# Interaction of Dextroamphetamine Sulfate with Dextrates in Solution

S. M. BLAUG[▲] and WEN-TZY HUANG*

**Abstract** □ The interaction between dextroamphetamine sulfate and dextrates (a partially hydrolyzed starch composed of 92% dextrose combined with 8% higher saccharides) was studied in buffered solutions at three different temperatures and dextroamphetamine sulfate concentrations. On heating, solutions containing dextroamphetamine sulfate and dextrates became progressively darker than solutions containing dextroamphetamine sulfate or dextrates alone. Also, a new absorption maximum appeared at 298 nm. in the solutions containing dextroamphetamine sulfate and dextrates. The rate of browning in these solutions increased with increasing temperature and pH and decreased with increasing dextroamphetamine sulfate concentration. From the relationship shown in the plots of absorbance against time, the browning reaction was assumed to follow an apparent zero-order rate law and the rate constants, $k$, were calculated for all solutions containing dextroamphetamine sulfate and dextrates at pH 6 and 8 at 50, 60, and 70°. Arrhenius-type plots were also obtained and were used to approximate the browning rate at 25°. By using TLC, IR spectroscopy, and elemental analysis, the brown material isolated from the discolored solutions was identified as amphetamine-hydroxymethylfurfural. A Schiff base-type reaction was postulated involving the primary amine and the carbonyl groups of the sugar.

**Keyphrases** □ Dextroamphetamine sulfate and dextrates in solution—browning reaction, effect of temperature and pH, isolation of amphetamine-hydroxymethylfurfural □ Dextrates and dextroamphetamine sulfate in solution—browning reaction, effect of temperature and pH, isolation of amphetamine-hydroxymethylfurfural □ Amphetamine-hydroxymethylfurfural—isolated as brown material in solutions of dextroamphetamine sulfate and dextrates

Koshy *et al.* (1) studied the browning of spray-dried lactose and USP conventionally processed lactose in aqueous solutions buffered to various pH's. Spray-dried lactose was found to have a UV absorption maximum, whereas the USP conventionally processed and analytical reagent grade lactose did not. A relationship between the intensity of this maximum and the 5-hydroxymethylfurfural content was shown. This absorbance was related to browning. The pH profiles for lactose, dextrose, and galactose were similar except that galactose solutions discolored over a wider pH range, 5 and above, whereas the other two sugars discolored at pH 7 and above. The relative intensity of the browning of the three sugars was lactose > galactose > dextrose. These studies were conducted in the absence of added amines. The same authors also studied the browning of lactose spray-dried powder at different temperatures and relative humidities. Their results indicate that a combination of heat and moisture accelerates browning more than either heat or humidity. Castello and Mattocks (2) reported that the presence of amines accelerated the browning reaction in tablets containing lactose, particularly when the tablets were stored at elevated temperature and high humidity.

Brownley and Lachman (3) showed that the browning of lactose was related to the amount of free 5-hydroxymethylfurfural in the lactose. This relationship between free 5-hydroxymethylfurfural and browning was also found to exist for dextrose (4). However, the relative browning of dextrose and lactose formulations indicated that lactose was more susceptible to browning than dextrose.

The browning of lactose and dextrose in the presence of added amines was shown by Duvall *et al.* (5) to be predominantly a primary amine–carbonyl reaction. A relative visual comparison of the formulations under all accelerated conditions indicated that amine browning was worse with dextrose than with lactose. This type of browning, which has been referred to as Maillard-type browning (6), requires a relatively low order of energy for its initiation and exhibits autocatalytic qualities once it has begun.

Dextrates[1] were recently developed for use as an excipient in direct compression tablet production. Dextrates are produced by the controlled hydrolysis of starch and are composed of 92% dextrose combined with 8% higher saccharides. Henderson and Bruno (7) studied the physical properties and stability of dextrates with respect to tableting by direct compression. With regard to color stability, tablets prepared with dextrates and stored at different temperatures and humidities showed no substantial improvement over those prepared with spray-dried lactose.

To study and explain the browning reaction reported (7) to occur in solid–solid mixtures containing an amine and dextrates, it was necessary to investigate the effect of temperature and pH on the rate of the browning reaction in solutions containing dextrates and an amine such as dextroamphetamine sulfate. A later study will report the interaction between an amine and dextrates in solid–solid mixtures.

## EXPERIMENTAL[2]

**Reagents**—The following were used: dextroamphetamine sulfate USP, m.p. > 300°; dextrates, m.p. 150–152°; silica gel $GF_{254}$[3] for TLC; citric acid monohydrate[4]; analytical reagent grade dibasic anhydrous sodium phosphate[5]; and iodine USP.

**Procedure**—*Transmittance Measurements*—The reaction of dextrates with dextroamphetamine sulfate was studied in buffered aqueous solution at pH 6 and 8 using citric acid–disodium hydrogen phosphate buffers. These pH values were chosen since the browning of lactose, dextrose, and galactose solutions was reported

[1] Celutab, Penick and Ford Ltd., Cedar Rapids, Iowa.

[2] All transmittance measurements were made using the Beckman DK-2 and DU spectrophotometers. IR spectra were obtained using a Beckman IR-10 spectrophotometer equipped with sodium chloride optics and 0.1-mm. cells. Constant temperature was maintained with a Sargent heater and circulator equipped with a microset thermoregulator. All pH measurements were performed using a Beckman Zeromatic II pH meter.

[3] Hexagon Laboratories, New York, N. Y.

[4] Fisher certified, Fisher Scientific Co., Fair Lawn, N. J.

[5] Mallinckrodt Chemical Works, St. Louis, Mo.

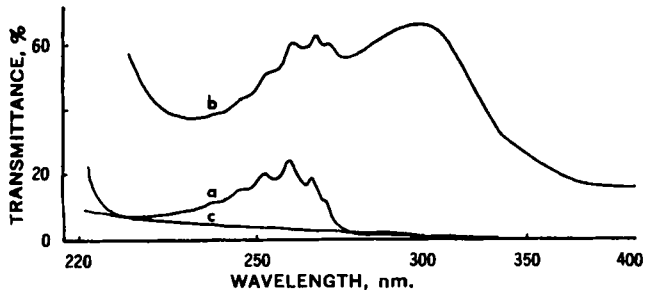



**Figure 1**—*Absorption spectra of solutions containing:* (a) *1% dextroamphetamine sulfate,* (b) *1% dextroamphetamine sulfate and 10% dextrates, and* (c) *10% dextrates in citric acid–phosphate buffer, pH 8. All solutions were heated for 2 days at 60°.*

(1) to be minimal at pH 5 and accelerated at pH 8 in the absence of added amines. Duvall *et al.* (5) studied the reaction of dextrose and galactose with amphetamine in pH 8 buffer and reported that browning was apparent in 1 day with both monosaccharides. Three solutions were prepared: (*a*) a 1% dextroamphetamine sulfate solution, (*b*) a solution containing 1% dextroamphetamine sulfate and 10% dextrates, and (*c*) a 10% dextrate solution. The solutions were heated at 60 ± 0.1° in a constant-temperature oil bath for 2 days. At the end of this time, 2-ml. aliquots were withdrawn and diluted to 100 ml. with water. The absorption spectra of these solutions were determined from 700 to 220 nm. using a spectrophotometer[6]. The blank consisted of a 2-ml. aliquot of the buffer solution that had been diluted to 100 ml. with water. The absorption spectra obtained at pH 8 are shown in Fig. 1. Similar spectra were obtained at pH 6.

*Identification of Reaction Products*—Identification of the reaction products was carried out using TLC techniques and IR spectrometry. TLC plates were prepared with an applicator[7], using silica gel $GF_{254}$ (0.25 mm. thick) as an adsorbent. Solutions containing: (*a*) 1% dextroamphetamine sulfate, (*b*) 1% dextroamphetamine sulfate plus 10% dextrates, and (*c*) 10% dextrates, buffered to pH 8 and heated for 2 days at 60° were spotted on a prepared plate. Also spotted on the plate were: (*d*) a chloroform solution of the precipitated brown material which had appeared in Solution (*b*), and (*e*) an aqueous solution containing 1.0% dextroamphetamine sulfate and 0.05% 5-hydroxymethylfurfural. The lower phase of a mixture of ethyl acetate–pyridine–water (2:1:2) was used for development, and iodine vapor and UV light were used for visualization. A composite chromatogram is shown in Fig. 2.

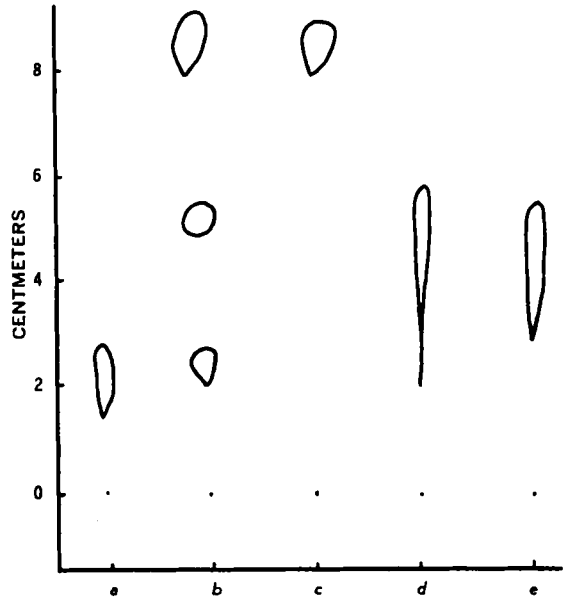



**Figure 2**—*Composite thin-layer chromatogram of dextroamphetamine sulfate–dextrates solutions (buffered to pH 8 and heated for 2 days at 60°). Key:* a, *1% dextroamphetamine sulfate solution;* b, *1% dextroamphetamine sulfate and 10% dextrate solution;* c, *10% dextrate solution;* d, *chloroform solution of precipitate from solution* b; *and* e, *1% dextroamphetamine sulfate and 0.05% 5-hydroxymethylfurfural solution. The spots were detected by iodine vapor and UV light.*

[6] Beckman DK-2.
[7] Beckman model S.

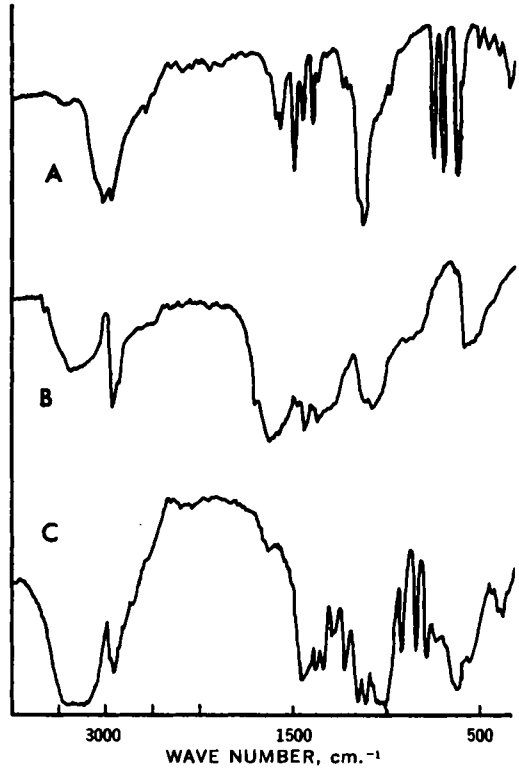



**Figure 3**—*IR spectra of:* (*A*) *dextroamphetamine sulfate,* (*B*) *the brown precipitate isolated from a solution containing 1% dextroamphetamine sulfate and 10% dextrates, and* (*C*) *dextrates. All samples were obtained after heating for 2 days at 60°.*

IR spectra of dextroamphetamine sulfate and dextrates were obtained, using KBr pellets, after heating each powder for 2 days at 60° in a constant-temperature oven. The IR spectrum of the brown material obtained from Solution (*b*) was determined in chloroform (Fig. 3).

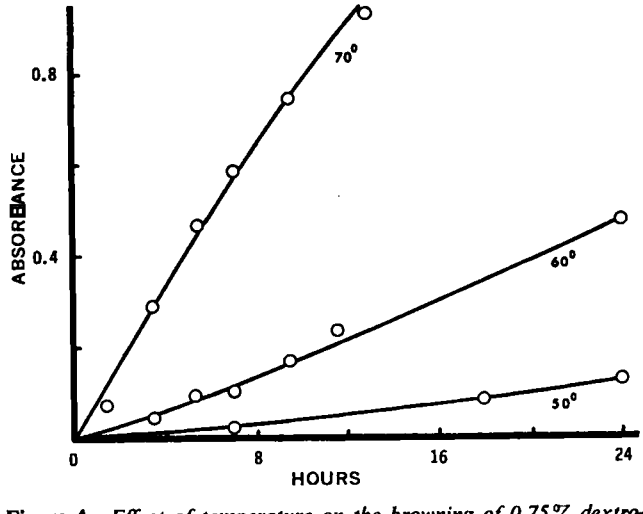



**Figure 4**—*Effect of temperature on the browning of 0.75% dextroamphetamine sulfate + 10% dextrate solutions in citrate–phosphate buffer, pH 8.*

**Table I**—Apparent Zero-Order Rate Constants for the Browning of Dextroamphetamine Sulfate–Dextrate Solutions at pH 6

| Temperature | 0.75% Dextroamphetamine Sulfate + 10% Dextrates—k, day$^{-1}$ | 0.75% Dextroamphetamine Sulfate + 10% Dextrates—log k | 1% Dextroamphetamine Sulfate + 10% Dextrates—k, day$^{-1}$ | 1% Dextroamphetamine Sulfate + 10% Dextrates—log k | 1.25% Dextroamphetamine Sulfate + 10% Dextrates—k, day$^{-1}$ | 1.25% Dextroamphetamine Sulfate + 10% Dextrates—log k |
|---|---|---|---|---|---|---|
| 50° | 0.115 | −0.9393 | 0.070 | −1.1549 | 0.065 | −1.1871 |
| 60° | 0.286 | −0.5436 | 0.200 | −0.6990 | 0.100 | −1.0000 |
| 70° | 1.063 | 0.0265 | 0.800 | −0.0969 | 0.450 | −0.3468 |

**Table II**—Apparent Zero-Order Rate Constants for the Browning of Dextroamphetamine Sulfate–Dextrate Solutions at pH 8

| Temperature | 0.75% Dextroamphetamine Sulfate + 10% Dextrates—k, day$^{-1}$ | 0.75% Dextroamphetamine Sulfate + 10% Dextrates—log k | 1% Dextroamphetamine Sulfate + 10% Dextrates—k, day$^{-1}$ | 1% Dextroamphetamine Sulfate + 10% Dextrates—log k | 1.25% Dextroamphetamine Sulfate + 10% Dextrates—k, day$^{-1}$ | 1.25% Dextroamphetamine Sulfate + 10% Dextrates—log k |
|---|---|---|---|---|---|---|
| 50° | 0.326 | −0.4868 | 0.220 | −0.6576 | 0.140 | −0.8539 |
| 60° | 0.834 | −0.0788 | 0.652 | −0.1858 | 0.400 | −0.3979 |
| 70° | 1.810 | 0.2577 | 1.313 | 0.1183 | 0.813 | −0.0899 |

*Effect of Temperature, pH, and Drug Concentration on Browning Reaction in Aqueous Solution*—Solutions containing 10% dextrates and 0.75, 1.0, and 1.25% dextroamphetamine sulfate, in pH 6 and 8 citric acid–disodium hydrogen phosphate buffers, were placed in a constant-temperature oil bath at 50, 60, and 70 ± 0.1°. Buffer solutions containing 10% dextrates were also heated in the constant-temperature baths for use as blanks. At periodic time intervals, 2-ml. aliquots of these solutions were withdrawn and diluted to 100 ml. with water. The absorbance of each solution was determined at 298 nm. in a spectrophotometer[8] equipped with 1-cm. silica cells, using the diluted dextrate solutions as blanks. Plots of absorbance against time were prepared for all solutions at pH 6 and 8 and at 50, 60, and 70 ± 0.1°. Because of the similarity in the plots, the effect of temperature on the browning reaction is shown in Fig. 4 for a solution containing 0.75% dextroamphetamine sulfate and 10% dextrates at pH 8 and the effect of pH on the browning reaction is shown in Fig. 5 for a solution containing 1% dextroamphetamine sulfate and 10% dextrates at 70°. From the relationships shown, the browning reaction was assumed to follow an apparent zero-order rate law and the rate constants, $k$, were calculated for all solutions containing dextroamphetamine sulfate and dextrates at pH 6 and 8 at 50, 60, and 70°. The calculated values are shown in Tables I and II. Arrhenius-type plots indicating the temperature dependence for the browning of dextroamphetamine sulfate–dextrate solutions in citrate–phosphate buffer, pH 8, are shown in Fig. 6.

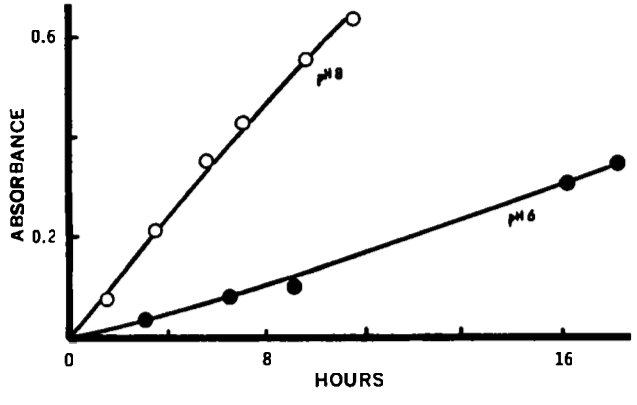



**Figure 5**—*Effect of pH on the browning of 1% dextroamphetamine sulfate + 10% dextrate solutions at 70°.*

[8] Beckman DU.

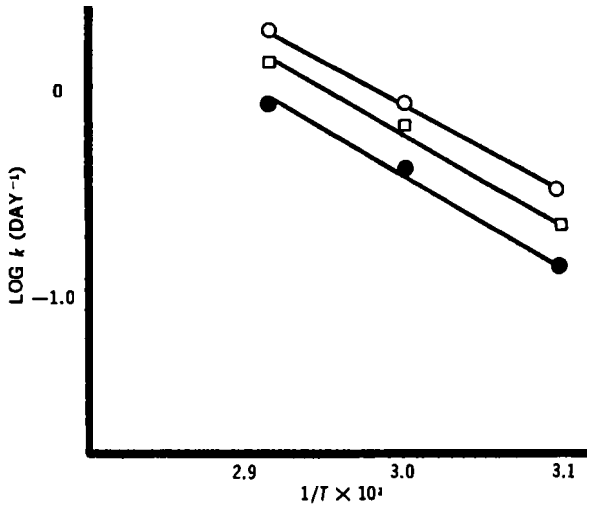


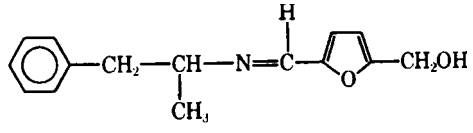

**Figure 6**—*Arrhenius-type plots showing the temperature dependence for the browning of dextroamphetamine sulfate–dextrate solutions in citrate–phosphate buffer, pH 8. Key: ○, 0.75% dextroamphetamine sulfate + 10% dextrates; □, 1% dextroamphetamine sulfate + 10% dextrates; and ●, 1.25% dextroamphetamine sulfate + 10% dextrates.*

## RESULTS AND DISCUSSION

The absorption spectra shown in Fig. 1 indicate a marked change in the absorbance curve of Solution (*b*) when compared with the spectra obtained on Solutions (*a*) and (*c*) at pH 8. The results obtained at pH 6 were the same as those obtained at pH 8, except for a decrease in the rate of browning at pH 6. On heating at 60°, Solution (*b*) became progressively darker than Solutions (*a*) and (*c*), and a brown-black precipitate appeared in Solution (*b*) after 2 days at 60°. The intensity of absorbance at 257 nm. increased considerably in curve (*b*), and a new peak appeared at 298 nm. On dilution of Solution (*b*) with water, there was a marked decrease in the absorbance at 298 nm. This phenomenon, associated with the maximum at 298 nm., is consistent with a report (8) concerning the absorption characteristics of a solution following the reaction of a primary amine with a carbonyl compound. Pigman (9) showed that reaction occurs between primary amines and aldehyde groups of open chain forms of the carbohydrates to form a Schiff base, as well as with ring forms of the carbohydrates to form glycosylamines. In either reaction, the resulting solution was colored.

Solution (*a*) did not discolor on heating at 60° and it showed a very slight increase in the intensity of the absorbance at 257 nm., the characteristic absorption maximum of dextroamphetamine sulfate, when compared with an unheated dextroamphetamine sulfate solution.

After Solution (*c*) was heated, an absorption maximum appeared at about 283 nm., which was not present in the spectrum of the unheated solution. The undiluted solution was light brown in color; however, when a 2-ml. aliquot was diluted to 100 ml. with water, the solution became colorless and the absorption peak at 283 nm. disappeared. The appearance of an absorption maximum at 283 nm. and discoloration of the dextrate solution were attributed to the decomposition of dextrose, the major constituent (92%) in dextrates. Wolfram *et al.* (10) reported that the decomposition involved the conversion of dextrose to 5-hydroxymethylfurfural, with the subsequent breakdown of this material to formic and levulinic acids and a colored material. Scallet and Gardner (11) and Joslyn (12) at-




amphetamine-hydroxymethylfurfural

tributed the discoloration of dextrose solutions to the polymerization of 5-hydroxymethylfurfural.

The discoloration of the dextrate solution was negligible compared to the browning reaction that occurred in Solution (*b*) which contained both dextrates and dextroamphetamine sulfate. Duvall *et al.* (4) reported that amines increased the extent of the browning reaction in tablets prepared from dextrose. The solubility characteristics of the brown material obtained from Solution (*b*), which had been heated for 2 days at 60°, differed from those of the brown material obtained from Solution (*c*). The residue from Solution (*b*) was soluble in chloroform, ethanol, and acetone and could be extracted from aqueous solution by these organic solvents. However, the residue from Solution (*c*) was very water soluble and could not be extracted with organic solvents.

Identification of the reaction product(s) was carried out using TLC. A composite chromatogram is shown in Fig. 2. It indicated the presence of one reaction produced at $R_f$ 0.513, which was present in Solutions (*b*), (*d*), and (*e*).

As shown in Fig. 3, the appearance of a strong absorption band at 1650 $cm.^{-1}$ (C=N) in the IR spectrum of the brown material isolated from Solution (*b*) offered further proof of the occurrence of a reaction between the amine and the carbonyl group of the sugar (dextrates). Since decomposition of dextrose involves its conversion to 5-hydroxymethylfurfural, the reaction product was postulated as amphetamine-hydroxymethylfurfural.

The brown residue obtained from Solution (*b*) was subjected to elemental analysis.

*Anal.*—Calc. for $C_{15}H_{17}NO_2$ (amphetamine-hydroxymethylfurfural): C, 74.07; H, 6.99; N, 5.76. Found: C, 73.01; H, 6.69; N, 5.98.

Elemental analysis of the precipitate was compatible with the postulated structure of the reaction product, amphetamine-hydroxymethylfurfural.

Results of the study on the effect of temperature, pH, and drug concentration on the rate of the browning reaction in solutions containing dextroamphetamine sulfate and dextrates are shown in Figs. 4 and 5 and Tables I and II. Figures 4 and 5 show that the rate of browning was faster at higher temperatures and at pH 8. In fact, the browning reaction was so slow at 50° and pH 6 that no discoloration occurred even after heating for 1 day. Data in Tables I and II also show that the rate of browning increased substantially with decreasing concentrations of dextroamphetamine sulfate. Temperature and pH were major factors contributing to the browning reaction. Browning was faster and more intense at 70° and pH 8 than it was at lower temperatures and pH 6. The calculated rate constants at 50, 60, and 70° and at pH 6 and 8 are shown in Tables I and II for the three dextroamphetamine sulfate–dextrate solutions.

Typical Arrhenius-type plots obtained at pH 8 are shown in Fig. 6. A straight-line relationship between log $k$ and $1/T$ was obtained, with a negative slope at each dextroamphetamine sulfate concentration studied. The time required for browning to occur at 25° can be obtained from such plots by determining the rate constant, $k$, at 25°. For example, the time required for browning to occur at 25° and pH 8 in the solutions containing 0.75, 1, and 1.25% dextroamphetamine sulfate and 10% dextrates was calculated as 33.4, 40.94, and 43.02 days, respectively. Except for slower browning rates, similar plots would be obtained at pH 6.

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