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Complexation of Procainamide with Hydroxide-Containing Compounds

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Abstract □ The complexation of procainamide with hydroxide-containing compounds, ethanol, fructose, glucose, glycerin, lactose, maltose, propylene glycol, sorbitol, and sucrose, have been studied. Procainamide formed a complex with glucose, lactose, and maltose, all of which contain a hemiacetal group, whereas fructose and sucrose do not. The percent of complex formed was dependent on the pH of the solution, with an optimum range of ~4–5.2. As with glucose, the percent of complex formed was directly related to the concentration of lactose in the solution. In dry mixtures, procainamide did not form a complex with glucose or lactose. The complex formed with lactose or maltose could be completely reversed by adding hydrochloric acid. A similar observation with glucose was reported earlier. In the optimum pH range, equilibrium was established in ~24 hr, and the process of complexation followed the equation for reversible reactions.

Keyphrases □ Complexation—procainamide with hydroxide-containing compounds □ Procainamide—complexation with hydroxide-containing compounds □ Hydroxide-containing compounds—complexation with procainamide

An earlier report (1) reviewed the literature concerning stability and complexation problems of procainamide in the presence of glucose. The report also presented the results of a study on the complexation of procainamide with glucose. (These two compounds are often mixed in hospitals for intravenous infusion for the treatment of cardiovascular diseases.)

Since procainamide oral dosage forms also are used widely, the formation of complex with some of the excipients seemed possible. The present report investigated the formation of procainamide complexes with hydroxide-containing compounds, ethanol, fructose, glucose, glycerin, lactose, maltose, propylene glycol, sorbitol, and sucrose.

EXPERIMENTAL

Materials—All chemicals and reagents were USP, NF, or ACS grade and were used as received. Procainamide hydrochloride[1] (I) was used without further purification.

A high-performance liquid chromatograph[2], equipped with a multiple wavelength detector[3], a recorder[4] and digital integrator[5], was used.

A semipolar column[6] (30 cm long × 4-mm i.d.) consisting of a monomolecular layer of cyanopropylsilane permanently bonded to silica gel was used.

Chromatographic Conditions—The mobile phase was 40% (v/v) acetonitrile in water containing 0.02 *M* ammonium acetate (pH ~7)[7], and the flow rate was 2.0 ml/min. The detector was set at 280 nm (the wavelength of maximum absorption), the sensitivity was 0.04, the temperature was ambient, and the chart speed was 30.5 cm/hr.

Methods—The stock solutions of procainamide hydrochloride (1.0 mg/ml) and the internal standard, methapyrilene hydrochloride (5.0 mg/ml) in water, were prepared fresh daily. A standard solution was prepared by transferring a 1.5-ml quantity of the stock solution of I and a 4.0-ml quantity of the stock solution of methapyrilene hydrochloride (II) to a 100-ml volumetric flask and then diluting with water to volume.

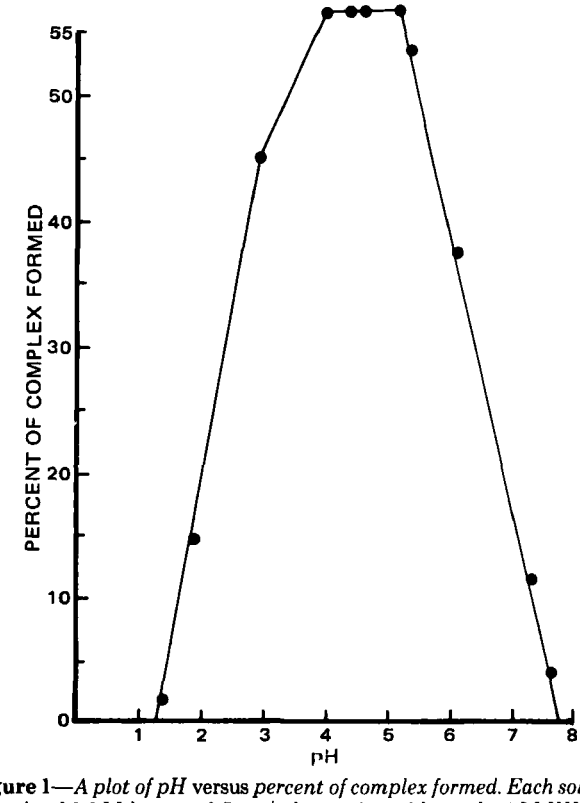

Figure 1—*A plot of pH* versus *percent of complex formed. Each solution contained 0.2* M *lactose, 0.5 mg/ml procainamide, and 0.2* M KH_2PO_4. *Solution of pH 1.4 was buffered with ~1* N *HCl. A similar plot was obtained with glucose.*

[1] Supplied by E. R. Squibb & Sons, Princeton, N.J.
[2] Waters ALC 202 equipped with U6K universal injector, Milford, Mass.
[3] Schoeffel SF770, Westwood, N.J.
[4] Omniscribe 1513-12, Houston Instruments, Austin, Tex.
[5] Autolab minigrator, Spectra Physics, Santa Clara, Calif.
[6] Waters, μBondapak/CN.
[7] Beckman Zeromatic (SS-3) pH meter.

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Table I—List of Procainamide Aqueous Solutions Prepared

Solution Number	Other Ingredients[a] If Any (Final Concentration)	pH Initial (+0.1)	pH After 1 Day	Percent Retained After 1 Day
1	0.5 *M* Ethanol	6.0	6.3	98.2
2	0.5 *M* Glucose	6.1	6.2	90.3
3	0.5 *M* Glycerin	6.0	6.2	97.1
4	0.5 *M* Lactose	4.2	4.1	32.8
5	0.5 *M* Propylene Glycol	6.0	6.2	99.1
6	0.5 *M* Sorbitol	6.2	6.3	97.4
7	0.5 *M* Sucrose	5.1	5.2	98.6
8	0.2 *M* Ethanol[b]	4.6	4.6	100.3
9	0.2 *M* Glucose[b]	4.6	4.6	45.3
10	0.2 *M* Glycerin[b]	4.6	4.6	101.0
11	0.2 *M* Lactose[b]	4.6	4.6	42.6
12	0.2 *M* Lactose[b]	4.6	4.6	42.4
13	0.2 *M* Propylene[b] glycol	4.6	4.6	99.1
14	0.2 *M* Sorbitol[b]	4.6	4.6	99.7
15	0.2 *M* Sucrose[b]	4.6	4.6	98.9
16	0.2 *M* Lactose and 0.5 *M* KH_2PO_4	4.6	4.6	42.4
17	0.025 *M* Lactose[b]	4.5	4.5	88.3
18	0.05 *M* Lactose[b]	4.5	4.5	76.2
19	0.075 *M* Lactose[c]	4.5	4.5	67.4
20	0.1 *M* Lactose[c]	4.5	4.5	60.8
21	0.1 *M* Lactose[d]	4.4	4.4	59.8
22	0.2 *M* Lactose[d]	4.4	4.4	41.7
23	0.3 *M* Lactose[d]	4.4	4.4	31.4
24	0.4 *M* Lactose[d]	4.4	4.4	25.1
25	0.2 *M* Lactose and enough ~1 *N* HCl	1.0	1.0	100.5
26	0.2 *M* Lactose and enough ~1 *N* HCl	1.4	1.4	97.7
27	0.2 *M* Lactose[d]	1.9	1.9	85.1
28	0.2 *M* Lactose[d]	2.9	2.9	55.0
29	0.2 *M* Lactose[d]	4.0	4.0	42.6
30	0.2 *M* Lactose[d,e]	4.0	4.0	42.9
31	0.2 *M* Lactose[d]	5.2	5.2	42.8
32	0.2 *M* Lactose[d]	6.1	6.1	62.4
33	0.2 *M* Lactose[d]	7.3	7.3	88.8
34	0.2 *M* Glucose[d]	3.0	3.0	59.0
35	0.2 *M* Glucose[d]	4.2	4.2	43.2
36	0.2 *M* Glucose[d,e]	4.2	4.2	42.4
37	0.2 *M* Glucose[d]	4.4	4.4	42.7
38	0.2 *M* Glucose[d]	5.4	5.4	46.2
39	0.2 *M* Glucose[d]	6.2	6.2	71.7
40	0.2 *M* Glucose[d]	7.6	7.6	95.9
41	0.1 *M* Fructose[d]	4.4	4.4	99.7
42	0.1 *M* Maltose[d]	4.4	4.4	59.1

[a] All solutions contained 0.5 mg/ml of procainamide except solutions 1–7, which contained 1.0 mg/ml. [b] Each solution also contained 0.05% of sodium edetate and 0.5 *M* KH_2PO_4 as buffering agent except solution 12, which did not contain sodium edetate. [c] Each solution also contained 0.1 *M* KH_2PO_4. [d] Each solution also contained 0.2 *M* KH_2PO_4. In solutions 27–40, enough hydrochloric acid (~1 *N*) or NaOH (~1 *N*) was added to adjust the pH. More solutions of different pH values in both lactose and glucose were studied (Fig. 1). [e] The solution also contained 0.1 *M* KCl to study the effect of ionic strength.

Table II—Assay Results of Dry Mixtures and some Selected Solutions

Storage duration, hr	Solution Number[a] 9[b]	12	17	18	19	20	Dry Mixture With Glucose	Dry Mixture With Lactose
0	99.7	100.4	—	—	—	—	99.8	99.5
1	73.3	70.5	—	—	—	—	—	—
2	58.4	56.8	—	—	—	—	—	—
4	46.4	46.2	—	—	—	—	—	—
6	43.8	42.2	—	—	—	—	—	—
24	42.7	41.7	88.3	76.2	67.4	60.8	99.5	98.9
144	42.3	41.8	84.4	76.8	67.4	60.2	—	—

[a] See Table I. [b] Without sodium edetate.

All solutions prepared for the investigations of procainamide complexes are reported in Table I. All were prepared using a simple solution method. The solutions were assayed, transferred to amber-colored bottles[8], and stored at room temperature (24 ± 1°). They were assayed after appropriate intervals, and pH values were also determined.

All solutions were diluted with water to contain 15.0 μg/ml of I (based on the label claim) and 200.0 μg/ml of II (internal standard).

A 20.0-μl aliquot of the assay solution was injected into the chromatograph using the described conditions. For comparison, an identical volume of the standard solution was injected after the assay solution eluted.

[8] Brockway Glass Co., Brockway, Pa.

Calculations—The results were calculated using:

$$\frac{(Ph)_a}{(Ph)_s} \times 100 = \text{Percent of the label claim} \qquad \text{(Eq. 1)}$$

where $(Ph)_a$ is the ratio of the peak heights of procainamide and methapyrilene of the assay solution and $(Ph)_s$ is that of the standard solution of identical concentrations.

Other Experiments—A 1.5-ml quantity of 1-day-old solution in 0.2 *M* lactose (solution 12 in Table I) or in 0.1 *M* maltose (solution 42 in Table I) was mixed with 1.5 ml of ~5 *N* HCl. The mixture was allowed to stand for ~15 min, then 4.0 of the stock solution of the internal standard was added, the mixture brought to volume (100.0 ml) with water, and assayed.

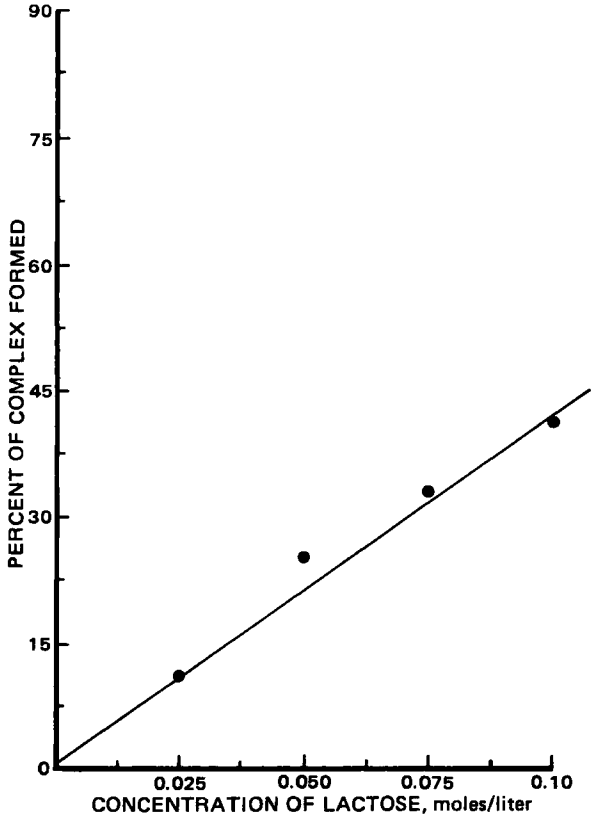

Figure 2—*A plot of lactose concentration (moles/liter)* versus *percent of complex formed.*

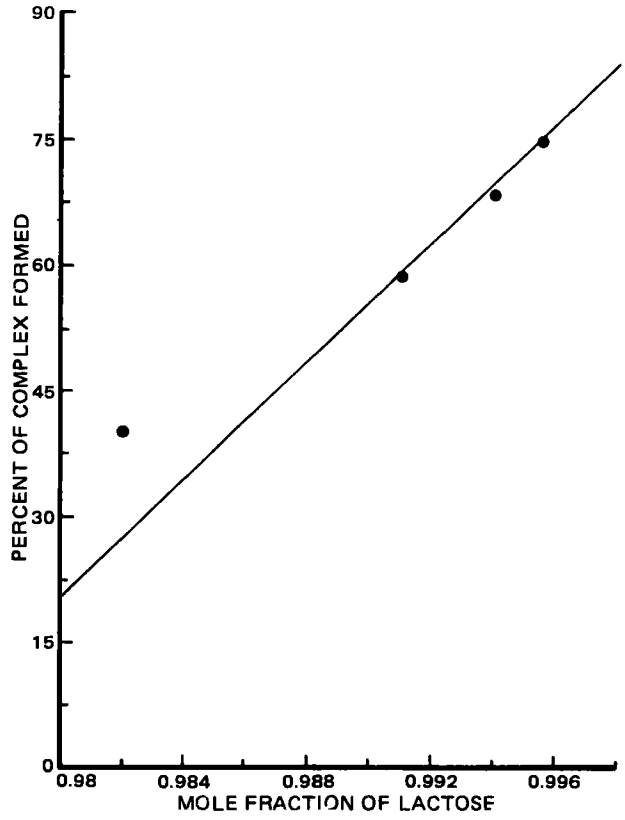

Figure 3—*A plot of lactose concentration (mole fraction)* versus *percent of complex formed.*

A 25.0-mg quantity of procainamide was mixed thoroughly with either 1.8 g of glucose or 3.6 g of lactose; the dry mixtures were allowed to stand overnight and assayed.

The solutions containing 0.2 *M* glucose/lactose, 0.2 *M* KH_2PO_4, and 0.5 mg/ml of procainamide were prepared and assayed at appropriate intervals up to 144 hr.

RESULTS AND DISCUSSION

The results indicate (Table I) that procainamide forms complexes with glucose, lactose (solutions 1–15, Table I), and maltose (solution 42 in Table I). The other hydroxide-containing compounds, ethanol, fructose, glycerin, propylene glycol, sorbitol, and sucrose, did not form complexes with procainamide (Table I). Therefore, it appears that a hemiacetal group is necessary for the formation of a complex. This group is present only in glucose, lactose, and maltose and not in other hydroxide-containing compounds.

The percent of procainamide complexed with lactose (as with glucose) was dependent on the initial pH value of the solution (solutions 25–40, Table I). For both glucose and lactose, the optimum pH range for the formation of complex appears to be ~4–5.2 (Fig. 1). The percent of complex formed with lactose and maltose were similar (solutions 21 and 42, Table I).

In a biologically useful pH range (7.3–7.5), the formation of complex was low (solutions 33 and 40, Table I). For example, only 11.2% of procainamide was complexed with lactose at pH 7.3, whereas almost 57% complexed between pH 4 and 5.2. Similar results were obtained with glucose.

Initially, when solution 2 in Table I was compared with solution 4, the percent of complex formed with lactose appeared much higher than with glucose. Nevertheless, in buffered solutions of identical pH (solutions 9 and 11, Table I), the difference was negligible.

The formation of complex was not affected by the addition of sodium edetate (solutions 11 and 12, Table I) or potassium chloride (solutions 29 and 30 and 35 and 36, Table I). As in glucose, the percent of complex formed was directly related to the concentration of lactose in the solution. At lower concentrations, molar concentrations of lactose were related and higher concentration mole fractions were related (Figs. 2 and 3). The formation of the complex could be completely reversed by adding hydrochloric acid (a similar observation was reported earlier with glucose). For example, solution 12 in Table I had only 42.4% of free procainamide after 24 hr of storage. On treatment with hydrochloric acid (*Other Experiments*), the concentration of free procainamide was 100.3%.

When solutions 17–20 (Table I) were reassayed after 6 days, there was only slight change in the concentration of free procainamide in solution 17 (Table II). In others, no significant change was noted (Table II). In solutions 9 and 12, the equilibrium was established in ~24 hr (Table II). The process of complexation followed the equation of reversible reactions as explained previously (1) for glucose.

In dry mixtures (*Other Experiments*), procainamide did not form a complex with glucose or lactose (Table II). Apparently, water is necessary for the formation of the complex.

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