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Synthesis and Spectral Characterization of Zirconium Complex of Pioglitazone : A New Oral Antidiabetic Drug

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ABSTRACT: Present paper deals with the synthesis, physico-chemical and spectral characterization of Zr(IV) complex with Pioglitazone a new oral antidiabetic drug. The conductometric titration using monovariation method indicate that complex is ionic and L_2M type which was further confirmed by Job's method of continuous variation as modified by Turner and Anderson. Analytical data agree with the molecular formula of complex viz. $[(C_{19}H_{19}N_2O_3S)^+_2\ Zr]\ 2NO_3^-$. Structure of complex was assigned as tetrahedral, in which ligand molecules lies horizontally joining the central Zr(IV) atom, supported by IR and ^{1}H NMR studies. The structure for complex was proposed on the basis of analytical data and elemental analysis.

Keywords: Pioglitazone, antidiabetic drug, complex, transition metal, IR, ^{1}H NMR.

I. INTRODUCTION

Pioglitazone hydrochloride is an oral antidiabetic agent that has been shown to affect abnormal glucose and lipid metabolism associated with insulin resistance by enhancing insulin action on peripheral tissues in animals. It is used in the treatment of type-II diabetes also known as non-insulin-dependent *diabetes mellitus* [1] (NIDDM) or adult-onset diabetes. Currently, it is marketed under the trade name Actos [2] in USA. It belongs to a class of compounds known as the "thiazolidinediones". Pioglitazone hydrochloride (C19H20N2O3S·HCl) exists as an odourless white crystalline powder. It has structural formula as shown in Fig.1, with a molecular weight 392.90 daltons. It has low solubility and high permeability. It is insoluble in water and ether, little soluble in acetonitrile and acetone, and completely soluble in dimethylformamide (DMF). For oral administration it is available in the form of tablets in market. It exhibits slow gastrointestinal absorption rate and inter individual variation of its bioavailability [3].

A survey of literature reveals that metal complexes of many drugs have been found to be more effective than the drug alone [4] therefore, much attention is given to the use of thiazolidinedione hydrochloride due to their high complexing nature with essential metals. In view of the above and in continution of our work, it is interesting to have an insight into the synthesis of zirconium complex with pioglitazone and to diagnose various structural aspects of the isolated complex. Here the synthesis and characterization of zirconium nitrate with pioglitazone hydrochloride has been described.

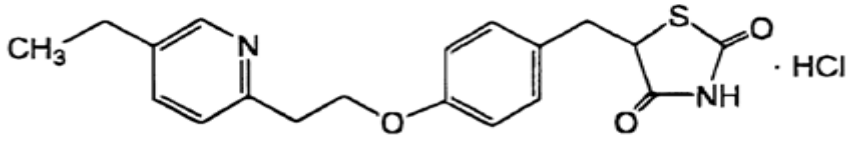


Fig. 1: Structure of Pioglitazone HCl.

II. EXPERIMENTAL

A. Ligand- Metal ratio

To find out the ligand metal ratio, initially conductometric titration using monovariation method were carried out at 27 ±1 ºC and 0.005 M solution of pioglitazone HCl drug was prepared in DMF. Similarly, solution of metal salt $Zr(NO_3)_4$ was prepared in the ethanol of 0.01M concentration. 20ml of ligand was diluted to 200ml with the same solvent. The ligand was titrated conductimetrcally aganist zirconium nitrate taken in burette using fraction of 1ml. Conductance was recorded after each addition with proper stirring. Results were plotted in the form of graph between corrected conductance and volume of metal salt added. From the equivalence point in the graph, ratio between ligand and metal was noted to be 2:1 (L_2M).

Formation of complex in 2:1 (L_2M) ratio was also confirmed by Job's method [5] of continuous variation as modified by Turner and Anderson [6], using conductance as index property (Table 1, 2 and Fig. 2 (a, b)). From these values the stability constant (log k) and free energy change (ΔF), were also calculated by using formula [7-12] $k = \frac{x}{(a_1-x)(b_1-2x)^2} = \frac{x}{(a_2-x)(b_2-2x)^2}$.

Table 1. Pioglitazone with Zirconium Nitrate (Modified Job's Method).

Pioglitazone-0.005 M — $Zr(NO_3)_4$ – 0.005 M
Solvent: 90 % Ethanol — Temperature-27ºC ±1

Mole Metal Ligand Ratio	Conductance ×10^{-3} Mhos S:L C_1	M:S C_2	M:L C_3	Δ Conductance ×10^{-3} Mhos (C_1+ C_2- C_3)	Δ Corrected Conductancee ×10^{-3} Mhos
0:12	0.130	0.009	0.129	0.01	0
1:11	0.118	0.041	0.142	0.017	0.008
2:10	0.109	0.099	0.177	0.031	0.022
3:9	0.097	0.134	0.189	0.042	0.034
4:8	0.084	0.174	0.208	0.05	0.042
5:7	0.071	0.206	0.230	0.047	0.039
6:6	0.060	0.243	0.261	0.042	0.036
7:5	0.048	0.268	0.279	0.037	0.03
8:4	0.037	0.296	0.303	0.03	0.023
9:3	0.028	0.326	0.329	0.025	0.019
10:2	0.021	0.356	0.359	0.018	0.012
11:1	0.014	0.392	0.394	0.012	0.006
12:0	0.004	0.434	0.432	0.006	0

Table 2. Pioglitazone with Zirconium Nitrate (Modified Job's Method).

Pioglitazone-0.002M — $Zr(NO_3)_4$ - 0.002M
Solvent: 90 % Ethanol — Temperature 27ºC ±1

Mole Metal Ligand Ratio	Conductance ×10^{-3} Mhos S:L C_1	M:S C_2	M:L C_3	Δ Conductance × 10^{-3} Mhos (C_1+ C_2- C_3)	Δ Corrected Conductance ×10^{-3} Mhos
0:12	0.115	0.004	0.114	0.005	0
1:11	0.099	0.032	0.120	0.011	0.006
2:10	0.085	0.061	0.127	0.019	0.014
3:9	0.077	0.092	0.139	0.03	0.025
4:8	0.071	0.116	0.147	0.04	0.035
5:7	0.065	0.133	0.161	0.037	0.032
6:6	0.059	0.151	0.178	0.032	0.028
7:5	0.053	0.168	0.193	0.028	0.023
8:4	0.045	0.191	0.211	0.025	0.02
9:3	0.030	0.214	0.223	0.021	0.016
10:2	0.016	0.245	0.247	0.014	0.009
11:1	0.011	0.280	0.283	0.008	0.003
12:0	0.003	0.305	0.304	0.004	0

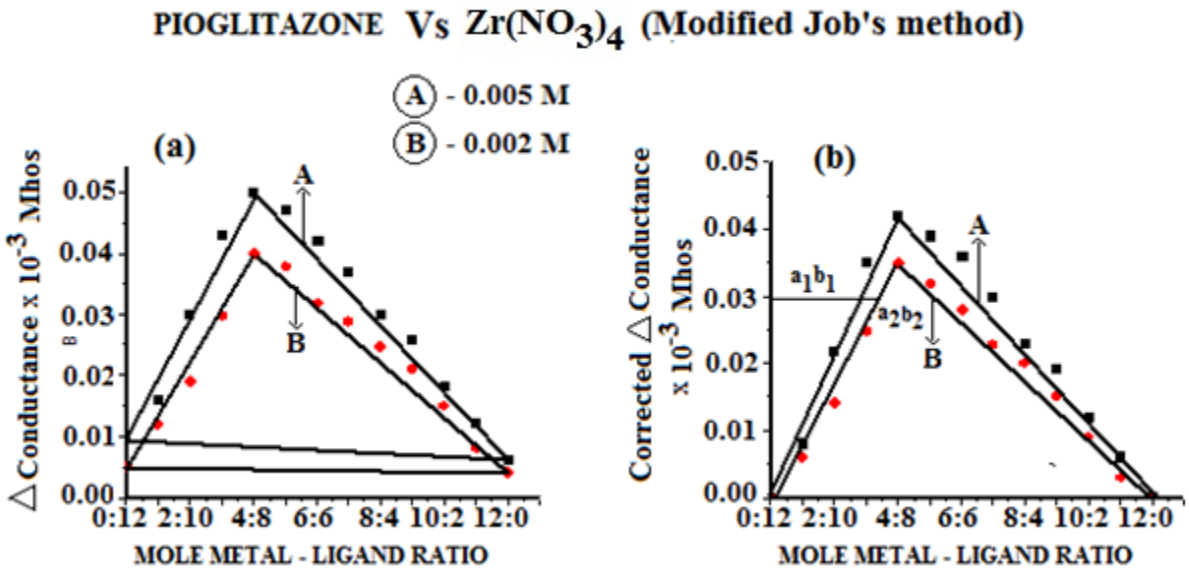


Fig. 2. (a) Represent Job's curve and Fig. 2(b) represent modified Job's curve.

B. Material and Method

All chemicals used were of analytical grade (A.R.) and of highest purity. They include pure pioglitazone HCl with molecular formula ($C_{19}H_{20}N_2O_3S.HCl$), received from Morepen Laboratories, Distt. Solan (H.P.) India. The metal salt of zirconium nitrate $(ZrNO_3)_4$ obtained from Hi media Laboratory, Mumbai, India. Ethanol and DMF were used as a solvent.

C. Synthesis of Complex

A weighed quantity of pioglitazone (2 mole) was dissolved separately in minimum quantity of DMF. The zirconium solution was prepared by dissolving separately in the ethanol. Ligand solution was added slowly with stirring into the solution of metallic salt at room temperature; maintain the pH between 6.0 to 6.5 by adding dilute NaOH solution. On refluxing the mixture for 3-4 h and on cooling, the precipitate of metal complex was obtained, which were filtered off, washed well with DMF and ethanol, finally dried in vacuum and weighed.

D. Instrumentation

Molar conductance of complex was measured by using Systronics Digital Conductivity meter.

Melting point was determined by Perkin Elmer model melting point apparatus and is uncorrected. The elemental analysis of the isolated complex was carried out by using Coleman analyzer model at the Departmental Micro Analytical Laboratory, CDRI, Lucknow, India. IR spectra of ligand and complex were recorded with Perkin Elemer Model 577 Spectrophotometer in the range of 4000-450 cm^{-1} as KBr pellets CDRI, Lucknow, India. ^1H NMR spectra of the ligand and isolated complex were recorded on a Bruker DRX-300 Spectrophotometer and DMSO- d_6 was used as solvent CDRI, Lucknow, India.

III. RESULTS AND DISCUSSION

The formation of metal complexes with organic compounds have long been recognized. The synthesized complex are coloured and stable, being soluble in DMSO and insoluble in water, ethanol etc. It is revealed from analytical data and conductometric studies that ligand and metal are in 2:1 ratio. The proposed structure for pioglitazone-zirconium complex is given in Fig. 3.

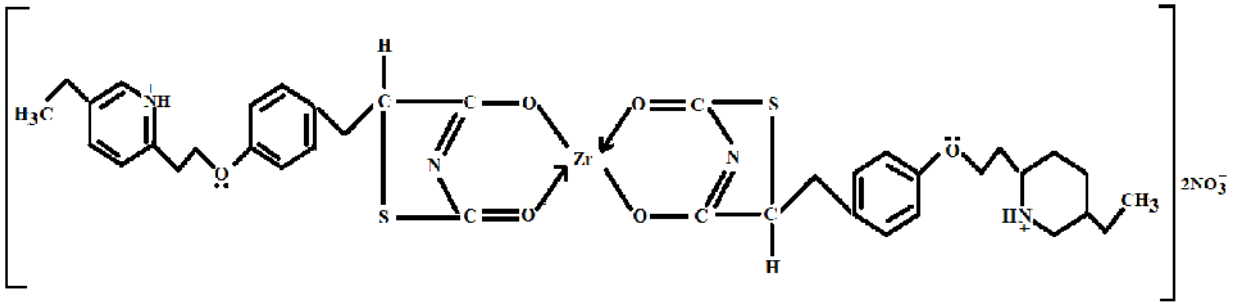


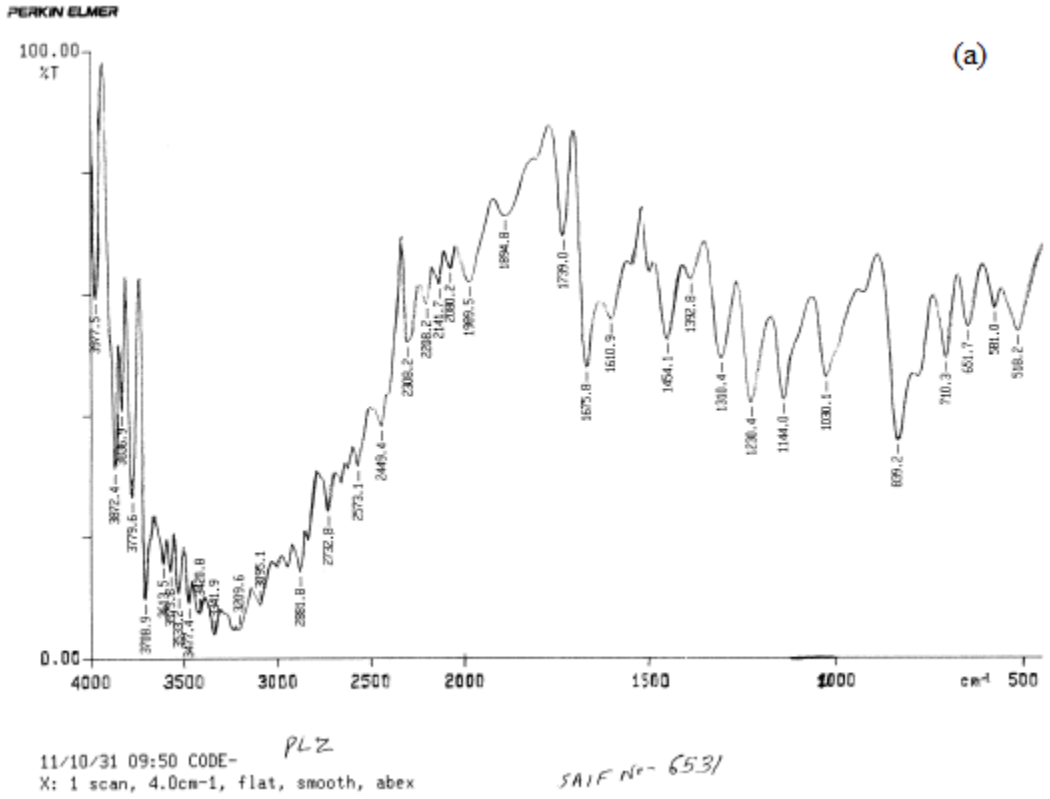
Fig. 3. Structure of Pioglitazone –zirconium complex.

A. Physico-chemical Characterstics of Pioglitazone - zirconium complex

Molecular formula of complex i.e. $[(C_{19}H_{19}N_2O_3S)^{+}{}_2$ Zr]$2NO_3^-$. Mol. wt: 1001.02; Colour: off white; Yield: 52.34%; m.p: 204°C; Log K = 11.80 (L/mole), ΔF = -16.25 (K cal/mole), Anal. data Calcd (found) %; C, 45.55 (45.30); H, 3.79 (3.72); N, 5.59 (5.46); S,6.39 (6.24); Zr, 9.11 (8.96); NO_3^-, 6.19(6.02).

B. Infra-red Spectral Studies of Pioglitazone – zirconium complex

The IR spectra of ligand and isolated complex were recorded within the range 4000-400 cm^{-1}. In order to determine the coordination sites that may be involved in chelation, we compared the IR spectra of complex with free pioglitazone ligand as shown in Fig. 4(a)-(b).



The tautomeric equilibrium depends on the degree of conjugation, nature and position of the substituents, polarity of the solvent etc. This phenomenon has drawn considerable attention by several investigators and characteristic spectral bands have been assigned to the individual tautomers.

Assignments of the infrared spectral bands are based on literature. IR spectrum of pioglitazone–zirconium complex Fig. 4(b) shows important bands due to ν(M-O) 531±10 cm^{-1}, ν (Aromatic C-H streatching) 774 cm^{-1}, ν(C=O) 1710 cm^{-1}, ν(C-H streatching) 2686±20 cm^{-1}, (C-H streatching) 2867±20 cm^{-1}, ν(Ar-H streatching) 3058 cm^{-1},ν(N-H) 3348 cm^{-1}, ν(N-H) 3448 cm^{-1}. The proposed structure for the isolated complex is also supported by IR absorptions [13-16].

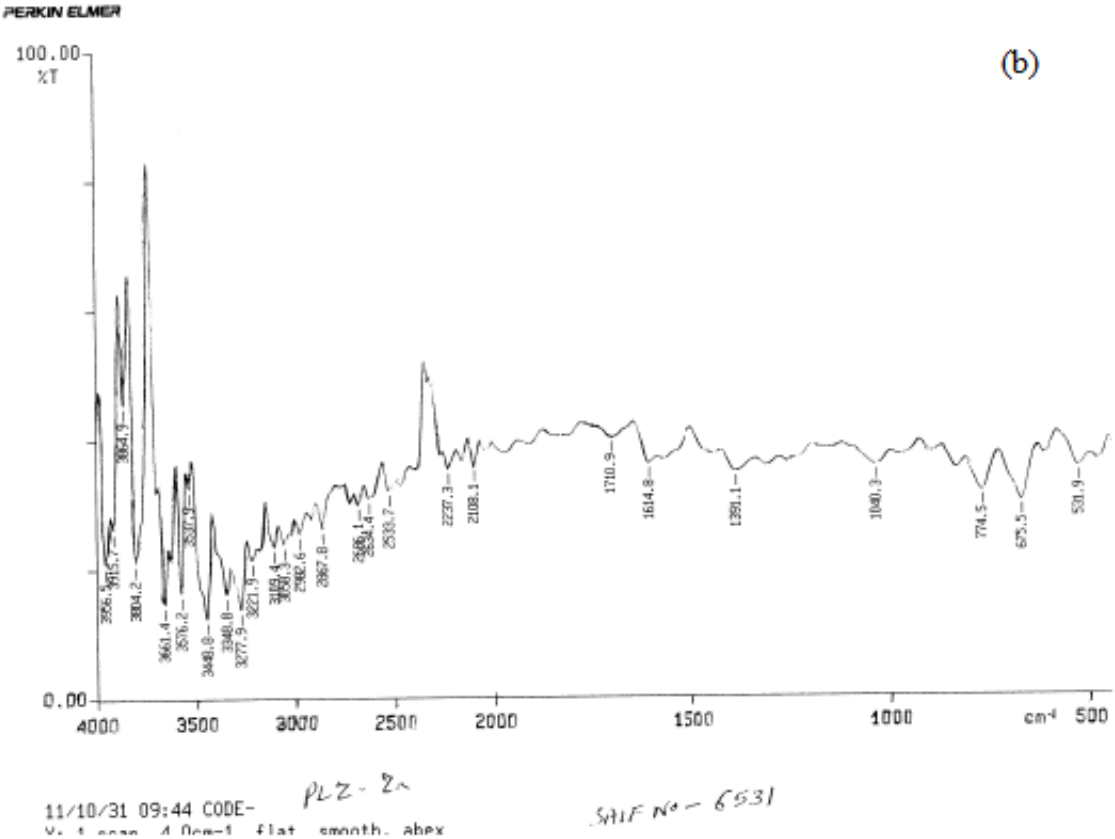


Fig. 4. (a)-(b**)** IR spectra of pioglitazone drug and pioglitazone- zirconium Complex.

C. ^{1}H NMR Studies of Pioglitazone – zirconium complex

This technique give us informtion about the number and types of atoms in molecule and also provide useful information regarding the environment of protons present in the complex. Fig. 5 shows the ^{1}HNMR spectra of complex. Assignment of pioglitazone-zirconium complex, molecular formula $[(C_{19}H_{19}N_2O_3S)^{+}{}_2\ Zr]2NO_3^{-}$ (M. Wt. = 1001.02), δ8.72 (s, 1H,2-pyridine), δ8.39-8.42 (d,1H, 2-pyridine), δ7.95-7.98(d1H, 2-pyridine), δ7.12-7.15(d,2H, 2-CH_2-Benzene), δ6.85-6.88(d, 2H, 2-CH_2-Benzene) δ4.84-4.88(m,1H methine-CH), δ4.36-4.41(t, 2H methylene-CH_2), δ3.46-3.93(t, 2H methylene-CH_2), δ3.01-3.39(d, 2H methylene-CH_2), δ2.50-2.80(s, Residual solvent DMSO-d_6), δ1.25(t,3H methyl-CH_3) respectively. The proposed structure for the isolated complex is also supported by [17-23].

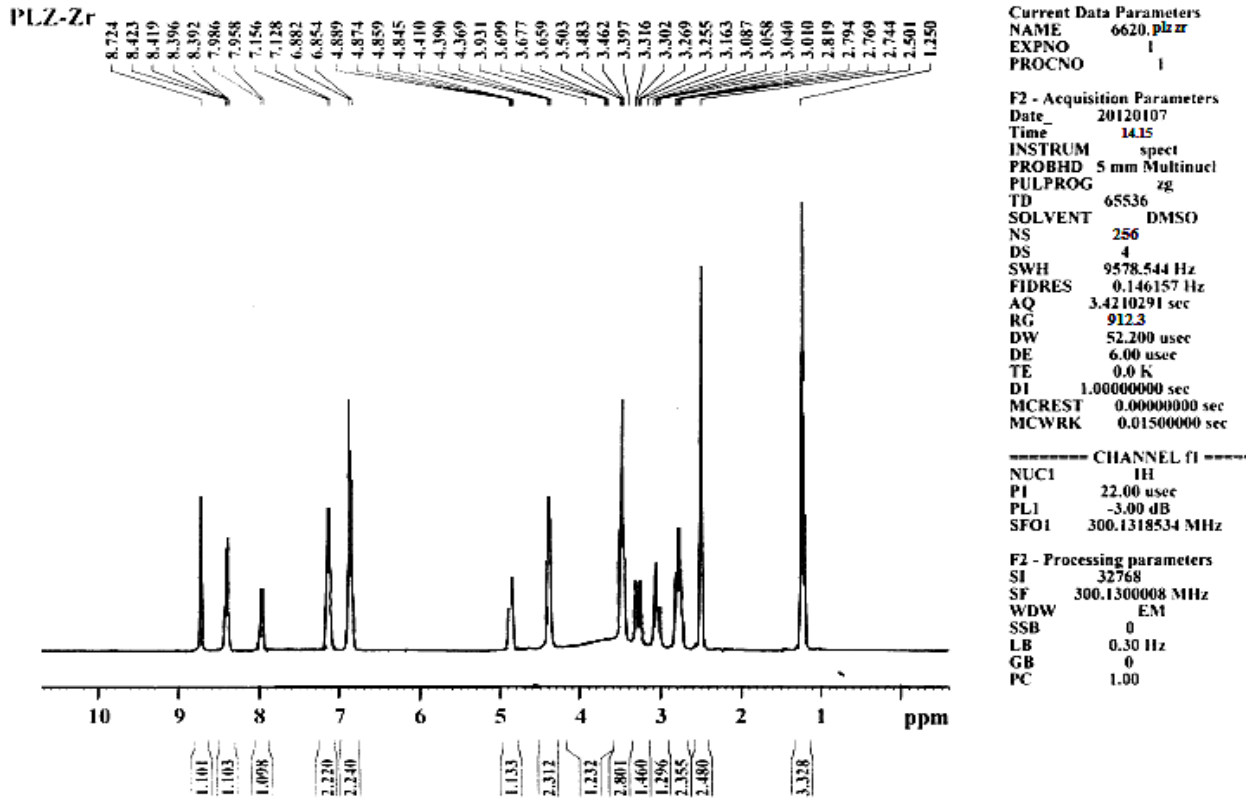


Fig. 5. ^{1}H NMR spectra of pioglitazone- zirconium Complex.

IV. CONCLUSION

For supporting the proposed structure of zirconium complex with pioglitazone initially monovariation method was conducted that indicate 2:1 ligand metal ratio which was further confirmed by Job's method of continuous variation as modified by Turner and Anderson. Moreover, stability constant and free energy change were also calculated. Analytical data agree to the molecular formula viz. $[(C_{19}H_{19}N_2O_3S)^{+}{}_2\ Zr]\ 2NO_3^-$. For the complexation of pioglitazone with zirconium, it was concluded that the pioglitazone undergoes enolization before complexation so as to form a hetrocyclic chelate ring. The formation of complex through enolization is also supported from the frequencies of IR and NMR. The thiazolidinedione unit inside the coordination sphere has a positive charge while $2NO_3^-$ occupies the outer place of the coordination sphere.

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