in the gut might also have been important. Houston and Levy reported that by inhibiting gastric emptying and GI motility, the same carbonated beverage used in this study altered the absorption rates of riboflavin and salicylamide (14). These effects were due to the phosphoric acid and carbohydrate in the carbonated beverage. In another study (15) the authors showed that propantheline bromide, an inhibitor of gastric emptying and GI motility, decreased the rate and extent of lead absorption by ~50%, suggesting that lead absorption is modified by the degree of agitation of the gut contents, among other factors. The phosphate-buffered, saline laxative functions as such by retaining water in the gut, and indirectly increases GI motility (16). Both of these actions could have counteracted the effect of decreased solubility on lead absorption.

Although abolition of lead absorption was not achieved by these products, the inhibitory effects are comparable to those shown for excess calcium and iron; administration of lead with 250-fold and 1000-fold molar excesses of calcium decreased lead absorption 46 and 43%, respectively, in rats (17, 18). Iron, at amounts 100-fold and 1000-fold greater than lead, decreased lead absorption in rats 20 and 80%, respectively (19).

Since the consequences of lead intoxication are severe (20), especially in children, prevention of undue lead exposure is very important. The household products identified here have been shown to significantly reduce lead absorption in rats when administered acutely. These agents might, therefore, also be useful in decreasing lead exposure after lead ingestion in humans. Their relatively nontoxic nature and easy accessibility make them attractive candidates for such use, particularly for children with a history of pica. Of course, the potential for use of these products is suggested only as an adjunct or supportive measure, and is not intended to replace therapeutic intervention for relief of the symptoms of lead toxicity.

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Zn(II)–Theophylline–Ethylenediamine: Structure and pH Stability

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Abstract □ A zinc-containing salt of theophylline, Zn(II)-aminophylline, was synthesized and its structure determined by X-ray diffraction techniques. The zinc ion is coordinated to two theophylline anions and a molecule of ethylenediamine in a tetrahedral arrangement. The solubility of the compound in water at 30° (0.047 mg/ml) is 180-fold lower than that of theophylline (8.40 mg/ml). The complex is relatively stable in the alkaline pH range, but it hydrolyzes, releasing theophylline in acidic environments. The rate of theophylline release is pH dependent. These properties are useful in formulating chewable tablets and liquid suspension dosage forms that overcome the characteristic bitter taste of theophylline, yet provide for efficacious treatment of diseases involving the respiratory tract.

Keyphrases □ Zn(II)–Aminophylline—structure determination by X-ray diffraction, release rate of theophylline, potential for use in oral preparation □ X-ray diffraction—Zn(II)–aminophylline, release rate of theophylline, potential for use in oral preparations □ Theophylline release rate—Zn(II)–aminophylline complex, X-ray diffraction, potential for use in oral preparations

Theophylline, a naturally occurring xanthine alkaloid derivative, possesses potent bronchodilating properties. Consequently, for nearly half a century both it and its ethylenediamine salt, aminophylline, have been used extensively in the treatment of diseases involving the respiratory tract (1). In particular, they have been shown to be efficacious in the treatment of asthma (2), exercise-induced bronchospasm (3), Cheyne-Stokes respiration (4), and chronic bronchitis/emphysema (5).

Although the pharmacologic properties of this drug are beneficial for such disorders, some of its physicochemical properties hinder totally effective therapy. First, the

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Table I—Positional Parameters [a]

Atom	x/a	y/b	z/c
Zn(II)	0000	5604(2)	2500
N(1)	−3874(11)	5243(9)	−383(6)
C(2)	−4880(12)	6247(12)	−762(7)
N(3)	−4619(10)	7302(10)	−283(6)
C(4)	−3445(11)	7676(11)	501(6)
C(5)	−2500(11)	6345(11)	843(6)
C(6)	−2666(12)	5232(11)	374(7)
N(7)	−1474(10)	6681(9)	1627(6)
C(8)	−1861(12)	7814(12)	1706(7)
N(9)	−3081(11)	8266(10)	1037(6)
C(1)	−4189(14)	4131(13)	−930(8)
O(2)	−5897(9)	6152(9)	−1458(5)
C(3)	−5613(14)	8360(12)	−631(8)
O(6)	−1873(9)	4292(9)	619(6)
N(E)	1009(11)	4192(9)	2294(6)
C(E)	772(14)	3047(13)	2594(8)

[a] Estimated standard deviations in parentheses (all times 10^4).

aqueous solubilities of theophylline and aminophylline at 25° are 8.33 and 200.00 mg/ml, respectively (6). Such solubilities lead to considerable dissolution of the compounds in human saliva. This coupled with the fact that xanthine derivatives impart a characteristic bitter taste (7), leads to palatability problems. Of special concern are chewable tablets and liquid preparations. Attempts to mask this characteristic bitter taste in the latter dosage form have not been highly successful (8), and this has resulted in noncompliance problems (8, 9). Failure to take this drug as prescribed could be exacerbated further by the characteristics of the population most likely to be medicated with these oral dosage forms. In particular, Blackwell (9) has reported that noncompliance occurs most often in the extreme age groups: the pediatric and geriatric patient populations.

Second, once ingested as a conventional tablet dosage form, theophylline is rapidly absorbed from the GI tract. This can result in a spiking effect, where theophylline serum concentrations rise very quickly. It is widely accepted that serum concentrations of theophylline should be maintained within the range of 10–20 μg/ml to facilitate effective therapy and avoid side effects (10). Such rapid

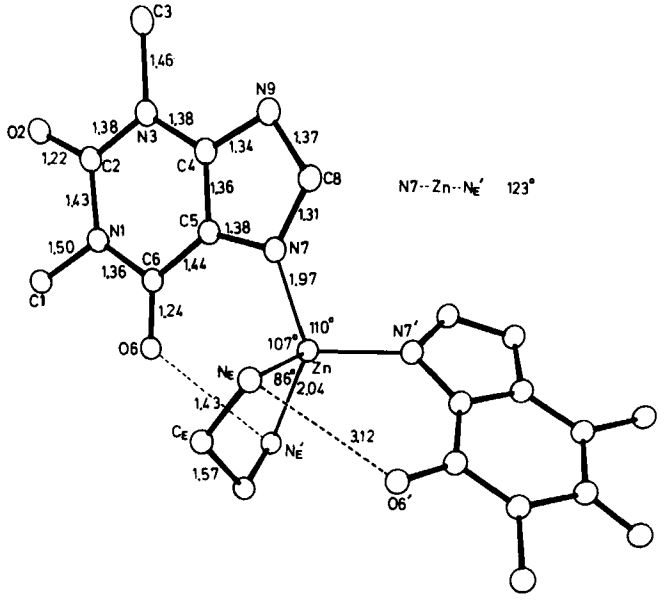

Figure 1—*Molecular structure of Zn(II)–aminophylline as determined by single-crystal X-ray diffractometry. Relevant bond angles and lengths are indicated.*

Table II—Intermolecular Contacts

Atom	Atom	Symmetry Operation Applied to Coordinates of Second Atom	Distance
N(E)	O(2)	1 + x, 1 − y, 0.5 + z	3.00(2)Å
N(E)	O(6)	x, y, z	3.12(2)Å
N(E)	N(7)	−x, y, 0.5 − z	3.23(2)Å
N(E)	N(9)	0.5 + x, y − 0.5, z	3.27(2)Å
C(8)	O(2)	0.5 + x, 1.5 − y, 0.5 + z	3.32(2)Å

absorption of theophylline can lead to serum concentrations that exceed 20 μg/ml, resulting in toxic side effects.

In an effort to overcome some of the problems associated with the use of theophylline, a zinc–aminophylline complex has been prepared. The preparation, molecular structure and physicochemical properties of this salt are discussed.

EXPERIMENTAL

Preparation—Fifty grams of anhydrous theophylline[1] was dissolved in 250 ml of an ethylenediamine solution (4.2% by volume) and subsequently diluted to 2.5 liters. It is important to maintain the pH of the solution between 8.0–9.0 to maximize the yield; it should be adjusted by the addition of ethylenediamine.

After warming the solution to approximately 60°, 250 ml of a 10% aqueous solution of $ZnSO_4 \cdot 7H_2O$[2] was added. The crystals of the zinc–aminophylline complex that formed were filtered and washed with cold water.

The initial precipitate that was formed in the reaction vessel had a colloidal appearance, but slowly transformed into octahedral prisms. The transformation could be accelerated by heat.

Recently, Zitzman *et al.* (11) used a similar procedure to prepare zinc(II) complexes of theophylline with ammonia and methylamine.

Crystal Structure Analysis—The isolated crystals were subjected to X-ray diffraction analysis to determine their molecular structure. They were found to be monoclinic, belonging to space group C 2/c based on systematic absences observed in the diffraction pattern of single-crystal crystals. The measured cell dimensions for these crystals are a = 11.222(4), b = 10.550(3), c = 19.496(10) Å, and β = 122.66(3) Å.

Intensity data were measured by the stationary counter-stationary crystal technique using balanced filters for the CuK radiation used on a diffractometer[3]. In the range of data collection ($20 \leq 110°$) 1154 reflections of the 1303 unique data had peak intensities significantly greater than background. An absorption correction, based on the anisotropy of transmission of the X-rays as a function of the diffractometer angle ϕ, was applied to the data as well as the usual Lorentz-polarization correction.

A trial structure was obtained by direct methods using the program MULTAN (12). The structure was refined by the Fourier and least-squares methods. The positions of the hydrogens could not be accurately assessed from difference electron density maps and were excluded from the refinement. The final R value (usual crystallographic reliability factor) was 0.11 for the observed data. The final positional parameters for the molecule are listed in Table I.

Solubility—The apparent aqueous solubilities of the complex and theophylline were determined at 30°. An excess quantity of material was added to a flask containing deionized water. The flasks were then placed in a water bath (30°) and allowed to equilibrate with agitation. Samples were withdrawn through a 1-μm millipore filter[4] and subsequently assayed for theophylline by a high-performance liquid chromatographic technique (13).

Hydrolysis of Complex—The hydrolysis of the complex was evaluated by placing 300 mg into 200 ml of a buffered solution (0.1 *N* HCl, pH 0.96; 0.1 *N* NaOAc, pH 4.73; 0.1 *N* Na_3PO_4, pH 7.39). These solutions were agitated by means of a magnetic stirrer and their temperature maintained at 25°. Filtered samples were withdrawn at regular intervals and assayed for theophylline spectrophotometrically at 270 nm.

[1] Ruger Chemical Co., Hillside, N.J.
[2] Fisher Scientific Co., Fair Lawn, N.J.
[3] General Electric XRD-6.
[4] Millipore Corp., Bedford, Mass.

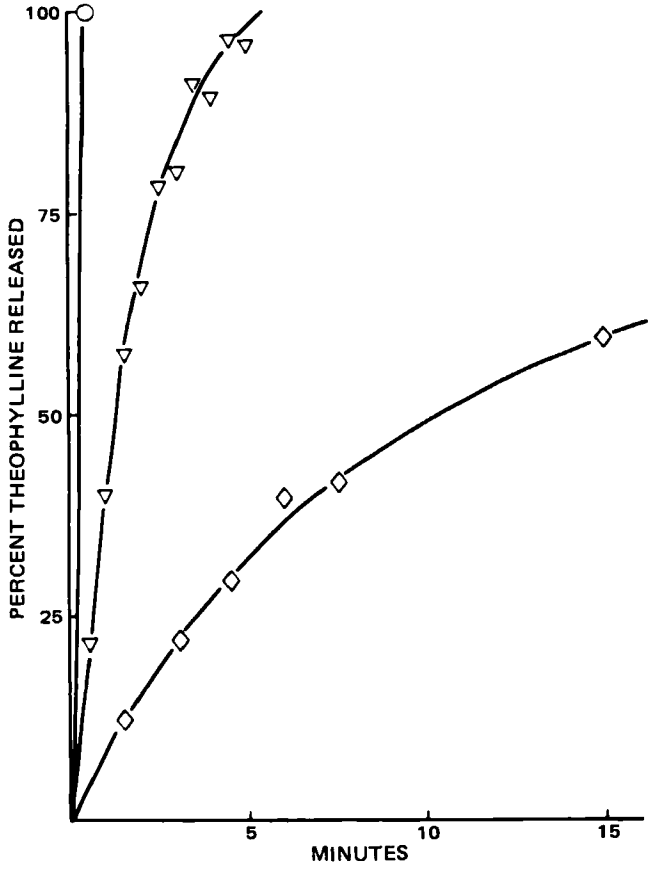

Figure 2—*Apparent hydrolysis of Zn(II)–aminophylline as a function of time at various pH values. Key: (○) 1; (▽) 4.8; (◇) 7.4.*

Though the same batch of material was used throughout these studies, its particle size distribution was not determined.

Two hundred milligrams of pure theophylline was placed in 200 ml of the appropriate buffer for each system. These solutions were sampled in tandem with the complex–buffer systems to serve as appropriate controls. The pH of the solution was monitored periodically throughout the course of these studies.

RESULTS AND DISCUSSION

Molecular Structure—The spatial disposition of theophylline and ethylenediamine around the zinc ion is shown in Fig. 1. The zinc atom is tetrahedrally coordinated. The distortion of the coordination angles from their ideal tetrahedral value of 109.5° is to a large measure due to steric factors and hydrogen-bond interactions.

Zinc is commonly found to be tetrahedrally coordinated in complexes with nitrogen ligands. The Zn—N distances in such complexes range from 1.99 to 2.10 Å (14–16). The more basic the nitrogen ligand the shorter the length; in this case the distances between theophylline and zinc are significantly shorter than those between ethylenediamine and zinc.

In general, the intramolecular bonding parameters found for the theophylline anion are quite similar to those reported for the acidic form of theophylline (17–19). There is one bond which appears to undergo a substantial change upon dissociation of the N(7) proton. The C(9)—N(9) is longer in the anionic form (1.37 Å) than the acidic form (range 1.31–1.33 Å).

The theophylline moiety exhibits a small but significant degree of distortion from planarity. This has previously been observed for theophylline (18, 19), and a wide variety of purine compounds. In most instances the purine ring is bent above the C(4)—C(5) bond. The two rings comprising the purine nucleus are only slightly tilted from planarity (0.7 Å) in this structure.

The ethylenediamine residue is in the *synclinal* conformation. The torsion angle about the ethylene bond is 53°.

Intermolecular Bonding—The ethylenediamine nitrogen atoms, N(E), are in close proximity to a number of atoms (Table II). Although the hydrogen atoms attached to N(E) were not clearly discernible from electron density maps, geometrical considerations of these short contacts suggest that they are hydrogen bond interactions. It appears that both hydrogen atoms on N(E) are involved in bifurcated hydrogen bonds: one hydrogen being shared by N(7) and O(2) and the other by N(9) and O(6). In addition to these intermolecular interactions, the hydrogen on C(8) appears to be involved in a weak hydrogen bond with O(2). This type of interaction has been observed in the other reported theophylline structures (17–19).

Apparent Hydrolysis—The hydrolysis of the Zn(II)–aminophylline complex was found to be strongly affected by changes in pH (Fig. 2). The lower the pH the faster the hydrolysis. Complete hydrolysis is accomplished in <1 min at pH 1. At pH 7.4, the apparent hydrolytic rate was markedly reduced. As noted in Fig. 2, after 15 min only 60% of the total theophylline content in the complex was released. Since this phenomenon is directly influenced by particle size, the hydrolytic rate could be slowed by increasing the particle size of the sample.

A separate solubility experiment was conducted at 30° to determine the apparent aqueous solubility of the complex in relation to that of theophylline. It was determined that the apparent aqueous solubility of the complex was 0.047 mg/ml as compared with 8.40 mg/ml for theophylline. This reflects a 180-fold difference. Apparent solubility studies for the complex alone are impossible to conduct at pH values lower than 8.2, due to hydrolysis.

Figure 2 gives some insight into the usefulness of this new salt in formulating liquids and chewable tablets. At salivary pH, 6.40–8.24 for children (20) and 5.8–7.1 for adults (21), these profiles predict relatively slow release of theophylline from the complex, and consequently a substantial reduction in the bitterness associated with theophylline therapy.

Once the complex is ingested, the pH of the gastric environment is sufficiently low to effect rapid hydrolysis. This has been borne out in some preliminary human and animal bioavailability studies[5]. The theophylline plasma concentration after oral administration of the complex was comparable to those following dosing with anhydrous theophylline. However, with the use of appropriate buffering excipients, formulations have been designed that can control the hydrolysis rate and, therefore, the release rate of theophylline from the complex in the GI tract.

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