lower surface tension, it is able to penetrate into fissures and crevices which water cannot readily enter, resulting in a decreased rate of solution.

The addition of polyvinylpyrrolidone into Formulations B and D (Table I) does not alter the surface tension. Therefore, the decrease in dissolution when compared to Formulations C and E, respectively, must be a function of the rate of solution of polyvinylpyrrolidone, causing a decrease in the rate of solution of a rather soluble drug in water.

The results of this study show that the method used to incorporate drug into a solid dosage form can affect the dissolution rate of that drug.

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Received February 22, 1973.
Accepted for publication June 14, 1973.

NMR Spectroscopy: Chloro-(tetra-*p*-methylphenylporphinato)indium (III)

Key phrases □ Chloro(tetra-*p*-methylphenylporphinato)indium (III)—NMR spectra □ Porphine complexes with indium—NMR spectra of chloro(tetra-*p*-methylphenylporphinato)indium (III) □ Indium (III), chloro(tetra-*p*-methylphenylporphinato)—NMR spectra □ NMR spectroscopy—identification, chloro(tetra-*p*-methylphenylporphinato)indium (III)

Sir:

Porphine complexes are important biologically and chemically. Structural studies of these complexes may provide information relative to their mechanisms of action. We wish to report NMR studies on the complex chloro(tetra-*p*-methylphenylporphinato)indium (III).

Chloro(tetra-*p*-methylphenylporphinato)indium (III) was prepared and purified as previously reported (1, 2). NMR spectra were obtained using a spectrometer[1] equipped with a variable-temperature probe and operated at power levels below saturation. Temperatures were measured with a thermocouple mounted in the probe; temperature calibration was done with ethylene glycol. Spectra were obtained in 1,1,2,2-tetrachloroethane which had been purified by distillation from phosphorus pentoxide under nitrogen. Spectra were obtained with the spectrometer locked on the solvent resonance, and chemical shifts were reported relative to the solvent.

[1] Varian-HA-100.

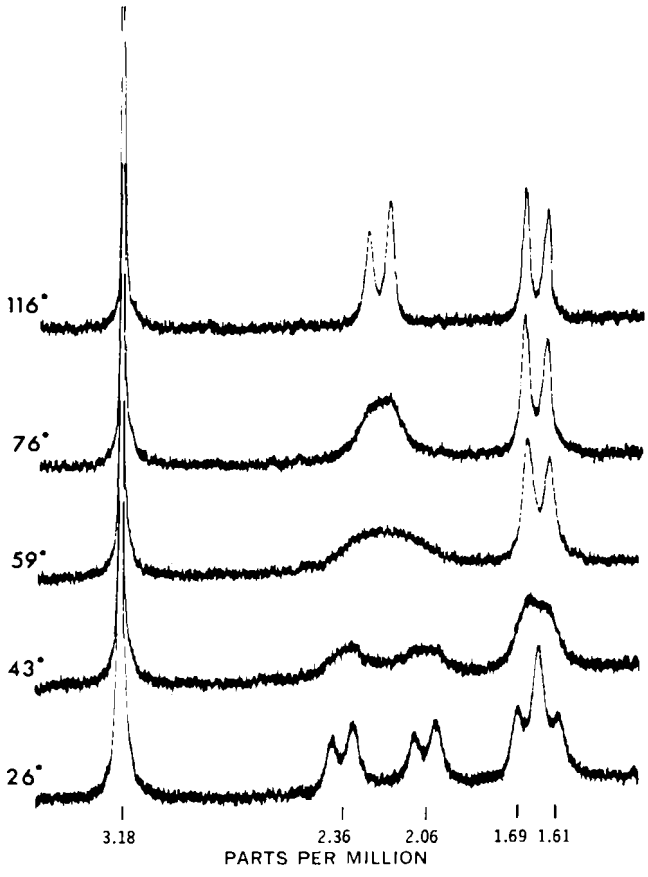

Figure 1—*NMR spectra (100 MHz.) of chloro(tetra-*p*-methylphenylporphinato)indium (III) at various temperatures.*

It has been shown that the NMR spectra of indium–tetraphenylporphine complexes at room temperature exhibit nonequivalence of the phenyl ring protons (2). The NMR spectrum of chloro(tetra-*p*-methylphenylporphinato)indium (III) in Fig. 1 shows that as the temperature rises, the phenyl signals broaden and finally collapse into a pair of doublets at approximately 100°. Spectral changes were reversible with temperature. The resonance at 3.18 p.p.m. resulted from the porphine pyrrole protons. Resonances at 2.06 and 2.36 p.p.m. were assigned to the *ortho*-protons; resonances at 1.61 and 1.69 were assigned to the *meta*-protons (2).

The room temperature spectrum has been assigned an *AA'BB'* pattern in which the two different *ortho*- and *meta*-protons are nonequivalent due to restricted rotation about the *meso*-carbon to phenyl (carbon carbon) bond. As the temperature was elevated, the rotation became fast on the NMR time scale, appearing to yield equivalence of *ortho*- and the *meta*-protons. No attempt was made to obtain accurate kinetic parameters for this highly coupled spin system; the rate of averaging can be estimated (3) as 66/sec. at the coalescence temperature of approximately 60° for the *ortho*-protons: ($\Delta G^{\ddagger}_{333}$ = 16.8 kcal./mole).

The concept of restricted rotation about the carbon-to-carbon bond is strongly supported by X-ray diffraction studies on porphines and porphine complexes (4). Such studies have indicated that the *meso*-phenyl rings are tilted at an angle to the mean plane of the porphine ring (5–7). This angle was found to be approximately

90° in many metal complexes of tetraphenylporphine (4, 8), although angles as small as 69 (9) and 76° (10) were found in certain metal complexes. Steric interactions between pyrrole hydrogen and phenyl hydrogen atoms have been estimated to require a dihedral angle of 60 (10) or 70° (4).

The sequence of spectral changes given in Fig. 1 is nearly identical to those reported for tetrakis[(*p*-isopropylphenyl)porphinato]ruthenium carbonyl complexes (8, 11). The averaging process for the indium complex occurs at slightly lower temperatures than for the ruthenium complex.

Phenyl ring rotation has been observed in tetra-*o*-hydroxylphenylporphine and its copper complex (12). The rate constant for rotation of the free porphine at 23° in methanol was 1.5×10^{-5}/sec. ($\Delta G^{\neq} = 24$ kcal./mole); rotation was about 10 times slower for the copper complex. Isomers of tetra-*o*-tolylporphine and its nickel complex have also been studied (13). The NMR signals for the methyl resonances of this compound did not appreciably broaden up to 180°, indicating that $\Delta G^{\neq}$ for rotation exceeds 26 kcal./mole (13). The present studies of chloro(tetra-*p*-methylphenylporphinato)indium (III) confirm earlier observations on ruthenium complexes (II); there appears to be a more rapid phenyl group rotation when the *ortho*-substituent is hydrogen than when it is hydroxyl or methyl.

Alternative interpretations of the NMR spectrum for chloro(tetra-*p*-methylphenylporphinato)indium (III) appear less plausible. Since *AA'* and *BB'* coupling was not resolved for indium (III) tetraphenylporphine, it is possible to attribute the room temperature spectra to rapidly rotating phenyl groups in nonequivalent positions with accidental degeneracy of nonequivalent pyrrole and methyl resonances. The temperature dependence of such a spectrum would result from the interchange of nonequivalent phenyl sites. However, it has been demonstrated that phenyl rotation is slow in the ruthenium complexes at room temperature (8, 11); it is not likely that rotation would be fast in the chloro(tetra-*p*-methylphenylporphinato)indium (III) complex at the same temperature. If the chloride in the indium complex were dissociated, ion migration or inversion of a "dished" ring conformation could explain the NMR results; however, there are no data to substantiate such an interpretation.

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Received April 5, 1973.

Accepted for publication June 26, 1973.

The authors are indebted to the "Little Red Door" (Marion County Cancer Society) of Indiana for support of this research. The authors thank Dr. Frank P. Lloyd, Methodist Hospital; Dr. Eugene Cordes, Indiana University; and Dr. Harold Boaz, Eli Lilly & Co., for their interest and assistance.

Portions of this work were done in the laboratory of Professor R. H. Holm, Massachusetts Institute of Technology, whom S. S. Eaton and G. R. Eaton thank for support under National Institutes of Health Grant GM-15471.

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Specificity of Binding to Human Serum Albumin

Keyphrases ☐ Drug-human serum albumin binding—specificity, lipophilic dependency, equations ☐ Binding, drug-human serum albumin—specificity, lipophilic dependency, equations

Sir:

Whitehouse *et al.* (1) suggested the need for reevaluation of the widely held concept (2, 3) that the fraction of certain acidic drugs bound to plasma protein is pharmacologically inactive. In support of this suggestion, data were presented indicating that a correlation exists between the ability of certain anti-inflammatory agents and uricosuric agents to displace uric acid from its primary binding site on human serum albumin *in vitro* (1) and their ability to reduce uric acid binding capacity *in vivo*. The results of other studies were cited to support this thesis (4, 5). One cited study showed that fatty acids displace warfarin and phenylbutazone from their binding sites on human serum albumin *in vitro* (5).

A relationship was recently shown (6) between the ability of certain acidic drugs to displace albumin-bound uric acid and their affinity for the primary binding site of 5-dimethylaminonaphthalene-1-sulfonamide on human serum albumin. Analysis of these affinity data revealed that for certain members of two classes of nonsteroid anti-inflammatory and uricosuric agents—*viz.*, (*a*) carboxylic acids, and (*b*) benzenesulfonamides and