

## Potentiometric Determination of Alprazolam based on Carbon Paste and PVC membrane Electrodes

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In this work, two kinds of potentiometric sensors, based on PVC membrane and carbon paste electrodes, have been introduced. Both sensors respond according to the ion-exchange mechanism. Alprazolam-tetraphenylborate (ALP-TPB) was the ion-pair synthesized for using as a sensing element in both kinds of electrode. The best PVC membrane sensor response was obtained by a membrane composition of 30% PVC, 63% DBP, and 7% ALP-TPB. Carbon paste electrode was then designed to have an electrode with the better mechanical resistance. The best electrode was composed of 20% ion-pair, 20% paraffin oil, and 60% graphite. The proposed method was successfully applied in determination of alprazolam in some pharmaceutical formulations.

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**Keywords:** Alprazolam, Potentiometric Sensor, PVC membrane, Carbon Paste, Ion-Pair

### 1. INTRODUCTION

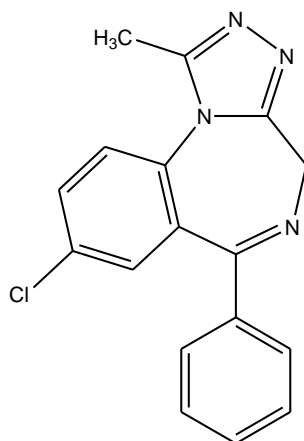
Alprazolam (Figure 1) (8-chloro-6-phenyl-1-methyl-4Hs-triazolo[4,3-a] [1,4] benzodiazepine) with trade name Xanax, is a short-acting anxiolytic of the benzodiazepine class of psychoactive drugs which are characterized by a unique triazolo structure, high potency, oral activity, and remarkably low toxicity [1]. Alprazolam is mainly used to treat anxiety disorders. Besides, alprazolam possesses anxiolytic, sedative, hypnotic, skeletal muscle relaxant, anticonvulsant, and amnesic properties [2]. Alprazolam is the most prescribed [3] and the most misused benzodiazepine on the U.S. retail market [4]. The potential for abuse is low and is similar to that of other benzodiazepine drugs [5]. Alprazolam is available for oral administration in compressed tablet (CT) and extended-release capsule (XR)

formulations.

A number of research describe the determination of Alprazolam in biological fluids and pharmaceutical formulation by several methods including voltammetry [6], UV spectroscopy [7], GC-MS [8-10], LC-MS [11], high performance liquid chromatography (HPLC) [12-14] and thin-layer chromatography [15]. However, potentiometric detection based on ion-selective electrodes (ISEs) offers the advantages of speed and ease of preparation and procedures, relatively fast response, reasonable selectivity thorough judicious choice of the membrane active materials, wide linear dynamic range, and low cost. These characteristics have inevitably led to the preparation of numerous sensors for several ionic species, and the list of available electrodes has grown substantially over the past years [16-25].

PVC membrane electrodes are one of the subdivisions of potentiometric sensors [25-28]. Although they are widely used, they have not sufficient physical and mechanical resistance for long-term usage. In contrast, carbon paste electrodes (CPEs) are another category of potentiometric sensors which are mechanically strong. They have attracted more attention than membrane electrodes because of their advantages such as improved renewability, stable response, and low ohmic resistance and no need for internal solutions [29-36].

Here, two kinds of potentiometric sensor were introduced. Both electrodes respond based on ion-exchange mechanism. Alprazolam-tetraphenyl borate ion-pair was as a sensing material in construction of both electrodes. First, PVC membrane electrode was made after series of experiments. Afterward, a carbon paste electrode was designed to improve the mechanical stability and analytical responses.



**Figure 1.** Chemical structure of alprazolam

## 2. EXPERIMENTAL SECTION

### 2.1. Apparatus

The glass cell, where the alprazolam indicator electrodes (PVC membrane or carbon paste

electrodes) were placed, consisted of two Ag/AgCl double junction reference electrodes (Azar-Electrode Co., Iran) internal and external reference electrodes. Both electrodes were connected to a Corning ion analyzer with a 250 pH/mV meter with  $\pm 0.1$  mV precision.

## 2.2. Materials and Reagents

Chemicals (of analytical reagent grade) were: high-molecular weight polyvinylchloride (PVC) (Fluka Co., USA), sodium tetraphenylborate (NaTPB), dibutyl phthalate (DBP), nitrobenzene (NB), benzylacetate (BA) and tetrahydrofuran (THF) (Merck Co., Germany). All materials were of the highest available purity without further modification. Alprazolam and its pharmaceutical formulation were obtained from local pharmaceutical manufacturer (Tehran, Iran) as gift samples.

## 2.3. Preparation of sensing element

Sensing element used in both sensors was an ion-pair compound composed of alprazolam-tetraphenylborate (ALP-TPB). It was prepared by mixing about 20 mL of 0.01 M acidic solution of alprazolam with 20 mL of 0.01 M solution of tetraphenylborate. The resulting precipitate was filtered, washed with water and dried in room temperature [37-39].

## 2.4. Preparation of the Electrodes

### 2.4.1. PVC membrane electrode

General procedure to prepare PVC membrane was as follow: different amounts of ion-pair along with appropriate amounts of PVC, plasticizer and additive were dissolved in tetrahydrofuran (THF), and the solution was mixed well into a glass dish of 2 cm diameter. Followed by THF was evaporated slowly until an oily concentrated mixture was obtained. A plastic tube (about 3 mm o.d.) was dipped into the mixture for about 10 s so a transparent membrane of about 0.3 mm in thickness was formed. The tube was then pulled out from the mixture and kept at room temperature for about 10 h.

Afterwards, the tube was filled with an internal filling solution ( $1.0 \times 10^{-3}$  M of alprazolam solution (pH=4.5)). The electrode was finally conditioned for 24 h by soaking in the same solution [37-39].

### 2.4.2. Carbon Paste Electrodes (CPEs)

General procedure for preparation of carbon paste electrode was as follows: various amounts of ion-pair along with appropriate amount of graphite powder, paraffin oil, were thoroughly mixed. After homogenization of the mixture, the resulting paste was transferred into a plastic tube with 6 mm o.d. and a height of 3 cm. The paste was carefully packed into the tube tip to avoid possible air gaps,

which often enhance the electrode resistant. A copper wire was inserted into the opposite end of the CPE to establish electrical contact. External surface of the carbon paste was smoothed with soft paper. The electrode was finally conditioned for about 48 h by soaking it in a  $1.0 \times 10^{-3}$  M of alprazolam solution [30-36].

### 2.5. Standard alprazolam solutions

A stock solution of 0.02 M alprazolam was prepared. The working standard solutions ( $1 \times 10^{-6}$  to  $1 \times 10^{-2}$  M) were prepared by appropriately dilution of the stock solution with distilled water.

### 2.6. The emf Measurements

Following cell assembly for the conduction of emf (electromotive force) measurements were used:

**A:** Ag-AgCl || internal solution,  $1 \times 10^{-3}$  M alprazolam solution | PVC membrane | sample solution || Ag-AgCl, KCl (satd.)

**B:** CPE | sample solution || Ag-AgCl, KCl (satd.)

These measurements were done using calibration of the electrodes with several standard solutions.

## 3. RESULTS AND DISCUSSION

### 3.1. PVC Membrane Composition Selection

Membrane composition effect on potential responses of the sensor was tested. The operating characteristics of PVC membrane sensor can be significantly modified by changing the relative proportions of the electrode membrane components. The main components of a membrane are PVC matrix, plasticizer and ion-pair. Each membrane component plays a special role in the membrane function and electrode response. Previous studies shows that the membrane prepared with a plasticizer/PVC ratio about 2.2 can show the best performance [40-45]. As it can be seen in Table 1, the optimum amount of PVC was selected 30 mg.

Plasticizer mainly acts as a membrane solvent allowing homogeneous dissolution and diffusional mobility of the ion-pair inside the membrane [39-41]. The plasticizer should be water-immiscible liquid of low vapor-pressure, compatible with PVC, no functional groups which can undergo protonation reactions. The selectivity of such electrode can be drastically influenced by the choice of the membrane solvent [46-53]. Nature of the plasticizer has a marked effect on analytical responses e.g. slope, linear domain and selectivity of PVC membrane electrodes. Here, three plasticizers with different polarity (dielectric constant) were tested, dibutyl phthalate (DBP

with DC of 6.4), nitrobenzene (NB with DC of 35.7) and benzylacetate (BA with DC of about 5.7), as listed in Table 1. The electrode responses showed that membrane had DBP better respond. DBP had the lowest dielectric constant among the used plasticizers, and provided an effective linear range and a lower detection limit due to the better extraction of the alprazolam in the organic layer of the membrane.

As it can be seen from Table 1, absence of ion-pair in the membrane causes a very poor response (membrane no. 7), which confirm significance of the ion-pair. As a conclusion, membrane no. 2 with the composition of 30% PVC, 7% ion-pair, and 63% DBP was the optimum one for the sensor design.

**Table 1.** Optimization of PVC membrane ingredients

No.	Composition (%)				Slope (mV per decade)	LR (M)	DL (M)
	PVC	Plasticizer	Ion-pair	NaTPB-additive			
1	30	DBP, 65	5	-	11.6±0.3	1.0×10 <sup>-6</sup> -1.0×10 <sup>-2</sup>	9.7×10 <sup>-5</sup>
2	30	DBP, 63	7	-	19.8±0.2	1.0×10 <sup>-6</sup> -1.0×10 <sup>-2</sup>	1.0×10 <sup>-6</sup>
3	30	DBP, 60	10	-	18.0±0.4	1.0×10 <sup>-6</sup> -1.5×10 <sup>-2</sup>	7.8×10 <sup>-5</sup>
4	30	DBP, 63	7	2	27.6±0.3	1.0×10 <sup>-6</sup> -1.5×10 <sup>-3</sup>	9.8×10 <sup>-5</sup>
5	30	NB, 60	7	-	16.4±0.3	1.5×10 <sup>-4</sup> -1.5×10 <sup>-2</sup>	1.1×10 <sup>-4</sup>
6	30	BA, 60	7	-	14.5±0.5	1.0×10 <sup>-4</sup> -1.0×10 <sup>-2</sup>	1.0×10 <sup>-4</sup>
7	30	DBP, 70	0	-	3.5±0.2	5.0×10 <sup>-4</sup> -5.0×10 <sup>-2</sup>	2.5×10 <sup>-4</sup>

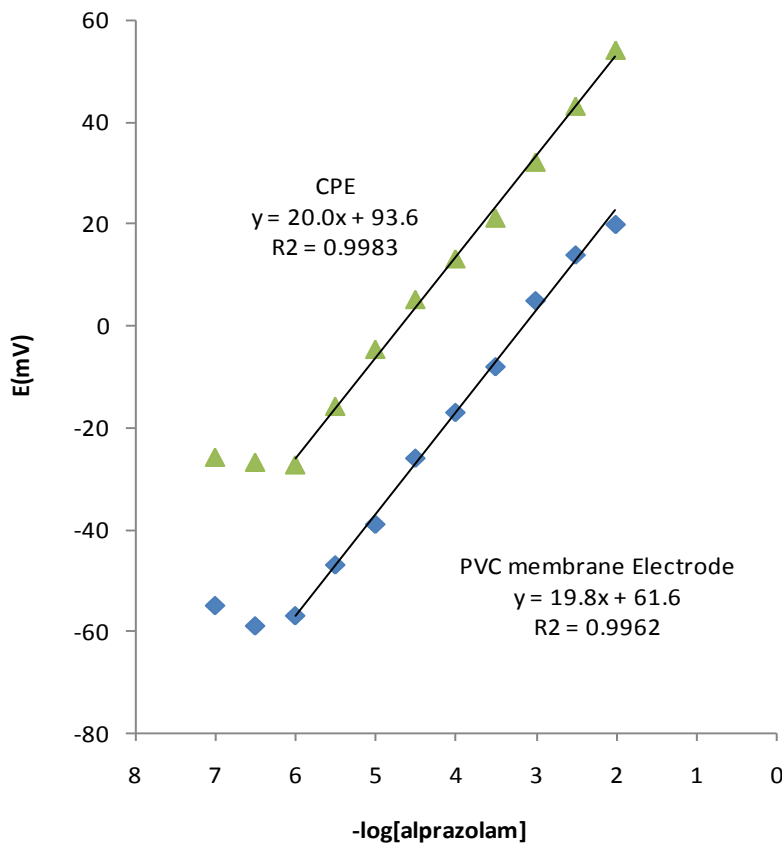
### 3.2. Carbon Paste Composition Selection

Two kinds of carbon paste were made; modified and unmodified CPEs with a variety of compositions. The results for these CPEs are given in Table 2. The electrode composed of 20% paraffin oil, 20% ion-pair, and 60% graphite powder (no. 5) was found to be optimal for alprazolam carbon paste electrode. This composition was selected for further examination.

From Table 2, it was obvious that in the absence of ion-pair and presence of other components (no. 1), the response of the modified CPE was very low (slope of 2.1±0.6 mV per decade).

### 3.3. Calibration Graph and Statistical Data

The measuring range of a potentiometric sensor is the linear part of the calibration graph as shown in Figure 2.



**Figure 2.** Calibration curves of CPE and PVC membrane electrode. The results are based on 8 measurements.

**Table 2.** Optimization of carbon paste electrode composition

No.	Composition (%)			Slope (mV per decade)	LR (M)	DL (M)
	Graphite	Paraffin	Ion-pair			
1	70	30	-	2.1±0.6	-	-
2	68	27	5	10.2±0.5	1.0×10 <sup>-6</sup> -1.0×10 <sup>-2</sup>	1.0×10 <sup>-6</sup>
3	65	25	10	13.9±0.4	1.0×10 <sup>-7</sup> -1.0×10 <sup>-2</sup>	5.5×10 <sup>-6</sup>
4	65	20	15	15.5±0.2	1.0×10 <sup>-6</sup> -1.0×10 <sup>-2</sup>	1.0×10 <sup>-6</sup>
5	60	20	20	20.0±0.3	1.0×10 <sup>-6</sup> -1.0×10 <sup>-2</sup>	1.0×10 <sup>-6</sup>
6	55	20	25	19.5±0.5	1.0×10 <sup>-6</sup> -1.0×10 <sup>-2</sup>	8.5×10 <sup>-5</sup>

Measurements could be performed in this lower range, but noted that more closely spaced calibration points are required for more precise determinations. For many electrodes the measuring range can extend from 1 molar to 10<sup>-6</sup> or even 10<sup>-7</sup> molar concentrations [45-53]. Calibration graph slope for PVC membrane electrode is 19.8 mV per decade of the alprazolam concentration and a standard deviation of ±0.2 mV after eight replicate measurements. A linear response

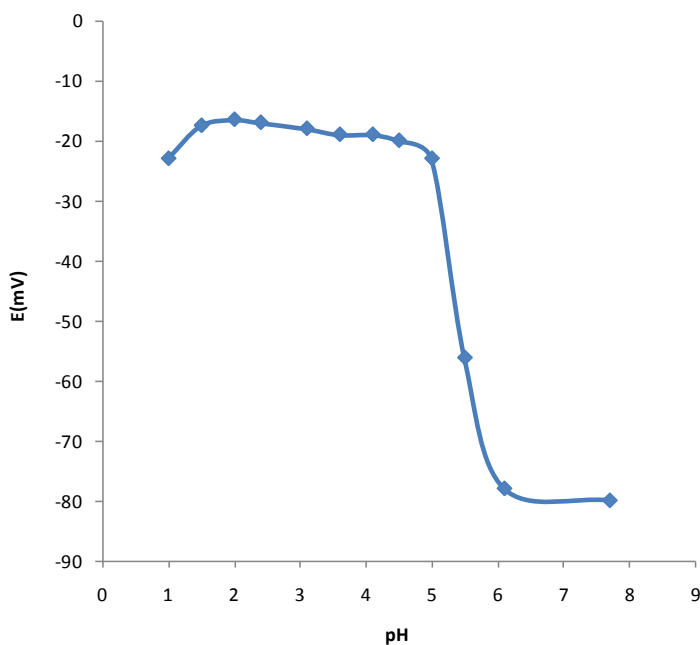
towards the alprazolam concentration was from  $1.0 \times 10^{-6}$ - $1.0 \times 10^{-2}$  M. Calibration graph slope for CPEs is 20.0 mV per decade of alprazolam concentration in the range of  $1.0 \times 10^{-6}$ - $1.0 \times 10^{-2}$  M with a standard deviation of  $\pm 0.3$  mV after eight replicate measurements.

Detection limit was calculated from the intersection of two extrapolated segments of the calibration graph. In this work, detection limit of both proposed sensor was  $1.0 \times 10^{-6}$  M which was calculated by extrapolating the two segments of the calibration curves.

### 3.4. Dynamic Response Time

Dynamic response time is the required time for the electrode to achieve values within  $\pm 1$  mV of the final equilibrium potential, after successive immersions in the sample solutions [48-53]. Its calculation involved the variation and the recording of the alprazolam concentration in a series of solutions from  $1.0 \times 10^{-6}$  to  $1.0 \times 10^{-2}$  M. Both sensors were able to quickly reach its equilibrium response in the whole concentration range. This time for CPE was about 10 seconds and for PVC membrane electrode was about 15 s in concentrated solutions.

### 3.5. pH Effect on the Electrodes Response



**Figure 3.** Applicable pH of the electrodes in the test solution of  $1.0 \times 10^{-4}$  M

To examine effect of pH on both electrode responses, the potential was measured at specific concentration of the alprazolam solution ( $1.0 \times 10^{-4}$  M) from the pH value of 1.0 up to 10.0 (concentrated NaOH or HCl solutions were employed for the pH adjustment). The results showed

that the potential remained constant despite the pH change in the range of 2.0 to 5.0, which indicates the applicability of this electrode in the specified pH range.

Relatively noteworthy fluctuations in the potential vs. pH behavior took place below and above the formerly stated pH limits. In detail, the fluctuations above the pH value of 5.0 might be justified by removing the positive charge on the drug molecule. Fluctuations below the pH value of 2.0 were caused by removal of the ion-pair in the membrane or analyte in the solution. In both electrodes the same trend were observed.

### 3.6. Life-time Study

Both electrodes lifetime was estimated with the calibration curve, periodical test of a standard solution ( $1.0 \times 10^{-6}$ - $1.0 \times 10^{-2}$  M) and calculation of its response slope.

**Table 3.** Lifetime of CPE and PVC membrane electrode

Week	PVC membrane Slope (mV per decade)	DL (M)	CPE Slope (mV per decade)	DL (M)
First	19.8	$1.0 \times 10^{-6}$	20.0	$1.0 \times 10^{-6}$
Second	19.6	$2.8 \times 10^{-6}$	19.9	$2.5 \times 10^{-6}$
Third	19.3	$3.5 \times 10^{-6}$	19.6	$2.8 \times 10^{-6}$
Fourth	19.1	$5.9 \times 10^{-6}$	19.4	$3.6 \times 10^{-6}$
Fifth	18.9	$6.7 \times 10^{-6}$	19.2	$4.7 \times 10^{-6}$
Sixth	18.6	$8.2 \times 10^{-6}$	18.9	$5.5 \times 10^{-6}$
Seventh	15.1	$1.3 \times 10^{-5}$	18.7	$7.1 \times 10^{-6}$
Eighth	14.2	$3.4 \times 10^{-5}$	16.5	$1.6 \times 10^{-5}$
Ninth	12.9	$5.5 \times 10^{-5}$	15.1	$4.2 \times 10^{-5}$
Tenth	10.6	$9.2 \times 10^{-5}$	14.5	$8.5 \times 10^{-5}$

For this estimation, four electrodes were employed extensively (1 hour per day) for 10 weeks. After 6 weeks utilization of PVC membrane electrode, two changes were observed: a slight gradual decrease in the slope (from 19.8 to 10.6 mV/decade) and an increase in the detection limit (from  $1.0 \times 10^{-6}$  M to  $9.2 \times 10^{-5}$  M). As can be seen from Table 3, this time in case of carbon paste was 7 weeks which shows the long-term stability of this kind of sensor in comparison with PVC membrane electrodes.

In PVC membrane electrodes after several time of usage, the membrane ingredients leak from the organic layer and affect the membrane response. While in CPEs the surface of the



electrode are renewable and can be used for longer time.

### 3.7. Analytical Applications

Linearity, limit of detection, recovery test, selectivity, precision, accuracy, and ruggedness/robustness were the parameters used for the method validation. As mentioned before, the sensors were measured between  $1 \times 10^{-6}$  and  $1 \times 10^{-2}$  M. The calculated detection limit of the sensors was  $1.0 \times 10^{-6}$  M (0.3  $\mu\text{g/mL}$ ).

#### 3.7.1. Recovery Test from Tablet

The proposed sensor was evaluated by measuring the drug concentration in some pharmaceutical formulations (Table 4).

**Table 4.** Potentiometric determination of alprazolam in pharmaceutical formulations

Sample	Labeled amount (mg/tab.)	Found by PVC membrane electrode*	Found by CPE*
Tablet 1	1	1.10 $\pm$ 0.06	1.11 $\pm$ 0.05
Tablet 2	1	1.09 $\pm$ 0.07	1.06 $\pm$ 0.06
Tablet 3	1	1.11 $\pm$ 0.07	1.09 $\pm$ 0.07

\* The results are based on five replicate measurements

The drug concentration was determined with the calibration method. The results are in satisfactory agreement with the labeled amounts. The corresponding recovery percentage value varied from 95.3-113.6%.

#### 3.7.2. Selectivity

**Table 5.** Selectivity coefficients of various interfering compounds for alprazolam sensors

Interfering ion	Log $K_{\text{MPM}}$ (PVC membrane electrode)	Log $K_{\text{MPM}}$ (CPE)
Na <sup>+</sup>	-3.9	-3.7
K <sup>+</sup>	-4.0	-3.8
NH <sub>4</sub> <sup>+</sup>	-3.6	-3.5
Ca <sup>2+</sup>	-3.1	-4.2
Mg <sup>2+</sup>	-4.3	-4.4
Cl <sup>-</sup>	-4.5	-4.7
NO <sub>3</sub> <sup>-</sup>	-4.4	-4.4
CO <sub>3</sub> <sup>2-</sup>	-3.9	-4.1
Banzoate	-4.2	-4.5
Lactose	-4.0	-4.3
Glucose	-4.1	-4.2

Selectivity, which describes an ion-selective electrode's specificity toward the target ion in the presence of interfering ions, is the most important characteristic of these devices. The potentiometric selectivity coefficients of the alprazolam sensor were evaluated by the matched potential method (MPM) [54-57]. The resulting values of the selectivity coefficients are shown in Table 5. Note that all selectivity coefficients are about  $10^{-3}$ , suggesting were interferences negligible in the performance of the electrode assembly.

### 3.7.3. Precision and accuracy

For repeatability monitoring, 5 replicate standard samples of 5, 50, 500  $\mu\text{g/mL}$  were measured. The mean concentrations by PVC membrane were  $5.2\pm 0.3$ ,  $55.5\pm 5.1$ ,  $514.6\pm 7.8$   $\mu\text{g/mL}$  with respective RSD values of 3.2, 4.1, and 3.4% and for CPE were  $5.2\pm 0.4$ ,  $54.5\pm 4.2$ ,  $515.8\pm 8.9$   $\mu\text{g/mL}$  with respective RSD values of 3.5, 3.9, and 3.0%.

### 3.7.4. Ruggedness/Robustness

For ruggedness of the methods a comparison was performed between the intra- and inter-day assay results for alprazolam obtained by two analysts.

The RSD values for the intra- and inter-day assays in the cited formulations performed in the same laboratory by the two analysts did not exceed 4.9%. On the other hand, the robustness was examined while the parameter values (pH of the solution and the laboratory temperature (changed slightly). Alprazolam recovery percentages were good under most conditions, and not showing any significant change when the critical parameters were modified.

## 4. CONCLUSIONS

In the present work, two types of potentiometric electrodes were constructed for determination of alprazolam. The sensors demonstrated advanced performances with a fast response time, a lower detection limit of  $1.0\times 10^{-6}$  M and potential responses across the range of  $1.0\times 10^{-6}$ - $1.0\times 10^{-2}$  M. The sensors enabled the alprazolam determination in pharmaceutical formulations. Both sensors respond based on ion-exchange mechanism. Alprazolam-tetraphenyl borate ion-pair was employed as a sensing element in construction of both electrodes. First, PVC membrane electrode was made after series of experiments. The best PVC membrane electrode performance was achieved by a membrane composition of 30% PVC, 63% DBP, and 7% ion-pair. Then, a carbon paste electrode was designed to improve the analytical responses. The best electrode was composed of 20% ion-pair, 20% paraffin and 60% graphite.

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