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Cycloheptaamylose Inclusion Complexes of Barbiturates: Correlation between Proton Magnetic Resonance and Solubility Studies

Keyphrases □ Cycloheptaamylose inclusion complexes—barbiturates □ Proton magnetic resonance—analysis

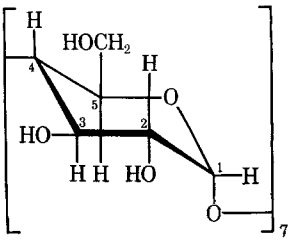
Sir:

In the past few years, Lach and his coworkers (1–5) reported extensively on the complexation of cycloamyloses (cyclodextrins) with various medicinally useful molecules. These studies, based upon the solubility method of Higuchi and Lach (6), are indicative of stereospecific interactions between drug and cycloamylose molecules; however, they do not provide *direct* evidence for inclusion of the solute within the cycloamylose cavity. Elucidation of the mechanism of such interactions, therefore, remains largely speculative.

We recently described a proton magnetic resonance (PMR) method for examining the mode of interaction of cycloheptaamylose with a variety of aromatic substrates (7). Our method is based upon the rationale that when an aromatic moiety is included within the cavity of the doughnutlike cycloheptaamylose molecule (I)[1], protons located within the cycloheptaamylose cavity (H-3, H-5, and, possibly, H-6) undergo appreciable shielding due to the anisotropy of the aromatic moiety, whereas protons located at the exterior of the torus (H-1, H-2, and H-4) are relatively unaffected. We have now extended our studies to complexation of some pharmacologically active barbituric acid derivatives (II). In the present communication, we demonstrate a correlation between results obtained by the conventional solubility method and by our PMR method.

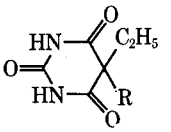
Formation constants (K_f), determined by the solubility method, and the substrate-induced chemical shift changes ($\Delta\delta$) for a variety of cycloheptaamylose–barbiturate complexes are listed in Table I. It is evident from the results shown in this table that a parallel trend exists between K_f and $\Delta\delta$; *i.e.*, K_f and $\Delta\delta$ for H-5 are of the order: barbital < amobarbital < pentobarbital < phenobarbital. From a comparison of the relative magnitudes of $\Delta\delta$ for H-5 and H-3, it appears that association takes place by approach of the barbiturate from the primary hydroxyl side of cycloheptaamylose. For phenobarbital, $\Delta\delta$ for H-5 is the largest, which indicates that the anisotropic moiety (the phenyl side chain) of this barbiturate penetrates the cycloheptaamylose cavity. This penetration is apparently rather shallow when compared with that previously observed for simple aromatic substrates (7), since $\Delta\delta$ for H-3 is minimal. For the other barbiturates also, $\Delta\delta$'s for H-5 are significant and positive. This observation would be consistent with the well-recognized upfield shifts due to hydrophobic interactions. Such interactions could result from inclusion of the nonpolar, aliphatic side chains of the barbiturates within the cavity.

The fact that barbital, amobarbital, and pentobarbital, with their respective ethyl, isopentyl, and *n*-pentyl side chains, show a corresponding order in the $\Delta\delta$ of H-5 and in the formation constants supports the suggested mode of interaction. The formation constant for phenobarbital is the highest, an apparent consequence of the snug fit of the phenyl ring relative to the aliphatic side chains of the other barbiturates. Hydrogen bonding between the heterocyclic barbiturate nucleus and the primary hydroxyl groups of cycloheptaamylose also could be partly responsible for the interaction. Such a possibility would not be precluded by the suggested hydrophobic interaction.



cycloheptaamylose

I



	R
barbital	$-CH_2-CH_3$
amobarbital	$-CH_2-CH_2-CH(CH_3)_2$
pentobarbital	$-CH(CH_3)-CH_2-CH_2-CH_3$
phenobarbital	$-C_6H_5$

barbiturates

II

[1] The constituent glucose units of cycloamyloses are known to have the Cl chair conformation (8–10). Space-filling molecular models (Corey–Pauling–Koltun) show that the interior of the cycloheptaamylose cavity has, from the primary hydroxyl side, successive layers of H-6, H-5, the ring oxygens, and H-3.

Table I—Formation Constants (K_f) for Cycloheptaamylose–Barbiturate Interactions and Substrate-Induced Shifts for Cycloheptaamylose Protons at 30°

Substrate	K_f[a]	$\Delta\delta$[b], p.p.m. H-1	H-2	H-3	H-4	H-5	H-6
Barbital	1.51×10^2	−0.10	−0.03	0.00	−0.03	+0.05	0.00
Amobarbital	1.24×10^3	−0.02	−0.02	+0.03	−0.03	+0.12	+0.01
Pentobarbital	1.82×10^3	−0.01	−0.02	−0.01	−0.02	+0.13	+0.00
Phenobarbital	3.60×10^3	+0.04	+0.03	0.00	+0.06	+0.31	+0.11

[a] Calculated according to Thoma and Stewart (9) from solubility data obtained by the method of Higuchi and Lach (6). [b] Substrate-induced shift $= \Delta\delta = (\delta_{free} - \delta_{saturated}$ with barbiturate). Determined from chemical shifts measured at 100 MHz. (relative to tetramethylsilane as external reference) of about 2% (w/v) solution of cycloheptaamylose in D_2O without, and saturated with, the respective barbiturates. Accurate to ±0.02 p.p.m.

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BOOKS

Pharmacognosy 6th Edition. By E. P. CLAUS, V. E. TYLER, and L. R. BRADY. Lea & Febiger, Philadelphia, PA 19106, 1970. xii + 518 pp. 18 × 26 cm. Price $17.50.

A fresh revision of a widely adopted, standard textbook is always a welcome event. The appearance of this, the 6th revised edition of Gathercoal and Wirth's classic contribution to pharmacognosy, is no exception.

This revision will continue to provide a useful service, particularly as an undergraduate textbook in pharmacognosy. The authors have attempted to organize and include information that is pertinent to the current concepts of the science and to satisfy the needs of the individual training to practice the profession of pharmacy.

The arrangement of the material is essentially the same as in the previous edition, but several changes have been made. A number of illustrations of histological sections of crude drugs and microscopic elements of powdered drug samples have been eliminated. Likewise, some of the botanical descriptive material has been reduced in bulk or deleted. On the other hand, the number of chemical structures and biosynthetic pathways of important plant and animal constituents has been increased which is in keeping with the current trend on more emphasis on the chemical rather than the botanical phases of the science. References to specific editions of the *United States Pharmacopeia* or *National Formulary* in which a drug was included have been omitted. The useful references, included at the end of each chapter, have been updated and in several instances are more comprehensive than in the previous edition.

The introductory material in several instances, including antibiotics, has been expanded and is quite complete. The photographs and illustrations are well chosen, are good in quality, and serve as a valuable addition to the written text.

It is somewhat unfortunate that the Appendix on Powdered Drugs has been deleted. Although this may be of minor importance for teaching purposes, it has served as a handy reference when this sort of information was needed.

The book will serve as a valuable teaching tool and is versatile enough to allow for the several avenues that may be employed in teaching the subject. The material is inclusive enough to make it a good reference as well. Those students and teachers who use it should want to make it a permanent part of their professional collection.

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Molecular Radiation Biology. By HERMANN DERTINGER and HORST JUNG. Springer-Verlag, Berlin, West Germany, 1970. 15 × 23 cm. x + 237 pp.

The field of radiobiology extends into a number of related disciplines. Since it is broad and important enough to accommodate scientists of many backgrounds and interests, it is quite difficult to define its borderlines. However, it would seem quite possible to establish some basic principles in determining the extension of radiobiology into other associated areas.

This book is a collection of lecture topics on radiobiology. It does not present the fundamental principles of molecular radiation biology *per se*, but it offers certain specific problems of this field