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Synthesis of New 14- and 15-Crown-Formazans and their Evaluation in Spectrophotometric Determination of Lithium

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Synthesis of New 14- and 15-Crown-Formazans and their Evaluation in Spectrophotometric Determination of Lithium

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The two new crown-formazans 1 and 2 with 14- and 15-membered rings have been synthesized, characterized and investigated as a selective spectrophotometric chelating agents for lithium. The effect of sodium ion concentration on the background lithium signal was studied. Sodium causes depression of the lithium signal and the relative effect diminishes as the total sodium concentration is increased. In a background sodium containing 140 mM sodium, a 10 mM increment of sodium is equivalent to 0.0017 mM Lithium using compound 1 and 0.0024 mM using compound 2.

Keywords: Crown-formazans, Lithium, Spectrophotometric

INTRODUCTION

Lithium is used in the treatment of manic depression psychosis. The lithium level in blood must be maintained between 0.5 and 2 mM. A higher level is toxic and a level of 5 mM can be lethal [1]. Hence, the level of lithium in the patient's blood must be frequently monitored [1, 2]. The determination of lithium is performed by the use of flame photometry or atomic absorption spectrophotometry [1, 2]. Also, several ion selective electrods were reported for determination of lithium [3]. The difficulty in determining lithium in blood or serum is their high content of sodium (ca. 140 mM). The success of any method of such determination is assessed by the possibility of accurate microdetermination in the presence of high concentration of sodium and other interfering ions present in blood serum. Several crown-formazans were recently investigated for determination of lithium spectrophotometrically [4-11]. Since improvement of easy and accurate method for determination of lithium is still a subject of current interest, we describe here the synthesis of two new macrocyclic crown-formazans, namely: 16-methylene-16, 17-dihydro-5H, 15H-dibenzo[b, i] [1, 11, 4, 5, 7, 8] dioxatetraazacylotetradecin-7-carbonitrile (**1**) and 5, 21-dihydro-11H-tribenzo[b, i, m] [1, 11, 4, 5, 7, 8] dioxatetraazacyclopentdecin-13-carbonitrile (**2**). Compounds **1** and **2** tested as a selective spectrophotometric chelating agents for the determination of lithium.

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EXPERIMENTAL

Reagents and Chemicals

The crown-formazans **1**, **2** were prepared according to the procedure described below. Acetone, analytical grade, was used as received. Chlorides of sodium and lithium were of the highest purity available. Doubly distilled water was used. The following solutions were prepared.

Solution I : a 0.1 nM of each of the formazans and 50 mM NaOH in 85% acetone and 15% water.

Solution II : a 0.1 nM of each of the formazans and 50 mM NaOH in 70% acetone and 30% water, with total sodium ion concentration of 440 mM from added NaCl.

Solution III : a 0.1 nM of each of the formazans and 50 mM NaOH in 50% acetone and 50% water, with total sodium ion concentration of 1050 mM from added NaCl. Higher water ratios were used at high sodium concentration to avoid turbidity from limited solubility.

Apparatus

Electronic absorption spectra were measured with a Perkin-Elmer Lambda 4B spectrophotometer.

Synthesis of the Crown-Formazans 1, 2

The crown-formazans **1**, **2** used in the present investigation have been synthesized as outlined in Scheme I. Thus, the bis-o-aminophenoxy derivatives **3**, **4** obtained as described previously by alkylation of o-acetamidophenol with 2-chloromethyl-3-chloropropene or α,α'-dibromo-o-xylene [12], were bis-diazotized to give the bisdiazonium salts **5**, **6**. The latter were coupled with cyanoacetic acid in pyridine in the presence of Cu^{2+} ions using the high dilution technique to give the corresponding crown-formazans **1** and **2**, respectively.

Synthesis of Compounds **1** and **2**: A solution of either of **3** or **4** (5 mM) in 10 mL of water and 3 mL of conc. HCl was diazotized at −5°C with a solution of sodium nitrite (0.7 g) in 5 mL of water during half an hour. The solution was then added dropwise with stirring over a period of 1 h to a solution of cyanoacetic acid (2.5 mM prepared as described previously [13]) in 100mL of pyridine, 0.5 g of $CuSO_4{\cdot}5H_2O$ and 20 mL of water at −5°C. The reaction mixture was kept in the freezer overnight. The solid obtained was collected, washed with water and purified over a column of silica gel using the suitable eluent.

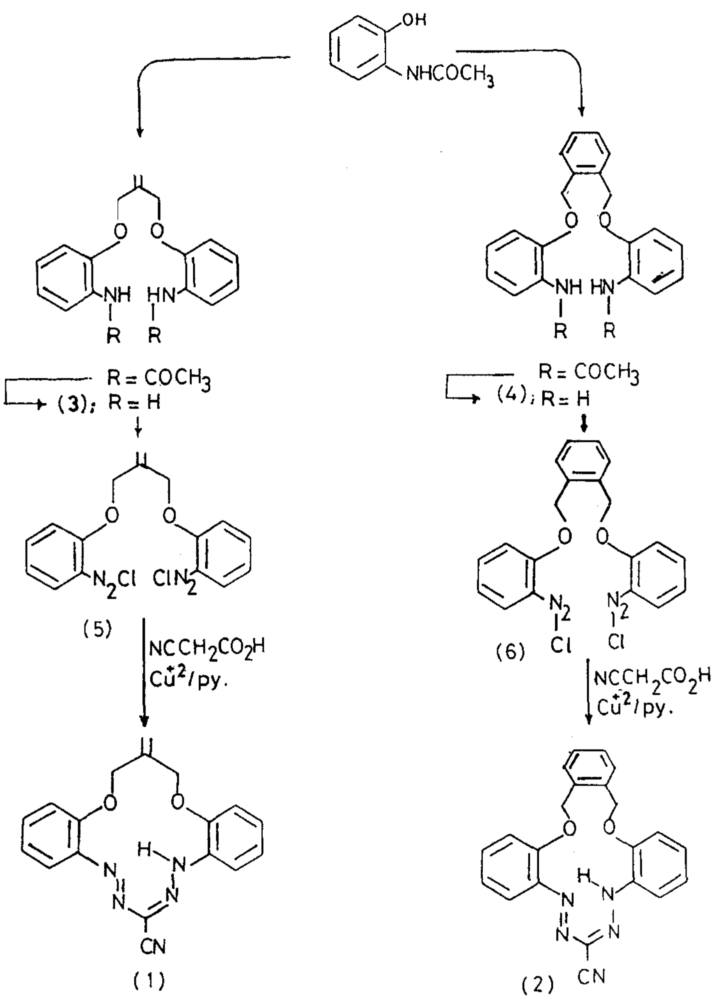
7-Cyano-16-methylene-16,17-dihydro-5H, 15H-dibenzo[b,i][1,11,4,5,7,8]dioxatetraazacyclotetradecine (**1**): this was purified using benzene as an eluent into red crystals mp 252-55°C; yield ca. 18% Ms: m/z 333 (M^+, 76.5%); ^1H NMR ($CDCl_3$) δ 4.8 (s, 4H, OCH_2), 5.6 (s, 2 H, $CH_2{=}$), 7.05-7.95 (m, 8H, ArH's), 16.0 (s, 1 H, NH); ^{13}C NMR δ 73.71, 73.83 (OCH_2), 119.6 (CN), 126.27 ($CH_2{=}$), 114.14, 117.85, 123.8, 132.33 (ArCH's), 126.43, 137.7, 140.58, 153.43 ($\underline{C}{=}CH_2$, ArC's, C=N); IR 3350 (NH), 2225 (CN). Anal. For $C_{18}H_{15}N_5O_2$ Calcd. C, 64.86; H, 4.54; N, 21.01. Found C, 64.70; H, 4.50; N, 21.10.

5,21-Dihydro-11H-tribenzo[b,i,m][1,11,4,5,7,8]dioxatetraazacyclopentadecin-13-carbonitrile (**2**): this was purified using $CHCl_3$/petroleum ether (60-80) (3:1) as an eluent into red crystals mp 215-17°C; yield, ca. 37%, Ms: m/z 383 (M+, 100%); ^1H NMR ($CDCl_3$) δ 5.35 (s, 4H, OCH_2), 7.02-7.8 (m, 12H, ArH's), 16.0 (s, NH); IR 2250 (CN).

Anal. for $C_{22}H_{17}N_5O_2$ Calcd. C, 68.92; H, 4.47; N, 18.27. Found C, 68.60; H, 4.40; N, 17.90.

Procedure

For spectrophotometric studies of lithium in the presence of sodium ion an aliquot of lithium standard ranging between 0.5-3 mM; 0.5-3.5 mM and 1.5-5 mM was dissolved in solutions I, II, III, respectively. The absorption



SCHEME I

spectra of these solutions were recorded using the solvent solution as a blank. The spectra of 3 mM lithium in solution I with increasing levels of sodium ranging from 50–160 mM and different interval of time up to 80 minutes was also recorded.

RESULTS AND DISCUSSION

The electronic absorption spectra of lithium-crown formazans in the presence of different levels of sodium ion concentration showed absorption in the visible region, however, the mixtures containing compound **1** and/or **2** with lithium in different acetone/water mixtures are found to exhibit an absorption spectra around 500 nm. Figures 1a, b show the change in absorbance as a function of lithium concentration at λmax = 504 and 545 nm, respectively, for the lithium solution III system which indicates that lithium as low as 1.5 mM was easily detected.

Plots of absorbance versus lithium concentration (calibration curves for lithium) at different sodium levels are given in Figures 2a, b. It is obvious that excellent correlation with lithium concentration is obtained. The regression lines obtained are expressed by equations 1–3.

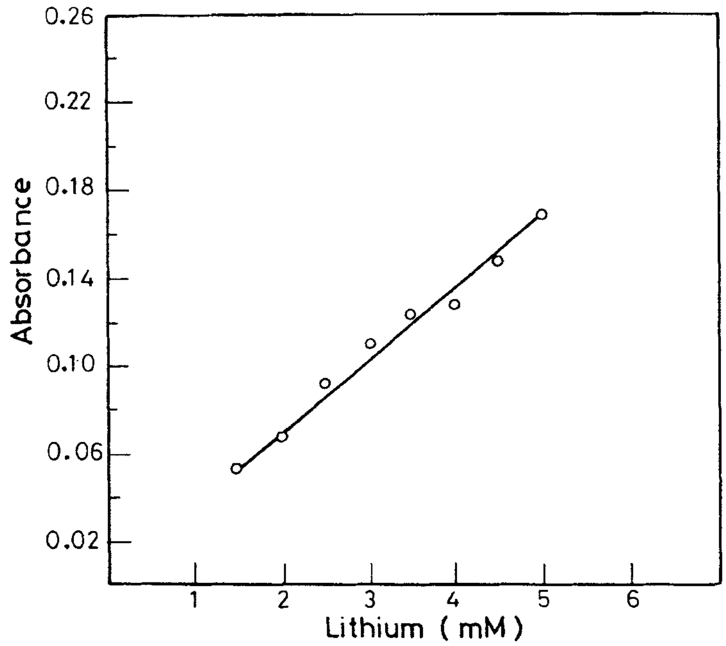


FIGURE 1a Calibration graph for lithium in the presence of 1050 mM sodium for formazan 1.

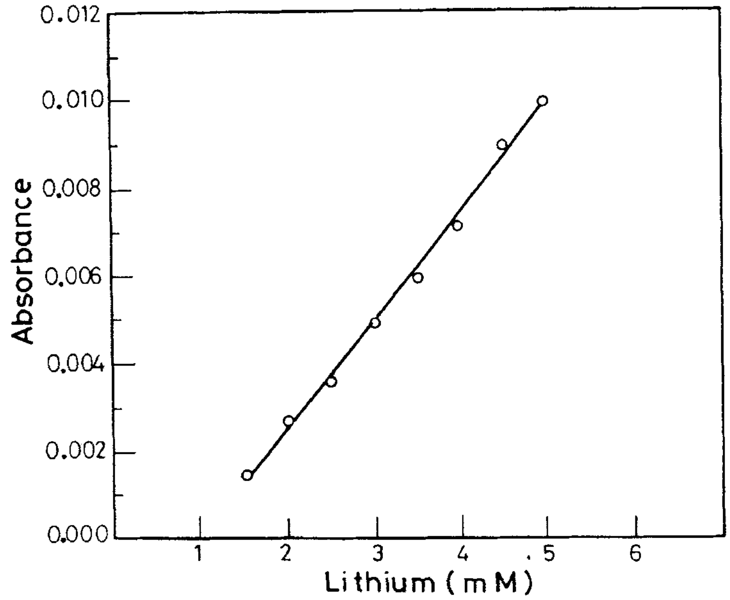


FIGURE 1b Calibration graph for lithium in the presence of 1050 mM sodium for formazan 2.

$$A_{Li} - \text{Soln I} = 0.4942 + 0.0469\,C_{Li} \qquad (1)$$

$r = 0.9196 \quad S = \pm 0.2$

$$A_{Li} - \text{Soln II} = 0.0883 + 0.125\,C_{Li} \qquad (2)$$

$r = 0.9950 \quad S = \pm 0.1282$

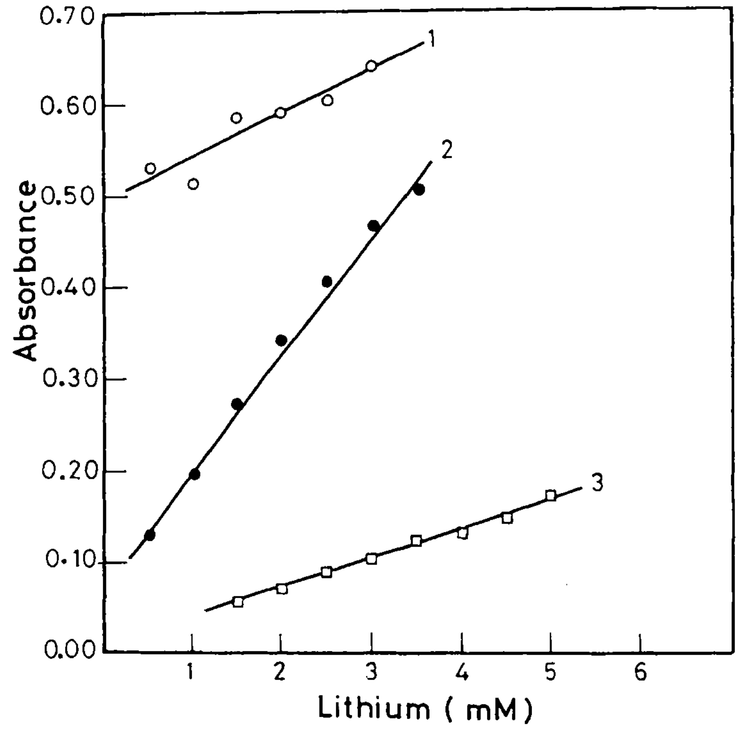


FIGURE 2a Calibration graphs of lithium in the presence of 50, 440 and 1050 mM sodium of formazan 1.

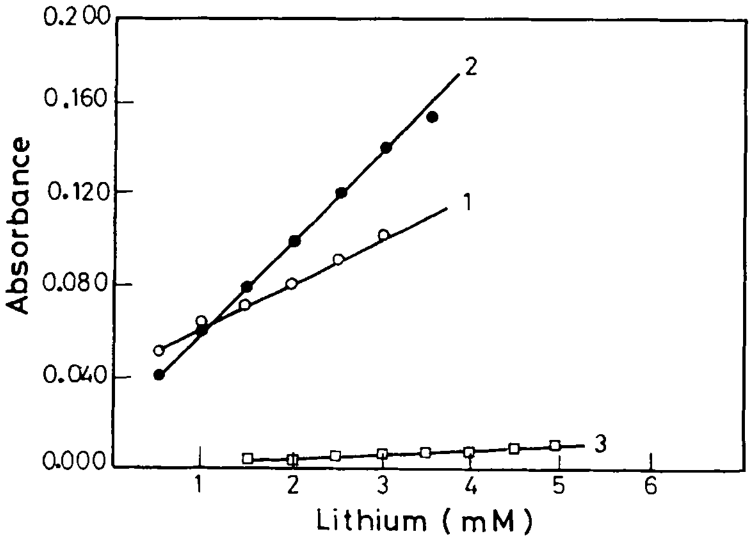


FIGURE 2b Calibration graphs of lithium in the presence of 50, 440 and 1050 mM sodium for formazan 2.

$$A_{Li} - \text{Soln III} = 0.03161 + 0.01067\,C_{Li} \quad (3)$$

$$r = 0.9848 \quad S = \pm 0.1266$$

Comparing the value of the slope of systems I, II and III one can conclude that the best curve was obtained for system II in both cases. Hence 0.5

mM lithium (the lower limit required in the biological samples) can be easily determined in the presence of 440 mM sodium which is three times higher than the level in the biological samples.

Effect of Sodium

In view of the fact that the slope of the lithium calibration curves decreases as the level of sodium concentration increases (Fig. 2), an attempt was made to examine the effect of increase in sodium level from 50 to 110 mM on the background signal of solution I. Figure 3 shows that sodium has an enhancing effect on the background signal until a solution level of 80 mM is reached for compounds **1** and **2** respectively, further increase in sodium level causes decrease in the signal. Therefore, it is obvious that sodium ion and its level does not interfer with both the background signal as well as with the lithium signal. This is in agreement with the results obtained by Attiyat *et al.* [5] for other 14-crown-formazan. In spite of this we succeeded in determining 0.5 mM lithium concentration in 440 mM sodium with fair accuracy and precision.

Effect of Time

Figure 4a, b depects the change in the absorbance signal of solution 1 at different time intervals. It is interesting to note that an increase in the signal (including sodium) in the first 50 minutes occurs and then the absorbance becomes constant in the range 50–80 minutes and then slightly increases. This is probably due to the deprotonation of the NH group by the action of NaOH (0.5 mM).

$$\mathrm{LH(acetone)} \overset{\mathrm{NaOH}}{\rightleftharpoons} \mathrm{L}^-$$

From the above it is clear that we must measure the absorbance of the system after 50 minutes.

For compound **1** the net relative effect of sodium on the lithium standard decreases as the

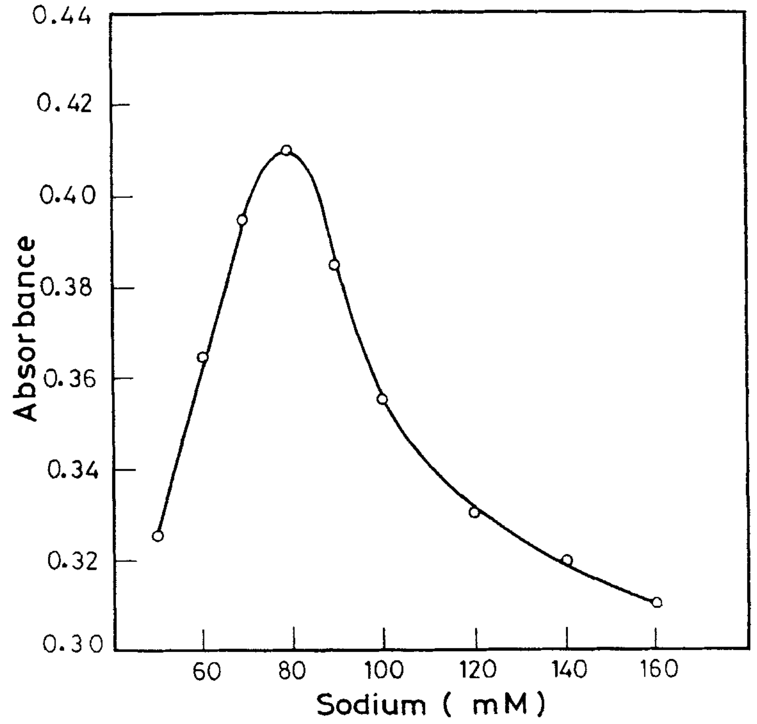


FIGURE 3a Effect of sodium ion concentration on the absorbance of 3 mM Li in solution 1 for formazan 1.

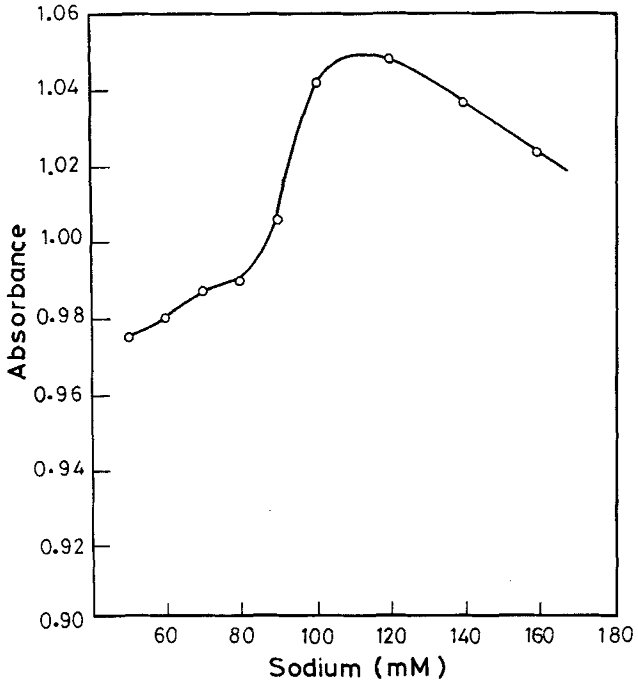


FIGURE 3b Effect of sodium ion concentration on the absorbance of 3 mM Li in solution 1 for formazan 2.

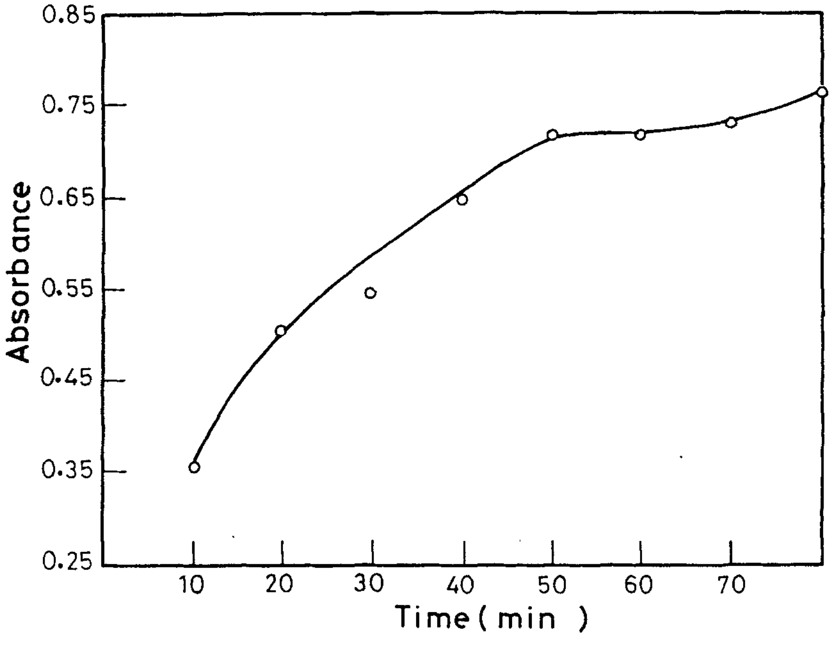


FIGURE 4a Effect of time on the absorbance signal of the back-ground solution of formazan 1.

sodium level is increased (Fig. 3). When 3 mM lithium was measured in 140 and 160 mM sodium a decrease of 0.01 in absorbance was recorded. This is equivalent to a decrease of 0.0017 in absorbance in measuring 1 mM lithium by increasing the sodium level by 10 mM in a

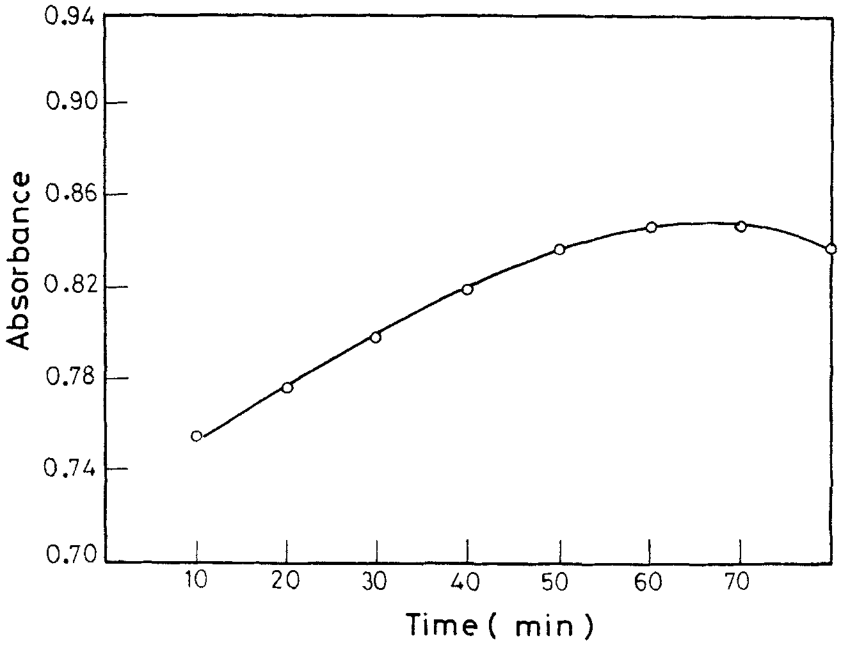


FIGURE 4b Effect of time on the absorbance signal of the back-ground sollution of formazan 2.

background sodium level of 140 mM. Since the sodium level in blood would not normally vary by more than ±10 mM, and so the maximum error due to such variation would be only 0.001 (i.e., 0.1%). Also, for compound 2, a similar effect of sodium revealed, as seen in Figures 3 a, b, that the measurement of 3 mM lithium in 140 and 160 mM sodium decreases by 0.014. Thus, at 140 mM sodium the effect of adding 10 mM sodium would decrease the absorbance of 1 mM of lithium by 0.0024 (i.e., 0.24%).

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