Probability and Complexation: A New Approach

By LLOYD KENNON and KUO-SIN CHEN†

A method is proposed which considers the ability of the ionic atmosphere surrounding a drug in solution to form "probability complexes" with the drug. These complexes are detectable both mathematically and physically. The method is described and illustrated with a study of the behavior of three solutions of phenothiazine derivatives with saccharin.

WHAT is a complex? For about the last ten years this question has been asked, with particular interest being expressed in the components of pharmaceutical solutions. When one attempts to answer this question with various mechanistic concepts, it is found that exact quantitation and definition may be somewhat elusive. However, an explanation which is unencumbered by mechanisms and, hence, probably completely uncontroversial is this: A and B are complexed when there are more A species around and/or closer to B species than a random distribution of A's and B's would bring about. It is such a concept which this communication seeks to explore and discuss.

THEORY AND BACKGROUND

Although the ordered state of crystalline solids, with their units locked into symmetrical and repeating patterns, and the disordered, randomized state of gas molecules have received much attention and investigation and are relatively well understood, the amorphous solid state (including glasses) and liquids have not been so explicitly characterized. At one time the latter two states had in general been considered to be somewhat similar, in that they are both structureless and amorphous. It is now well-known that both dissolved solutes and liquid solvents *per se* behave as if they have at least transitory structures.

The concept of incomplete dissociation, even with complete ionization resulting in nondistinguishable, truly unionized molecules and associated ion-pairs, is well accepted with regard to solutes. Fuoss and Kraus (1) have postulated the existence of ion triplets in addition to the pairs. The Debye-Hückel-Onsager treatments of the theory of electrolytic solutions which were made during their development of the interionic attraction concepts recognize that each ion is surrounded by its own ionic atmosphere of opposite charge. These phenomena, of course, more readily exist in solvents having lower dielectric constants. Also, Brady (2, 3) has demonstrated by X-ray measurements that ionic solutions have structure, *i.e.*, a large degree of local order. Other authorities such as Bailar (4) and Martell and Calvin (5) have drawn attention to chelation processes, coordination compounds, complex inorganic compounds such as amines, hydrates, and double salts, and olation and oxolation. Olation, whereby metal atoms are linked together by OH bridges, can cause the formation of polymers which may reach colloidal size when the olation process does not terminate early. Oxolation, conversion of *ol* groups to *oxo* groups by proton loss, can function similarly. Schlenk and Sand (6) have shown that even clathrates or inclusion compounds can exist in the liquid phase.

Solvents themselves are also capable of sustaining a structure, at least instantaneously. This has been recognized by workers such as Bernal (7–9). Even though the neighbors of a liquid's molecules appear to lie at apexes of various kinds of polyhedra, the highly condensed nature of liquids and their lack of long range order has made the problem of constructing realistic geometric models for mathematical analysis very difficult.

It is known that complexation concepts have explained some of the behavior noted in pharmaceutical solutions. For example Higuchi and Lachman (10) in their first paper on the inhibition of ester hydrolysis have shown that benzocaine does not hydrolyze in solution when it is present as a complex with caffeine. This, and similar observations along with the structure-in-liquids concepts, leads one to believe that another pharmaceutical observation may be explicable and studied as outlined in this paper. The observation is this: Often in pharmaceutical development it appears that different salts of the same compound exhibit not only different solubility characteristics but also differing stability properties. As a literature example we may cite the work of Macek (11) and Bird and Shelton (12) who noted differences in the stabilities of the hydrochloride and nitrate salts of thiamine.

These and similar results found in the course of pharmaceutical development work are somewhat surprising, because at any given pH the same fractions of the possible drug species exist in solution regardless of the acid salt used. Of course, some cases are not surprising and are more readily understood. Epinephrine fumarate or its equivalent has been shown by Romanian workers (13) to be more stable than epinephrine hydrochloride; a British patent (14) was issued to the Rhone-Poulenc Corp. on the use of chlorpromazine fumarate (or maleate, citraconate, itaconate, *etc.*) as preferred to the hydrochloride. These and similar cases may be explained by noting that an oxidizable olefinic linkage has been introduced and would be expected to impart some antioxidant properties. In fact, the Lindsey-Maxwell process (15) for stabilizing edible fatty oils is similar in that citric acid is added

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† Present address: Alco Oil and Chemical Company Philadelphia, Pa.

to the oil and then deliberately decomposed to form unsaturated, easily oxidized acids.

The thesis of this paper is that the surprising results mentioned above are due to the fact that the ionic environment *per se* plays a decisive role in the stability picture. This is true because the ions form a protective molecular overcoat—a loose ionic atmosphere complex—which is detectable both mathematically and physically and which may be reasonably termed a "probability complex." Thus, a probability complex mathematically just approaches the definition of a complex mentioned in the introduction; because of its physically demonstrable existence, we may say it does fit the definition.

Formulation work done in our laboratories by Gulesich and Marlino (16) showed that the presence of sodium saccharin in some chlorpromazine hydrochloride[1] ampul and syrup formulations surprisingly enhanced the light stability of the drug. Subsequent work indicated that saccharin also improved the stability to light of other phenothiazine derivatives such as prochlorperazine ethanedisulfonate[1] and trifluoperazine dihydrochloride.[1] These observations also supported the view that certain ions in solution may affect the stability of drugs. The aim of the experimental work was to show the existence of, isolate, and identify if possible the postulated probability complexes. The next section describes the probability method as part of the experimental work.

EXPERIMENTAL

Chlorpromazine and Saccharin.—The initial work was aimed at forcing the saccharin complexes out of solution. This was done by determining the maximum concentrations at which the phenothiazine derivative and sodium saccharin together would form a clear solution. The following illustration of the procedure will use chlorpromazine as the first example. It was found that the maximum permitted concentrations of the two components were 0.00625 *M* chlorpromazine hydrochloride and 0.00332 *M* sodium saccharin; this is a chlorpromazine: saccharin ratio of 1.88:1.00. The phenothiazine must be surrounded by both Cl and saccharin (S) species. At S = 1, Cl = 1.88, so the total possibilities of this (mutually exclusive) situation = 2.88. Therefore, the probability of the drug being in the saccharin form = Ps = 1/2.88 = 0.348; the probability of it being in the Cl form = PCl = 1.88/2.88 = 0.653. The sum of these two is 1.00 as, of course, the drug must be in either one or the other form. The total moles of drug in the just-clear liter of solution being 0.00625 as stated, the molar amount as drug-saccharate would be 0.00625 × 0.348 = 0.00217 moles. Postulating a 1:1 interaction, the molecular weight of the chlorpromazine saccharate = 502. Therefore, the grams of this complex per liter would be 502 × 0.00217 = 1.09 Gm./L.; this then should be the solubility of the complex. A solution containing both components at a concentration of 0.05 *M* each (17.7 Gm. drug hydrochloride plus 12.06 Gm. of sodium saccharin, *q.s. ad* 1 L.) was made so that the complex would be forced out of solution. The grams of complex possible would be 0.05 × 502 = 25.10 Gm.; 1.09 Gm. would be soluble as shown. Thus 24.01 Gm. should settle out; 24.0 Gm. was actually found.

Trifluoperazine and Saccharin.—Similarly to the above, the trifluoperazine dihydrochloride and saccharin case was treated probability-wise. This case differs somewhat from the chlorpromazine situation in that two moles of anion will surround the drug and the possibilities are altered. The drug may be surrounded by Cl-Cl, S-S, Cl-S, or S-Cl. Therefore, having found that the maximum permitted concentrations of the two components were 0.005 *M* drug and 0.00788 *M* saccharin (a drug:saccharin ratio of 1:1.576), the probabilities are: P_{Cl} = 1/2.576; Ps = 1.576/2.576. Hence the probabilities of the double combinations would be: $P_{Cl-Cl} = (1/2.576)^2 = 0.151$; $P_{S-S} = (1.576/2.576)^2 = 0.375$; $P_{Cl-S} = 2[1.576/(2.576)^2] = 0.474$. These probabilities again add up to 1.00, as the drug must be in the four mentioned forms; actually there are only three forms, ehnce the factor of 2 indicating that we could not distinguish between the Cl-S and S-Cl species. The total moles of drug in the just-clear liter of solution being 0.005, the molarity of drug-saccharate would be 0.005 × 0.375 = 0.001875 *M*. Postulating a 2:1 saccharin to drug interaction, the molecular weight of the trifluoperazine disaccharate = 774. Therefore, the grams of this complex per liter, *i.e.*, the solubility, would be 774 × 0.001875 = 1.45 Gm./L. A liter of solution containing 0.05 moles of trifluoperazine dihydrochloride (24.02 Gm.) and 0.10 moles of sodium saccharin (24.12 Gm.) was made. The grams of complex possible would be 0.05 × 774 = 38.7 Gm.; 1.45 Gm. would be soluble as shown. Thus, 37.25 Gm. should settle out; when the solution was made, 38.0 Gm. was actually found.

Before describing the work with prochlorperazine ethanedisulfonate and saccharin, which proved to be the most interesting case, some other comments are appropriate. All the complexes came out of solution as wet oils which when dried became hard glasses which could not be crystallized. [Incidentally, Japanese workers (17) were able to crystallize both mono- and di-saccharinates of thiamine. However, Hamilton and Turnbull (18) prepared many amine saccharinates, *i.e.*, substituted ammonium salts of saccharin, and found them generally difficult or impossible to crystallize.] An attempt to show that the complexes really existed in addition to their probability existence at concentrations lower than their maximum solubility was not successful. The method of continuous variations was employed, using the refractive indices of appropriate binary solutions as the characteristic property followed. The individual sodium saccharin and drug solutions *per se* exhibited easily measured changes in refractive index, but the binary solutions studied showed simple additive effects with no maxmin. This observation also supports the concept that the complexes in solution are somewhat elusive and consist essentially only of a certain ionic environment.

Prochlorperazine and Saccharin.—The probability analysis and subsequent precipitation study, in agreement in the two cases above, did not present a coherent picture in the prochlorperazine ethanedisulfonate–sodium saccharin case. It was evident

[1] Marketed as Thorazine, Compazine, and Stelazine, respectively, by Smith Kline & French Laboratories, Philadelphia, Pa.

that we were postulating the oil to be something that it was not. Therefore, it was decided to investigate in detail the composition of the oil.

The complex oil was made by mixing 0.3-*M* solutions of each component, separating the oil formed and drying it at 85°, whereupon it became a transparent, hard glass. The material was soluble in water and in alcohol with a strong acid reaction; it was insoluble in ether or chloroform. When a portion of the mass was dissolved in water and then neutralized with sodium hydroxide, a brown liquid which was acid- but not water-soluble separated. The physical appearance and solubility behavior paralleled those of prochlorperazine base. When two different aqueous complex solutions made from the glass were spectrophotometrically analyzed, the per cent of drug base in the oil was found to be 56.42% and 56.50%, for an average of 56.46%. Upon treating a small amount of the mass with dilute hydrochloric acid, a white, sweet precipitate was produced. The material melted in the range 227–230° and was obviously saccharin. Quantitative analysis for saccharin was done as follows: A sample of drug complex (1.519 Gm.) was dissolved in water, acidified (HCl), and extracted with chloroform-alcohol (9:1). The extract was evaporated to dryness, dissolved in water, neutralized with sodium hydroxide, and extracted with ether. The aqueous layer, containing the sodium saccharin and the sodium chloride, was evaporated, acidified, and extracted with chloroform-alcohol. The extract was evaporated to dryness and the residue taken up in water and titrated with 24.55 ml. of 0.0973 *N* sodium hydroxide. The per cent saccharin in the sample is then: $24.55 \times 0.0973 \times 183.2 \times 100/1519 = 28.82\%$.

Thus, it appeared that there was about 15% of a third component in the drug-saccharin complex. Evidence was soon obtained which indicated that there was another acid in the product: When the complex in water was titrated with base in the presence of ether (to remove the organic base), the amount of alkali needed was much more than that required for neutralization of the 29% saccharin. Naturally, the conclusion was that ethanedisulfonic acid was also present in the oil; this was verified, as will be shown.

The various possible drug-acid-saccharin interaction products were now considered. The one that fit the data was a complex consisting of 2 moles of saccharin, 2 moles of prochlorperazine, and 1 mole of ethanedisulfonic acid; this would contain about 57% drug, 28% saccharin, and 15% ethanedisulfonic acid. A titration made as described in the last paragraph indicated, after adjusting for the theoretical amount of saccharin in the postulated complex, that the ethanedisulfonic acid comprised about 12.5% of the complex. A further check on the acid content was made by mixing 5.64 Gm. (0.01 mole) of prochlorperazine ethanedisulfonate with 2.41 Gm. (0.01 mole) of saccharin sodium. After complex formation, the aqueous solution should contain 1.17 Gm. of disodium ethanedisulfonate; experimentally we recovered 1.02 Gm. of a white powder which was soluble in water, insoluble in alcohol, neutral to litmus paper as an aqueous solution, and had an equivalent weight of 116.5 (theoretical = 117.1). The equivalent weight was determined by running the sample alongside a known sample of disodium ethanedisulfonate through an analytical grade of cation exchange resin[2] and titrating the eluate with alkali. The known gave an equivalent weight of 116.8, the unknown, 116.5. The presence of the acid in solution corroborated the chosen composition of the complex, as it was consistent with the rest of the data, and it eliminated some alternate possibilities. Thus it appears that one molecule of ethanedisulfonic acid connects two prochlorperazine-saccharin interaction products.

As mentioned, the product defied all attempts to crystallize it. However, it was possible to obtain a powder (amorphous) by freeze-drying a solution. The material thus obtained was then checked for carbon-hydrogen and, for a compound which would not crystallize and must be obtained as a wet oil initially, the agreement is quite satisfactory.

Anal.—Calcd. for $C_{56}H_{64}Cl_2N_8O_{12}S_6$: C, 51.56; H, 4.95. Found: C, 53.44, 53.65; H, 4.95, 5.26.

CONCLUSIONS

The nature of the ionic atmosphere around a drug in solution may explain why different salts of the same drug can exhibit different stability characteristics.

The composition of the ionic atmosphere may be determined by examining the concentrations of all the species involved and using simple probability mathematics; the species involved may be changed and thus studied by varying the salt types in the solution.

Although the ionic atmosphere forms what may be termed a "probability complex" detectable only mathematically, these probability complexes can be forced out of solution and their composition verified.

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[2] Analytical Grade Amberlite IR-120 (H), marketed by Rohm & Haas Co.