the plot, the weakest binder studied with these two substrates was benzoate, the various substituents all causing an increase in the stability constants. The strongest of the complexing agents was sodium pamoate. Between those two lie the various compounds in an order which leads to several new observations.

It can be seen, for example, from the relative position of 2,5-dihydroxybenzoate and 2-hydroxy-5-iodobenzoate that iodo substitution has a greater effect on the stability of the complex than does the hydroxyl substitution. The large stabilizing effect of the iodo group is seen by the position of 3,5-diiodosalicylate. The same trends are observed with the naphthalene derivatives, the unsubstituted



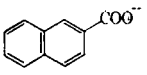
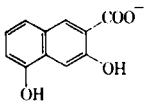
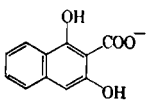
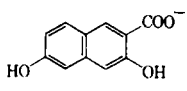
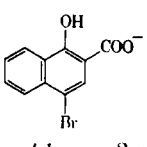
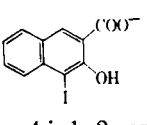
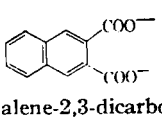
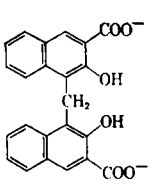
K STABILITY FOR PHENACETIN COMPLEXES, L./MOLE

Fig. 1.—A plot of the stability constants for prednisolone and for phenacetin with each of the indicated complexing agents. The unfilled circles represent data of Higuchi and Drubulis (1). The numbers refer to the compounds numbered in Tables I–IV. The unidentified circles represent the mono- and dihydroxybenzoates. The letters *a*, *b*, and *c* represent 3-hydroxy-2-naphthoate, 1-hydroxy-2-naphthoate, and 2-hydroxy-1-naphthoate, respectively.

naphthoate being the poorest complexing agent, and the hydroxy and halo substituted naphthoates complexing to a much greater extent. The naphthalene derivatives, however, showed more complexing ability than the corresponding benzene derivative.

Rationalizations of such effects can be devised either on the basis of a donor-acceptor theory, which maintains that intermolecular interaction involves the π orbitals of the aromatic nucleus with the electrons of the donor, or on the basis of the hydrophobic bonding mechanism. The strong

TABLE IV.—APPARENT STABILITY CONSTANTS[a] (L./MOLE) FOR THE INTERACTION OF SOME 2-NAPHTHOATE DERIVATIVES

Compd.	Theophylline	Phenacetin	Prednisolone
24  2-Naphthoate	1:1.2[b,c]	5.8[b]	20[b]
25  3,5-Dihydroxy-2-naphthoate	1:1.7[c]	11	...
26  1,3-Dihydroxy-2-naphthoate	...	7.6	100
27  3,6-Dihydroxy-2-naphthoate	...	7.5	97
28  1-Hydroxy-4-bromo-2-naphthoate	1:1.7[c]	12	64
29  3-Hydroxy-4-iodo-2-naphthoate	1:1.7[c]	17	...
30  Naphthalene-2,3-dicarboxylate	37	1.1	...
31  Pamoate	1:2.2[c]	33	160

[a] Calculated from the mass action equation assuming a 1:1 stoichiometry. [b] Data from Higuchi and Drubulis (1) included for comparison. [c] Stoichiometric ratios (salt:theophylline).

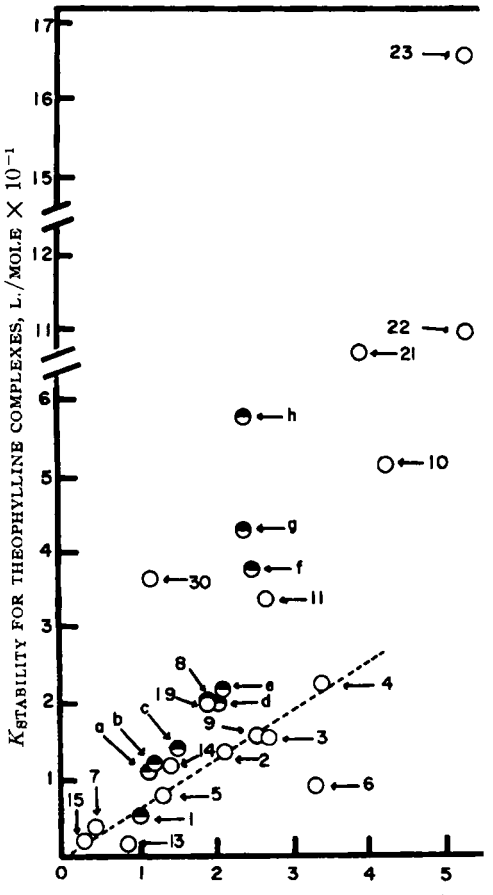


Fig. 2.—Plot showing the stability constants for complex formation of theophylline against the stability constants for complex formation of phenacetin with each of the indicated complexing agents. The numbers refer to the compounds numbered in Tables I–IV. The half closed circles refer to data of Higuchi and Drubulis (1). Key: *a*, 3-hydroxybenzoate; *b*, 4-hydroxybenzoate; *c*, 3,4-dihydroxybenzoate; *d*, 3,5-dihydroxybenzoate; *e*, 3,4,5-trihydroxybenzoate; *f*, 1-naphthoate; *g*, 2,5-dihydroxybenzoate; *h*, 2,4-dihydroxybenzoate.

binding with the halogenated compounds, for example, may be accounted for by the halogen atoms' electron withdrawing ability which would tend to make the aromatic nucleus more electrophilic and thereby more favorable for interaction with the substrate electrons. The enhanced binding over that of the unhalogenated derivatives, however, may be due, on the other hand, to the increase in the size and hydrophobic character of the complexing agents associated with halogen substitution, an effect which would tend to increase the amount of hydrophobic bonding.

The increased tendency toward complex formation observed with the expansion from a benzene ring to a naphthalene system would be expected on the basis of either hypothesis. Donor-acceptor complexing would tend to be facilitated by the increase in the size of the conjugated system, and the increase in the hydrophobic surface would certainly tend to increase the "squeezing out" effect.

The puzzling but substantial enhancement provided by the hydroxyl substitutions noticed earlier is confirmed in the present study. Since phenolic hydroxyl groups interact with water molecules to a considerable degree, they would not necessarily be expected to enhance hydrophobic bonding. Hydroxyl functions, moreover, are not generally considered as strong electron withdrawing groups, but from a consideration of their *ortho-para* directing nature are sometimes thought of as pushing electrons into the ring; any significant increase in the electrophilicity of the ring, therefore, seems unlikely. Higuchi and Drubulis (1) have discounted hydrogen bonding with the phenolic hydrogens as a major contributing factor in the formation of these complexes. This leaves the reason for the stronger complexing behavior of *meta* and *para* hydroxy compounds somewhat unresolved.

The strong binding observed with the *ortho* substituted hydroxy compounds and the dihydroxyphthalates may possibly be explained on the basis of increased area of the π cloud above and below the plane of the aromatic molecule. If the *ortho* hydroxy hydrogen forms a hydrogen bond with the carboxylate group, the rotation about the bond between C_1 and the carboxylate carbon would be arrested and the π electrons of the carboxylate function may resonate with the π electrons of the aromatic ring, and in effect increase the area of the π cloud. It can also be rationalized that in addition to the increase in the resonance effect, the planar configuration of the *ortho* hydrocarboxylates can increase the interaction by affording less steric hindrance to hydrophobic bonding.

The strong complex forming tendencies of the bis methylene derivatives, sodium pamoate and disodium 5,5′-methylenedisalicylate, may have been expected in view of the binding tendencies of sodium 3-hydroxy-2-naphthoate (K = 39 L./mole with prednisolone and 6.3 L./mole with phenacetin) and sodium salicylate. The fact that the stability constants for the methylene derivatives were not two but four to eight times that of the latter compounds on molar basis indicates that the effects which the additional hydroxy naphthoate and salicylate groups have on the compounds apparently are not necessarily those in which the extent of interaction are statistically additive. The significant displacement of the dihydroxy naphthoates from the line in Fig. 1 may mean a specific interaction with prednisolone or a specific hindrance to complex formation with phenacetin.

The stability constants for complex formation of theophylline and phenacetin with the various complexing agents listed in Tables I–IV are shown plotted against each other in Fig. 2. Those interactions where the phase solubility diagrams showed slopes of approximately one or greater for the theophylline system were excluded, since it was neither possible nor rational to calculate the stability constants based on a 1:1 stoichiometry in these instances. Again the data of Higuchi and Drubulis (1) are included for comparison.

It is obvious from the plot that the clearly linear relationship found between the formation constants of phenacetin and prednisolone does not exist in this case. The increasingly higher constants for theophylline with the stronger binders may be due at least in part to the tendency of the

xanthine to form higher complexes. The apparent 1:1 stability constants calculated from the phase solubility diagrams would then tend to be an exaggerated measure of the complexing tendencies. The linear relationship, perhaps for this reason, appears to hold better for the weaker complexing agents. It may be that for these compounds, the same mechanism operates in the complex formation with both phenacetin and theophylline, but with the stronger binders a second superimposed mechanism has a pronounced stabilizing effect on the theophylline complexes.

In view of the relative behavior of phenacetin interactions with respect to the steroid system, the pronounced scatter observed in Fig. 2 suggests that theophylline is subject to a much more specific type binding than the other two. It seems more logical to attribute the observed deviations to theophylline rather than to the phenacetin systems in view of the latter's notable correlation with the steroid system. In every case, however, the xanthine is substantially more strongly bound than phenacetin, a behavior which may be partly attributable to the planarity conferred on theophylline by its fused ring structure and partly perhaps to its ability to share electrons with bound molecules.

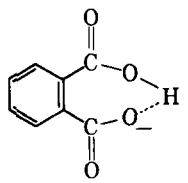
It appears from Fig. 2 that theophylline tends to have a greater relative affinity for the hydroxyl and carboxylate ion substituted compounds than for the halo and alkyl substituted compounds compared to phenacetin. The dashed line on the plot, drawn through the points representing the purely halogenated and alkylated carboxylate salts, appears to suggest a linear correlation within this class. These complexing agents may be expected to participate to a lesser degree than the phenolic hydroxy and carboxylate ion substituted compounds in specific interactions with the xanthine. It may be that electron sharing may be a more important factor in complexation with theophylline than it is with phenacetin.

Although much of the discussion on the complexation with prednisolone and phenacetin (Fig. 1) can apply to the data of theophylline and phenacetin in Fig. 2, some of the complexing agents not included in the former plot may warrant additional discussion. The rather poor complexing ability of isophthalate and terphthalate and 2,3-naphthalenedicarboxylate compared to plain benzoate and naphthoate again may be explained on the basis of the donor-acceptor theory or by hydrophobic bonding. The carboxylate ions of the phthalates may tend to push electrons into the ring and therefore decrease the electrophilicity of the aromatic nucleus. The introduction of the charged carboxylate ion might possibly also be detrimental to hydrophobic bonding in view of the possible additional hydration of the molecule.

The threefold increase in the stability constant for the binding of *p*-nitrobenzoate over unsubstituted benzoate with phenacetin may perhaps be better explained on the basis of the nitro group's electron withdrawing properties rather than on increased hydrophobic bonding, since it may be expected that the nitro group does not necessarily impart increased hydrophobic character to the carboxylate salt. The comparatively slight increase in the complex formation constant with theophylline (5.3 L./mole to 9.0 L./mole) in view of the marked increase in the phenacetin constant is somewhat surprising. Since it is uncertain whether this behavior represents unexpectedly weak complexing with theophylline or exceptionally strong complexing behavior with phenacetin, further explanations could only be speculative.

The similarity of the binding constants of *p*-aminosalicylate and salicylate places the role of the amino group in doubt. A comparison of the water solubilities of aniline and benzene suggests that the amino function possibly reduces the hydrophobic character of the compound and thereby lessens this type interaction. In addition, the amino group is generally referred to as electron donating, and on this basis a reduction in the electrophilicity of the aromatic nucleus may be expected to reduce any donor-acceptor interaction. It seems, however, that the amino group in the *para* position has apparently little effect on the binding behavior of salicylate with either theophylline or phenacetin.

Some evidence in Table I suggests the importance of the planarity of the complexing agent. For example, *ortho* substitution of chlorine hinders complex formation rather markedly, even though *para* substitution of chlorine significantly enhances it. It has been shown (4) that in the crystal structure of *o*-chlorobenzoic acid, the plane of the carboxyl group is 13.7° out of phase with the plane of the ring. In solution, restraining van der Waals forces operative in the crystal are disrupted, and it may be expected that in the ionized form the plane of the carboxylate ion and the benzene ring are out of phase to an even greater degree. When the *ortho* substituted function is a COOH group, however, the binding is increased substantially over that of benzoate. It may be that hydrogen bonding between the acidic hydrogen and the *ortho* carboxylate oxygen maintains the structure planar represented by



This greater planarity for reasons mentioned previously may render complex formation more favorable.

It has been reported by Eckert (5) that caffeine and procaine hydrochloride form a complex which exhibits a characteristic charge-transfer absorption band. In the present study with the same system, the existence of a rather sharp absorption band at 340 mμ was verified. A procedure similar to Eckert's was used with the theophylline 2,4-dihydroxybenzoate system, and absorption was observed to occur between 350 and 330 mμ, the existence of specific charge-transfer absorption being impossible to determine below 350 mμ due to the great absorption by the individual components. The possibility of charge-transfer absorption bands was also investigated with theophylline and 4-bromobenzoate. The spectrum of a mixture of the two components using as blanks two consecutively aligned cells with the corresponding concentrations of the individual components showed a rather broad absorption band with a maximum at approximately

295 mμ. The same experiment repeated with sodium 2-chlorobenzoate produced a similar band at 295 mμ. The above procedure repeated with the hydrochloride salt of 2-dimethylaminomethyl-4-methylphenol instead of the benzoates revealed a peak at approximately 307 mμ very similar in its sharpness to that obtained with the procaine hydrochloride-caffeine system.

These results indicate that theophylline appears to participate in charge-transfer complexation. The observed spectra with both the benzoates and the protonated Mannich base suggest theophylline's ability to share electrons with both positively and negatively charged aromatic compounds. It is evident, however, that further investigation of a more quantitative nature would be required to determine whether these charge-transfer interactions account for the total interaction by theophylline in aqueous solutions.

CONCLUSIONS

Solubility studies on the interactions of theophylline, prednisolone, and phenacetin with substituted benzoates, phthalates, and naphthoates produced the following observations.

Complex formation between aromatic carboxylate salts and the above drugs occurred in every instance, but with varying extents.

Introduction of substituents on the aromatic ring appears to have a marked effect on the binding tendencies.

There is a surprising absence of any significant "lock and key" specificity, particularly among the complexes of the aromatic acid salts with prednisolone and phenacetin.

The results suggest that both hydrophobic bonding and donor-acceptor interactions involving the nucleus of the aromatic carboxylates contribute to formation of the complexes.

The binding with theophylline appears to be at least partially due to specific charge-transfer interactions.

The extent of complex formation of the aromatic carboxylate salts with theophylline, phenacetin, and prednisolone is increased by (*a*) substitution of halo groups *meta* and *para* to the carboxylate, the enhancement increasing in the order chloro, bromo, and iodo; (*b*) methyl, nitro, and hydroxyl groups substituted *meta* and *para* to the carboxylate; (*c*) placement of carboxylic acid and hydroxy groups *ortho* to the carboxylate ion; (*d*) further substitution of the above substituents on the aromatic carboxylates; (*e*) expansion of a benzenoid system to a naphthalene structure and by generally increasing the planar surface of the substituted acid salts.

The extent of interaction of these systems is decreased by halogen substitution on the ring *ortho* to the carboxylate group and by substitution of carboxylate ion.

REFERENCES

(1) Higuchi, T., and Drubulis, A., THIS JOURNAL, 50, 36(1961).
(2) Cameron, D., Jesky, H., and Baine, O., *J. Org. Chem.*, 15, 223(1950).
(3) Baine, O., Adamson, G. F., Barton, J. W., Fitch, J. L., Swayampati, D. R., and Jesky, H., *ibid.*, 19, 510(1954).
(4) Ferguson, G., and Sim, G. A., *Proc. Chem. Soc. London*, 1961, 162; *Acta Cryst.*, 14, 1271(1961).
(5) Eckert, T., *Arch. Pharm.*, 295, 233(1962).

Emulsifying Effects of Some Nonionic Surfactants on a Nonaqueous Immiscible System

By R. V. PETERSEN, R. D. HAMILL, and J. D. McMAHON

Representative members of seven classes of nonionic surfactants and combinations of these agents were tested by hand methods of trituration for their ability to induce emulsification of glycerin and olive oil. No relation between HLB values and emulsifying capacity, method of mixing, or emulsion type was apparent. On the other hand, the chemical nature of the surfactant appeared to have an effect on the method of mixing and emulsion type. Only stearate ester surfactants induced emulsification when the surfactant was first added to olive oil. In addition, only stearate ester surfactants induced glycerin-in-oil emulsification.

IN A SEPARATE publication (1), the emulsifying effects of several anionic and cationic surfactants on the immiscible system, glycerin and olive oil, were reported. The present report describes the emulsifying effects of some *nonionic* surfactants on this system.

Received June 3, 1963, from the College of Pharmacy, University of Utah, Salt Lake City.
Accepted for publication September 10, 1963.
This investigation was supported by a grant from the University of Utah Research Fund.
Presented to the Scientific Section, A. PH. A., Miami Beach meeting, May 1963.

Various nonionic surfactants have been used in formulations which have been administered orally to humans (2). Ester type products are hydrolyzed in the digestive tract in a manner similar to edible fats and oils. The fatty acid portions are available for nutrition like those from natural fats, while the polyol moieties are eliminated (3). The glyceryl monostearate products (GMS 165,[1] glyceryl monostearate, self-

[1] Marketed as Arlacel 165 by Atlas Chemical Industries, Inc., Wilmington, Del.