# Thermal Dissociation of Sulfonylureas: Dissociation of Tolbutamide in a Series of Aliphatic Alcohols and in Polyethylene Glycol 400

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**Abstract** □ A study on the thermal dissociation of tolbutamide (I) in a series of 12 primary aliphatic alcohols, $C_1$ to $C_{18}$, and in polyethylene glycol 400 USP at 80° is presented. It is shown that the compound dissociates in only one of two possible fashions, *i.e.*, only to give butylamine and *p*-toluenesulfonyl isocyanate. In all cases, an *N*-(*p*-toluenesulfonyl)carbamate, formed by reaction of the sulfonyl isocyanate with the alcohols, was present in the equilibrium mixture. *p*-Toluenesulfonamide and alkyl *N*-butylcarbamates, arising from the other possible dissociation, were never evidenced. The results are consistent with a mechanism involving, as the first step, a preferential conversion of I into one of two possible tautomeric forms.

**Keyphrases** □ Sulfonylureas—thermal dissociation in alcohols, polyethylene glycol 400 □ Tolbutamide—thermal dissociation in alcohols, polyethylene glycol 400 □ Dissociation, thermal—tolbutamide in alcohols, polyethylene glycol 400 □ TLC—separation, identification □ UV spectrophotometry—analysis □ Alkyl *N*-(*p*-tosyl)carbamates—formation, synthesis

Although 1,3-disubstituted sulfonylureas, in view of their importance as oral hypoglycemic agents, have been widely investigated from the synthetic and analytical standpoint, little is known about their chemical reactivity. The acid hydrolysis of tolbutamide (I), carbutamide, and chlorpropamide has been investigated by Vogt (1), and Haussler and Hajdù (2) have reported on the hydrolytic breakdown of I in alkaline solution. More recently, Ulrich and Sayigh (3) have described a method for the preparation of isocyanates based on the pyrolysis of some sulfonylureas in high-boiling solvents.

In a previous communication (4), it was reported that the tolbutamide, carbutamide, or chlorpropamide content of some o/w creams for topical use showed a significant decrease when the said drugs were dissolved at 70–80° in the oil phase of the emulsions. No such decrease occurred when the sulfonylureas were incorporated into the bases at room temperature. A series of tests, carried out by heating at 80° the mixtures of I with the single components of the oil phase, showed that the observed effect was due to some components containing hydroxyl groups, such as stearyl alcohol or polyethylene glycol. This led to the investigation of the behavior of I, chosen as a representative member of the series, in a number of alcohols, in an attempt to establish the reaction course both on a qualitative and quantitative basis. Indeed, although the thermal dissociation[1] of symmetrical and unsymmetrical mono- and disubstituted ureas has been investigated under various experimental conditions (5, 6), no studies could be found in the literature on the dissociation of pharmacologically active sulfonylureas at relatively low temperatures and in media such as may occur in pharmaceutical vehicles.

The results of a preliminary investigation on the dissociation of I at 80° in 12 primary alcohols (methyl, ethyl, *n*-propyl, *n*-butyl, *n*-pentyl, *n*-hexyl, *n*-octyl, *n*-decyl, *n*-dodecyl, *n*-tetradecyl, *n*-hexadecyl, and *n*-octadecyl alcohols) and in polyethylene glycol (PEG) 400, a common constituent of pharmaceutical preparations, are the subject of this paper.

**Table I**—Tolbutamide (I), *N*-(*p*-Toluenesulfonyl)carbamates, and Butylamine Found in the Equilibrium Mixtures after 2 hr. at 80°. Initial Concentration of I was 10% w/w (37 mmoles/100 g.)

| Solvent | Tolbutamide, % w/w (mmoles/100 g.) | *N*-(*p*-Tosyl)-carbamate, % w/w (mmoles/100 g.) | Butylamine, % w/w (mmoles/100 g.) |
|---|---|---|---|
| Methyl alcohol | 7.2[a] (26.6) | — | 0.76 (10.4) |
| Ethyl alcohol | 5.8[a] (21.5) | — | 1.13 (15.5) |
| *n*-Propyl alcohol | 6.5 (24.0) | 3.1 (12.0) | 0.87 (11.9) |
| *n*-Butyl alcohol | 6.3 (23.3) | 3.5 (12.9) | 0.93 (12.7) |
| *n*-Pentyl alcohol | 6.4 (23.7) | 3.7 (13.0) | 0.93 (12.7) |
| *n*-Hexyl alcohol | 6.0 (22.2) | 4.4 (14.7) | 1.06 (14.5) |
| *n*-Octyl alcohol | 6.1 (22.6) | 4.4 (13.4) | 0.96 (13.2) |
| *n*-Decyl alcohol | 6.5 (24.2) | 4.5 (12.7) | 0.92 (12.6) |
| *n*-Dodecyl alcohol | 6.0 (22.2) | 5.6 (14.6) | 1.05 (14.4) |
| *n*-Tetradecyl alcohol | 6.0 (22.2) | 5.7 (13.9) | 1.01 (13.8) |
| *n*-Hexadecyl alcohol | 6.3 (23.3) | 6.0 (13.6) | 0.98 (13.4) |
| *n*-Octadecyl alcohol | 6.2 (23.0) | 6.5 (14.0) | 1.00 (13.7) |
| Polyethylene glycol 400 | 6.6 (24.5) | — | — |

[a] Calculated from the amount of amine found in the mixture.

## EXPERIMENTAL

A Beckman model DU spectrophotometer was used for all analyses. TLC separations were carried out on Merck F 254 silica gel plates, using the benzene–acetone–methanol–acetic acid (70:20:5:5) solvent system described by Kaistha and French (7). Tolbutamide (I) was the medicinal grade drug; it was crystallized from benzene to constant melting point (127–129°) and was shown by TLC to be free from contaminants or decomposition products. *p*-Toluenesulfonamide[2] was crystallized from ethanol, m.p. 136–137°. *n*-Butylamine was distilled prior to use, b.p. 77–78°. All alcohols (Table I) were anhydrous, analytical reagent grade products. Their purity was checked by gas chromatography. PEG 400 was found to contain 2% $H_2O$ by azeotropic distillation with toluene, and it was used as such. *p*-Toluenesulfonyl isocyanate (III) was prepared from *p*-toluenesulfonamide and oxalyl chloride as indicated by Franz and Osuch (8). *N*-(*p*-Toluenesulfonyl)carbamates, Compounds 1–12, were prepared from III and the appropriate alcohols by the method of McFarland and Howard (9); analyses and physical constants are reported in Table II. Some of the compounds had been described previously (footnotes [c] and [d], Table II), but no analytical data had been given. "PEG

[1] The term "dissociation" is preferred to the terms "decomposition" and "dearrangement" used by earlier authors, since the process is the reversal of the formation reaction (6).

[2] Fluka A.G.

**Table II**—Alkyl *N*-(*p*-Toluenesulfonyl)carbamates



| Compound No. | R | M.p.[a] | $R_f \times 100$[b] | Empirical Formula | Calcd. C | Calcd. H | Calcd. N | Calcd. S | Found C | Found H | Found N | Found S |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $-CH_3$ | 106–107°[c] | 69 | $C_9H_{11}NO_4S$ | 47.15 | 4.84 | 6.11 | 13.98 | 47.00 | 4.65 | 5.94 | 13.70 |
| 2 | $-C_2H_5$ | 82–84°[c] | 69 | $C_{10}H_{13}NO_4S$ | 49.37 | 5.38 | 5.76 | 13.18 | 49.21 | 5.42 | 5.63 | 12.89 |
| 3 | $-CH_2CH_2CH_3$ | 64–65°[c] | 72 | $C_{11}H_{15}NO_4S$ | 51.34 | 5.88 | 5.44 | 12.46 | 51.31 | 5.79 | 5.25 | 12.29 |
| 4 | $-CH_2(CH_2)_2CH_3$ | 118–120°[d] | 72 | $C_{12}H_{17}NO_4S$ | 53.12 | 6.32 | 5.16 | 11.81 | 52.98 | 6.27 | 5.12 | 11.71 |
| 5 | $-CH_2(CH_2)_3CH_3$ | 45–46°[c] | 73 | $C_{13}H_{19}NO_4S$ | 54.71 | 6.71 | 4.91 | 11.23 | 54.55 | 6.63 | 4.63 | 11.02 |
| 6 | $-CH_2(CH_2)_4CH_3$ | Oil[e] | 76 | $C_{14}H_{20}NNaO_4S$ | 52.32 | 6.27 | 4.36 | 9.98 | 52.25 | 6.11 | 4.30 | 9.77 |
| 7 | $-CH_2(CH_2)_6CH_3$ | 53–54°[c] | 77 | $C_{16}H_{25}NO_4S$ | 58.69 | 7.70 | 4.28 | 9.79 | 58.46 | 7.58 | 4.16 | 9.64 |
| 8 | $-CH_2(CH_2)_8CH_3$ | 72–74° | 79 | $C_{18}H_{29}NO_4S$ | 60.81 | 8.22 | 3.94 | 9.02 | 60.70 | 8.29 | 3.98 | 9.12 |
| 9 | $-CH_2(CH_2)_{10}CH_3$ | 87–89° | 81 | $C_{20}H_{33}NO_4S$ | 62.62 | 8.67 | 3.65 | 8.35 | 62.44 | 8.50 | 3.83 | 8.17 |
| 10 | $-CH_2(CH_2)_{12}CH_3$ | 86–87° | 81 | $C_{22}H_{37}NO_4S$ | 64.19 | 9.06 | 3.40 | 7.79 | 63.94 | 8.51 | 3.08 | 7.71 |
| 11 | $-CH_2(CH_2)_{14}CH_3$ | 86–87° | 82 | $C_{24}H_{41}NO_4S$ | 65.56 | 9.40 | 3.18 | 7.29 | 66.24 | 9.06 | 3.23 | 7.15 |
| 12 | $-CH_2(CH_2)_{16}CH_3$ | 97–98° | 86 | $C_{26}H_{45}NO_4S$ | 66.76 | 9.60 | 3.15 | 7.14 | 66.49 | 9.70 | 3.00 | 6.85 |
| 13 | PEG 400 | — | 29 | — | — | — | — | — | — | — | — | — |

[a] Determined on a Kofler block and uncorrected. All compounds were crystallized from petroleum ether, boiling range 60–80°. [b] Solvent system: benzene–acetone–methanol–acetic acid (70:20:5:5); see text. [c] *Cf.* L. Fishbein, *J. Chromatogr.*, **30**, 245(1967). [d] Synthesis described by A. Nováček and B. Vondráček, Czech. pat. 96,582 (Sept. 1960); through *Chem. Abstr.*, **55**, 15420g(1961). [e] Analyzed as the sodium salt.

400 *N*-(*p*-tosyl)carbamate," prepared from III and excess PEG 400, was not purified.

**Procedure for Study of Dissociation of I in Anhydrous $C_1$–$C_{18}$ Alcohols**—Mixtures containing I (50 mg.) and an alcohol (450 mg.) were placed in 5-ml. ampuls. The sealed ampuls were heated at 80° in an electrically controlled oil bath. The reaction temperature was selected after some preliminary trials; temperatures below 80° were insufficient for a quick dissolution of the drug in some alcohols, while higher temperatures favored formation of small amounts of unidentified side products. After 2 hr. or, for the reaction in *n*-octadecyl alcohol, at the time intervals specified in Fig. 1, the ampuls were cooled and their contents were quantitatively dissolved in acetone (25 ml.). Ten 50-μl. portions of the solution were applied on a chromatoplate as a row of points. Appropriate reference solutions [I, *N*-(*p*-tosyl)carbamates and butylamine] were also applied. After development, the areas corresponding to I ($R_f$ 0.68) and to the *N*-(*p*-tosyl)carbamates ($R_f$ reported in Table II) were evidenced by examination under a shortwave UV light and were marked. Their identity was confirmed by comparison with the standards. The marked areas were removed from the plate and quantitatively eluted with ethanol (10 ml.). The UV absorption of the solutions at 228 mμ (I) and at 226 mμ (carbamates) was recorded, applying a correction for the blank extinction value. The amounts of I and of *N*-(*p*-tosyl)carbamate were obtained by comparison with suitable standard curves. The procedure gave errors not exceeding ±5%, as proven by separate tests carried out with standard solutions of I and of carbamates. The location of butylamine ($R_f$ 0.04) was evidenced by spraying the "standard" portion of the plates with 0.5% ninhydrin solution and heating briefly at 60°. The corresponding "sample" area was removed and quantitatively eluted with ethanol (10 ml.). The determination of the butylamine content of the solution was carried out by the ninhydrin method outlined by Kaistha and French (7). In this case also, the error did not exceed ±5%.

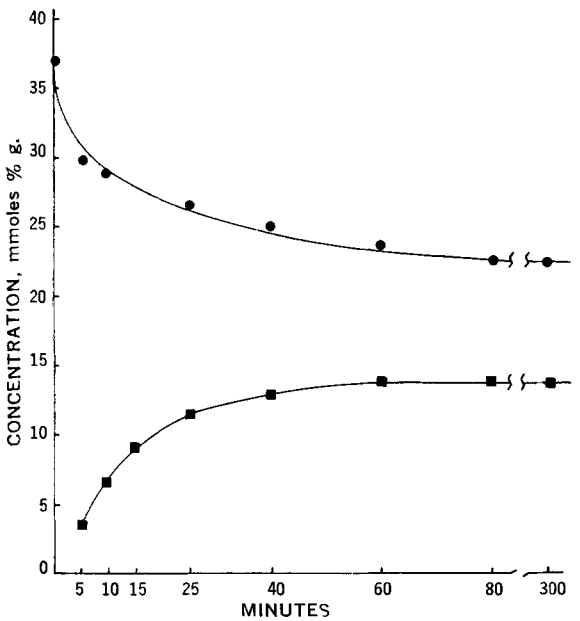



**Figure 1**—*Concentrations of tolbutamide (I)* (●) *and of* n-*octadecyl* N-(p-*tosyl*)*carbamate (Compound 12)* (■) versus *time at 80°. Initial concentration of I in* n-*octadecyl alcohol is 10% w/w (37 mmoles/100 g.).*

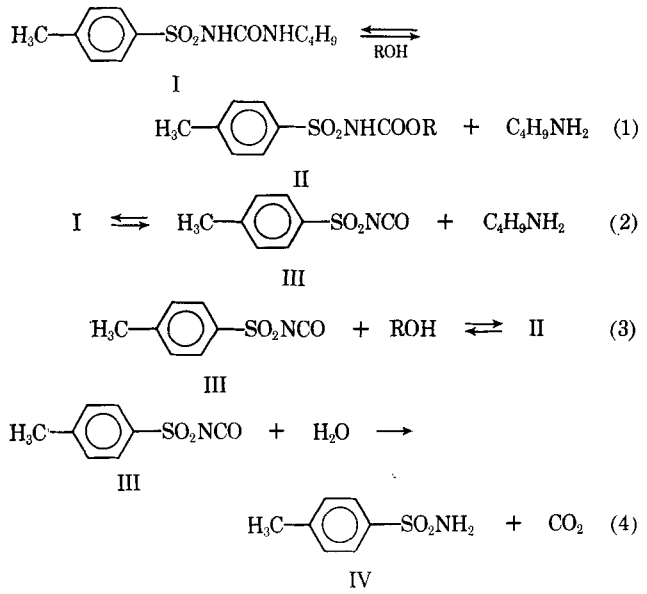
When methyl and ethyl alcohols were used as solvents, a quantitative estimation of I and of the *N*-(*p*-tosyl)carbamates was impossible, since the substances had almost identical $R_f$'s and could not be separated. In these cases, the extent of dissociation of I was calculated from the amount of amine found in the equilibrium mixtures.

**Dissociation of I in PEG 400 and in 2% Aqueous $C_1$–$C_8$ Alcohols**—One-gram samples of 10% w/w solutions of I were placed in 5-ml. flasks and heated 2 hr. at reflux temperature (methyl and ethyl alcohols) or at 80° (*n*-propyl, *n*-butyl, *n*-pentyl, *n*-hexyl, and *n*-octyl alcohols). Each flask was connected to a small gas absorption trap containing a $Ba(OH)_2$ solution. Evolution of $CO_2$ was qualitatively evidenced by a white precipitate in the trap. After cooling, a sample (500 mg.) of each mixture was dissolved in acetone (25 ml.) and processed as described previously. In this case, a *p*-toluenesulfonamide reference solution ($R_f$ 0.58) was also applied to the plates. For PEG 400, a quantitative estimation of the *N*-(*p*-tosyl)carbamate could not be effected.

**Reaction of III with Aqueous Alcohols**—To 1-g. samples of the alcohols mentioned in the preceding paragraph, placed in 5-ml. ampuls, 0.1 g. of III was added. The ampuls were sealed and heated 30 min. at 80°. After cooling, a sample (500 mg.) of each mixture was dissolved in acetone (25 ml.) and processed as described. The products consisted of a mixture containing approximately equal portions of *p*-toluenesulfonamide and of the *N*-(*p*-tosyl)carbamate of the alcohol used as solvent.

## RESULTS AND DISCUSSION

The results obtained heating 10% solutions of I in 12 straight-chain primary alcohols and in PEG 400 are summarized in Table I. In all cases, the reaction practically reached equilibrium within 2 hr., after which time about 40% of I had disappeared and other compounds, identified as *n*-butylamine and the *N*-(*p*-tosyl)carbamate of the alcohol used as solvent, were formed in stoichiometric amounts. All tosylcarbamates (Table II) were independently synthesized; some of them (Compounds 8, 9, 10, 11, and 12) were unknown. In the case of PEG 400, the carbamate had the same chromatographic behavior of a sample obtained from *p*-toluenesulfonyl isocyanate and PEG 400. No attempts were made at purification of this "PEG 400 *N*-(*p*-tosyl)carbamate" on consideration of its probably complex composition. The overall reaction of I with alcohols is indicated as (1) in Scheme I.



*Scheme I*

A more detailed study of the behavior of a 10% solution of I in *n*-octadecyl alcohol at 80° is shown in Fig. 1. The tolbutamide concentration (initially 37 mmoles/100 g.) was found to diminish as carbamate (and butylamine, not shown in the figure) formation increased, until an equilibrium mixture containing about 6.2% (23.0 mmoles/100 g.) of I, 6.5% (14.0 mmoles/100 g.) of *n*-octadecyl *N*-(*p*-tosyl)carbamate (Compound 12), and 1.0% (13.7 mmoles/100 g.) of butylamine was reached after about 1.5 hr.

In every case, the amounts of *n*-butylamine and of *N*-(*p*-tosyl)-carbamate present in the mixture satisfactorily accounted for the amount of I which had disappeared. A prolonged heating (5–10 hr.) of the solutions of I in higher alcohols resulted in formation of very small amounts of a third compound, evidenced by a fluorescent spot on the chromatographic plates. The $R_f$ of this spot (*e.g.*, 0.88 for the reaction in *n*-octadecyl alcohol) was in all cases different from those of all the possible dissociation products of I, and investigation in this direction was not pursued.

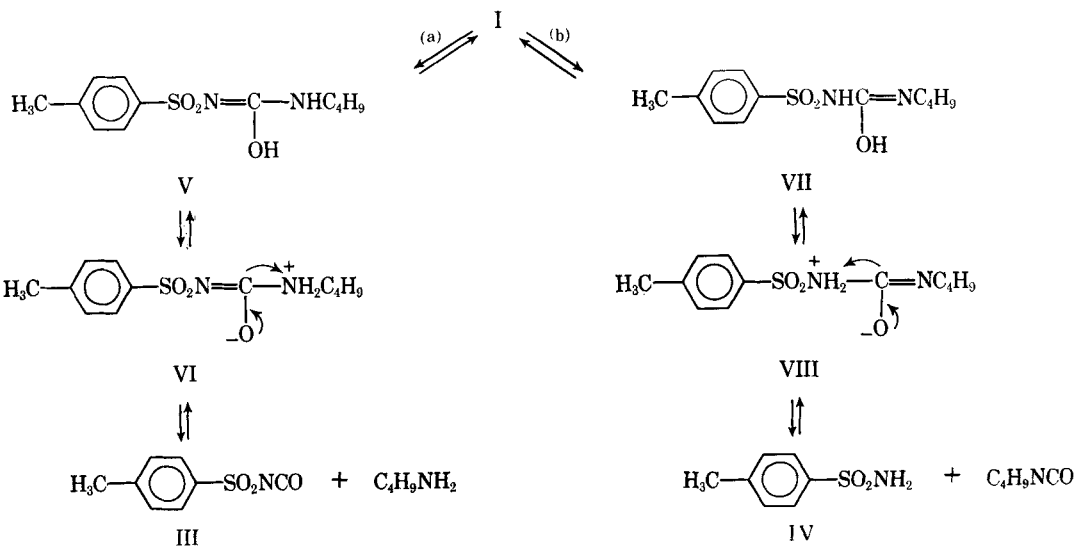
The presence of 2% water in some solvents (PEG 400 and alcohols $C_1$–$C_8$) did not influence the equilibrium concentrations of I and of *n*-butylamine. However, the equilibrium mixtures contained about 2% of *p*-toluenesulfonamide and a correspondingly reduced amount of *N*-(*p*-tosyl)carbamate. Furthermore, evolution of $CO_2$ during the reaction was observed when water was present.

The reported results might be rationalized as follows. Mono- and disubstituted ureas and some sulfonylureas are known to dissociate on heating to isocyanates and amines (3, 5, 6). The thermal dissociation of *p*-ethoxyphenylurea, for example, in aqueous solution leads to *p*-ethoxyphenyl isocyanate, ammonia, and, in minor amounts, phenetidine and isocyanic acid (10). The isocyanates originating from the dissociation are often evidenced indirectly, *e.g.*, through derivatives formed with suitable reagents. The reaction medium itself can function in some cases as one such reagent; *sym*-di-*p*-ethoxyphenylurea was assumed to dissociate to phenetidine and *p*-ethoxyphenyl isocyanate, since it gave phenetidine and *n*-butyl *N*-(*p*-ethoxyphenyl)carbamate on heating in *n*-butanol (11). The results seem to be in line with these data, and they suggest that tolbutamide dissociates on heating in the presence of alcohols to butylamine and *p*-toluenesulfonyl isocyanate. Interaction between the latter compound and the alcohol used as solvent would give the observed *N*-(*p*-tosyl)carbamate. The reactions are indicated as (2) and (3) in Scheme I.

The additional formation of *p*-toluenesulfonamide and carbon dioxide, when water is present in the reaction mixtures, can be explained assuming that water might compete with the alcohols for *p*-toluenesulfonyl isocyanate. The latter is known to react readily with water as indicated in (4), Scheme I (12). Support for this hypothesis came from experiments in which *p*-toluenesulfonyl isocyanate was allowed to react with a series of aqueous alcohols. In all cases, a mixture of *N*-(*p*-tosyl)carbamate and *p*-toluenesulfonamide was obtained, and $CO_2$ evolved during the reaction.

A significant outcome of the present study is the observation that tolbutamide, under the experimental conditions described, dissociates in only one of two possible fashions. The alternative dissociation leading to *p*-toluenesulfonamide and alkyl *N*-butylcarbamates as the end products could not be detected even to a minimal extent. A tentative rationalization of this phenomenon is presented in Scheme II, where the mechanism for the thermal dissociation of I has been patterned after that proposed by Hoshino *et al.* (6) for *sym*-diphenylurea. It can be seen that path (a), leading to the observed products, requires tautomerization of I to V, while path (b), leading to *p*-toluenesulfonamide and butyl isocyanate, requires tautomerization to VII. Tautomerization of I to V should be strongly favored by the high acidity of the NH group bound to the sulfonyl group. Furthermore, even if a small amount of VII was present at equilibrium, its subsequent conversion into the ion VIII should be rather difficult, since it would require protonation of a nitrogen atom endowed with a very low basicity. Conversely, formation of the ion VI from V should occur easily, on account of the greater degree of basicity of the nitrogen bound to the alkyl group.

Solvent effects and/or reaction temperature might play a significant role in determining the fashion and extent of the reaction. A relevant example is the formation of good yields of alkyl isocyanates and sulfonamides from 1,3-disubstituted sulfonylureas under pyrolysis conditions, where a completely different mechanism is probably operative (3). Moreover, although this proposed dissociation mechanism receives strong support from several analogous examples reported in the literature, alternative mechanisms, such as



*Scheme II*

alcoholysis, should not be entirely disregarded. Additional experiments are needed to obtain a satisfactory picture of the reaction. Further work, aimed at collecting kinetic data for the dissociation of I and of other pharmacologically active sulfonylureas in different media, is now in progress.

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# Molecular Association of Barbital and Caffeine in 2:1 Crystalline Complex


**B. M. CRAVEN and G. L. GARTLAND**



**Abstract** □ The crystal structure of the 2:1 complex of barbital with caffeine has been determined by X-ray diffraction methods. The crystals are triclinic, space group $P\bar{1}$, with $a = 14.627$, $b = 14.160$, $c = 6.902$ Å, $\alpha = 95°15'$, $\beta = 92°48'$, and $\gamma = 100°45'$, and with four barbital and two caffeine molecules in the cell. The block-diagonal least-squares refinement of 496 atomic positional and thermal parameters, based on 4665 X-ray intensity data, gave a final $R$ factor of 0.05. The structure consists of ribbons of barbital molecules linked by NH···O=C hydrogen bonds. Caffeine molecules are bound to the ribbon by an NH···N(9) hydrogen bond and by an unusual interaction involving C(8)H with two barbital oxygen atoms. Weak interactions of nonhydrogen-bonded caffeine carbonyl groups with barbital carbonyl groups may also be important in this crystal. There is minimal overlap of the flat ring systems of the component molecules.



**Keyphrases** □ Molecular association—barbital–caffeine 2:1 crystalline complex □ Barbital, molecular association—caffeine in 2:1 crystalline complex □ X-ray diffraction—barbital–caffeine 2:1 crystalline structure, determination


Barbiturates (1–3) and xanthines (4, 5) form crystalline complexes with a variety of other molecular species as well as with each other (6–8). The crystal complex of barbital with caffeine was chosen for study because consideration of the structure of the component molecules (Fig. 1) shows that the nature of barbital–caffeine association must differ in two important respects from that found in previously determined crystal structures of complexes of purines and pyrimidines.

The strong association by pairs of hydrogen bonds, which occurs in complexes of barbiturates with adenine derivatives (3, 9) and which is analogous to the hydrogen bonding in the crystal structures of nucleic acid base pairing model systems (10), cannot occur between barbital and caffeine. As a hydrogen-bonding donor caffeine can at most form a weak C(8)H hydrogen bond

The stacking together of flat molecules with extensive overlap of their $\pi$-bonded ring systems has been found in complexes of tetramethyluric acid with pyrene (11) and caffeine with 5-chlorosalicylic acid (5). This type of interaction, which has been termed polarization bonding, is postulated as an important cohesive factor in xanthine complexes (12). However, in the complex of caffeine with barbital, overlap of the two flat ring systems is largely prevented by the ethyl groups, which shield each side of the barbital ring.

The crystal structure of the 2:1 barbital–caffeine complex was determined to reveal the detailed geometry of molecular association.

## EXPERIMENTAL

Triclinic crystals (m.p. 142°) of the complex were obtained as described by Higuchi and Lach (6). The lattice parameters are $a = 14.627$, $b = 14.160$, $c = 6.902$ Å, $\alpha = 95°15'$, $\beta = 92°48'$, and $\gamma = 100°45'$. The space group is $P\bar{1}$, and there are four barbital and two caffeine molecules in the unit cell. The X-ray intensity data (4665 reflections) were collected on a four-circle automatic diffractometer using CuK$\alpha$ radiation. All 40 nonhydrogen atoms of the crystal chemical unit were found in the first E map, derived from an application of the direct method of phase determination similar to that described by Karle (13). All 34 hydrogen atoms were subsequently found in a difference Fourier synthesis. The positional and anisotropic thermal parameters for heavier atoms and positional and isotropic thermal parameters for hydrogen atoms were refined by a block-diagonal least-squares procedure to give a final $R$ factor of 0.05.

**Description of the Structure**—The crystal structure consists of stacks of hydrogen-bonded ribbons, one of which is shown in Fig. 2. The backbone of the ribbon is made up of the barbital molecules,