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THEORETICAL AND EXPERIMENTAL ^{1}H AND ^{13}C NMR SPECTRA OF 3-HYDROXYPYRIDINE, 3-METHOXYPYRIDINE, AND N-ETHYL-3-OXYPYRIDINIUM BETAINE*

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Abstract: ^{1}H and ^{13}C NMR chemical shifts for neutral (3-hydroxypyridine and 3-methoxypyridine) and zwitterionic (N-ethyl-3-oxypyridinium betaine and 3-pyridone) molecules were calculated by GIAO/B3LYP/6-31G(d,p) and IGLO/deMon/NMR approaches. Linear correlations between the calculated and experimental ^{1}H and ^{13}C NMR chemical shifts for 3-hydroxypyridine, 3-methoxypyridine, and N-ethyl-3-oxypyridinium betaine suggest that the 3-hydroxy tautomer is dominant in DMSO-d_6. The lack of such a correlation for 3-pyridone indicates an absence of this species in DMSO-d_6 solution.

1. INTRODUCTION

Of various physicochemical methods, none is more popular than nuclear magnetic resonance [1]. Its applications are unlimited. By far, the most common nuclei studied in the NMR of organic and bioorganic molecules are ^{1}H and ^{13}C [2, 3]. One of the necessary conditions for further progress in this field is gaining a theoretical insight into the nature of the dependence of NMR shielding tensors on the geometrical and electronic structure of the system. This work is a small step in this direction and aims in a determination of the tautomer structure based on computed and measured NMR signals. The second point is to check if calculation methods can reproduce chemical shifts for zwitterionic molecules.

N-substituted-3-oxypyridinium betaines have already been a subject of extensive studies due to their pharmaceutical activity, their relevance to biochemistry of pyridoxine, and the potential of reduction to pharmacologically interesting piperidines [4, 5]. 3-Hydroxypyridine (3-pyridinol) is in tautomeric equilibrium with 3-pyridone, zwitterionic form or betaine, in which the hydroxy proton has been transferred to the nitrogen atom [6, 7]. The tautomeric equilibrium strongly depends on solvent. In aqueous solution both forms are in equal proportions, while in alcoholic solution the hydroxy form is dominant [8]. 3-Hydroxy- and 3-methoxy-pyridine yield very similar spectra of ABMX type in DMSO-d_6 [9], which suggests that the hydroxy form dominates in DMSO-d_6 solution. This theoretical study supplies additional arguments which enable interpretation of the experimental data and determination of the prototropic equilibrium shift towards one of the tautomers present in the solution. In this work we give a detailed interpretation of the ^{1}H and ^{13}C NMR spectra measured in

* Dedicated to the memory of Professor Jacek Rychlewski

DMSO-d_6 for 3-hydroxypyridine (HOP), 3-methoxypyridine (MeOP), 3-pyridone (PON) and N-ethyl-3-oxypyridinium betaine (EtPB). Assignments of the observed proton and carbon chemical shifts arebased on the quantum chemical calculations by IGLO/deMon/NMR [10] and GIAO/B3LYP/6-31G(d,p) [11] approaches.

2. EXPERIMENTAL

2.1. Synthesis

N-Ethyl-3-hydroxypyridinium bromide (EtPBH-Br). A solution of 3-hydroxypyridine with 20% excess of $BrCH_2CH_3$ in 1-propanol was heated at 30°C for 10 hours. The excess of the solvent was removed under reduced pressure and the crude product was recrystallized from ethanol and diethyl ethermixture (10:1), m.p. 100-102°C, 74% yield, lit. 99-102°C [4].

N-Ethyl-3-oxypyridinium betaine (EtPB). EtPBH-Br (10 g) was dissolved in distilled water (50 cm^3) and treated with an anion-exchange resine, Amberlite IRA 420 (OH^-) (140 g). The mixture was stirred until the organic layer gave a negative Beilstein test for halide. The residue was separated, washed with methanol and the eluates were concentrated under reduced pressure below 70ºC. The crude product was recrystallized from acetonitryle, m.p. 48°C, 68% yield.

2.2. Measurements

The ^1H and ^{13}C spectra in DMSO-d_6 solution were recorded on a Varian Gemini 300VT spectrometer operating at 300.07 and 75.46 MHz for proton and carbon-13, respectively. Chemical shifts were confirmed by HETCOR experiment.

3. COMPUTATIONS

Density Function Theory (DFT) was employed to fully optimize molecular structures of the studied molecules. The model chemistry was chosen to be B3LYP/6-31G(d,p) (Becke's three parameter exchange functional [12] and the Lee-Yang-Parr correlation functional [13]) as implemented in the Gaussian 98 program package [14]. For the optimized geometries the NMR shielding constant tensors were computed using two different approaches.

The first approach relies on the magnetic-field-dependent DFT method based on the IGLO (Individual Gauge Localized Orbital) scheme and Perdew density functional which are adapted in the deMon/NMR program [10]. The one-electron basis set used in these calculations was the IGLO-3 basis [15]. In the second approach the standard GIAO (Gauge-Independent Atomic Orbital) method [11] of Gaussian program was employed within the same level of theory as for the geometry optimization. Additionally, a solvent simulation using the PCM (Polarized Continuum Model) approach [18] was performed. However, because no significant differences in NMR results between the solvent and gas-phase calculations was observed, only the latter are reported in this work.

4. RESULTS AND DISCUSSION

4.1. Geometrical parameters

The chemical structures of the investigated compounds are shown in Fig. 1. The forms involved in the tautomeric equilibrium correspond to the neutral form of 3-hydroxypyridine with the hydroxyl hydrogen *cis* and *trans* to N(1) (HOPc and HOPt, respectively) and the

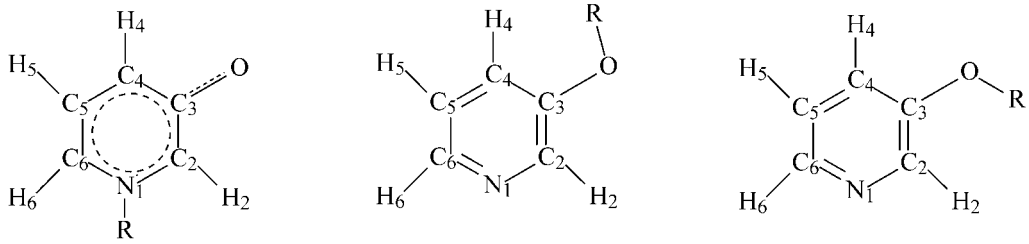

Fig. 1. Molecular scheme of the investigated compounds

Table 1. X-ray and B3LYP calculated structural parameters of *cis* and *trans* 3-hydroxypyridines (HOPc, HOPt), *cis* and *trans* 3-methoxypyridines (MeOPc, MeOPt), 3-pyridon (PON), and N-ethyl-3-oxy-pyridinium betaine (EtPB)

	X-ray [16]	Computed					
	HOPc	HOPc	HOPt	MeOPc	MeOPt	PON	EtPB
				Bond length (bohr)			
N(1)-C(2)	1.440	1.333	1.335	1.339	1.330	1.345	1.346
N(1)-C(6)	1.337	1.341	1.338	1.335	1.343	1.353	1.359
C(2)-C(3)	1.379	1.403	1.401	1.402	1.407	1.452	1.452
C(3)-C(4)	1.386	1.395	1.397	1.401	1.397	1.458	1.455
C(4)-C(5)	1.377	1.394	1.391	1.388	1.397	1.380	1.379
C(5)-C(6)	1.380	1.394	1.397	1.398	1.391	1.398	1.397
C(3)-O	1.351	1.364	1.364	1.362	1.362	1.241	1.242
O-H	1.045	0.967	0.967				
O-C(9)				1.422	1.420		
N(1)-H						1.010	
N(1)-C(7)							1.483
C(7)-C(8)							1.527

Table 1 - continued

				Valence angle (deg)			
C(2)-N(1)-C(6)	118.6	118.0	117.8	118.2	117.8	125.0	122.5
N(1)-C(2)-C(3)	122.5	123.2	123.5	123.0	123.6	121.7	123.2
N(1)-C(6)-C(5)	122.0	123.0	123.0	122.8	122.9	117.1	118.4
C(2)-C(3)-C(4)	118.7	118.5	118.5	118.3	118.3	112.6	112.7
C(3)-C(4)-C(5)	118.6	118.3	118.1	118.6	118.0	122.6	121.8
C(4)-C(5)-C(6)	119.5	119.0	119.2	119.0	119.2	121.0	121.3
C(2)-C(3)-O	118.2	117.6	123.0	125.2	116.0	122.3	122.0
C(4)-C(3)-O	123.1	123.9	118.5	116.5	125.7	125.2	125.3
C(3)-O-H	114.5	109.4	109.1				
C(3)-O-C(9)				118.1	118.0		
C(2)-N(1)-C(7)							118.7
N(1)-C(7)-C(8)							112.2
				Dihedral angle (deg)			
N(1)-C(2)-C(3)-C(4)	–0.7	0.0	0.0	180.0	0.0	0.0	0.2
N(1)-C(2)-C(3)-O	179.9	–179.9	180.0	180.0	180.0	180.0	–179.8
N(1)-C(6)-C(5)-C(4)	0.2	0.0	0.0	0.0	0.0	0.0	0.0
C(2)-C(3)-O-H	–176.5	–180.0	0.0				
C(2)-C(3)-O-C(9)				0.0	180.0		
C(4)-C(3)-O-H	4.2	0.1	180.0				
C(4)-C(3)-O-C(9)				180.0	0.0		
C(2)-C(3)-C(4)-C(5)	0.8	–0.0	0.0	0.0	0.0	0.0	–0.2
C(3)-C(4)-C(5)-C(6)	–0.6	0.0	0.0	0.0	0.0	0.0	0.1
C(5)-C(4)-C(3)-O	–179.8	180.0	180.0	180.0	180.0	180.0	180.0
C(2)-N(1)-C(7)-C(8)							–85.6
E (hartree)		–323.51137	–323.51230	–362.81694	–362.81680	–323.48993	–402.12271
Dipole moment (debye)		3.480	1.288	1.793	3.589	6.584	7.156

3-pyridone (PON). Moreover, two other molecules were investigated: N-ethyl-3-oxypyridinium betaine (EtPB) and 3-methoxypyridine in the same fashion as 3-hydroxypyridine, e. i. with the methyl group *cis* and *trans* to N(l) (MeOPc and MeOPt, respectively). The calculated structural parameters, total energy, and dipole moment are collected in Table l. The bond lengths and angles determined for cis and *trans* tautomers of 3-hydroxypyridine from the DFT calculations are in good agreement with the X-ray data [16], of course apart from angels related to *cis* and *trans* tautomery. This fact makes us believe that the chemistry model selected for the minimum geometry determination is sufficient. In PON and EtPB the C(3)-O distance is significantly shorter than in the other molecules and is typical for N-methylpyridones [17].

4.2. Chemical shifts

The shielding constants calculated for the investigated compounds are listed in Tables 2 and 3. The GIAO shielding constants are higher than those calculated within the IGLO by 0.4-1.1 units for proton and 17-34 units for carbon. The relations between the computed screening constants (σ_{calc}) and the experimental ^{1}H and ^{13}C chemical shifts (δ_{exp}) are assumed linear (Figs. 2-5) and described by the following equation:

$$\delta_{exp} = A \cdot \sigma_{calc} + B .$$

As we are interested in correlations between theoretical and experimental data no reference to TMS was performed. Values of the slope and intercept were determined through a fit of the computed shielding constants to the experimental chemical shifts. As the experiment supplies the chemical shifts for a *cis-trans* mixture of 3-hydroxypyridine and 3-methoxypyridine, the same data were used to perform correlation with σ_{calc} obtained for both forms, *cis* and *trans*. The parameters A and B for all the studied molecules are listed in Table 4. Their values were employed to compute the chemical shifts given in Tables 2 and 3. The experimental chemical shift for OH proton in HOP(c,t) and for NH proton in PON is significantly affected by the hydrogen bond formed between the molecule and the solvent. For this reason it was excluded from the least-square procedure.

Several conclusions can be drawn from the analysis of the correlation coefficients collected in Table 4. Except for the PON, the quality of the fit of the ^{13}C data is significantly higher than that of the proton signals. This can be partially attributed to a larger affinity of the hydrogens to the interaction with the environment. GIAO and IGLO methods perform equally well in the case of ^{13}C, whereas for ^{1}H the IGLO shielding constants correlate slightly better

Table 2. Comparison of the IGLO and GIAO results for 3-hydroxypyridine (HOPc and HOPt) and 3-methoxypyridine (MeOPc and MeOPt). The predicted IGLO and GIAO chemical shifts were computed from the linear equation $\delta_{exp} = A\ \sigma_{calc} + B$ with A and B determined from the fit to the experimental data

	Shielding constant, σ		Chemical shift, δ [ppm]		
Atom label	IGLO	GIAO	IGLO	GIAO	Exp. [9]
HOPc					
H-2	22.8	23.7	8.20	8.09	8.36
H-4	23.7	24.7	7.34	7.28	7.31
H-5	23.8	24.6	7.25	7.36	7.26
H-6	22.7	23.4	8.29	8.35	8.15
O-H	26.8	28.2			9.9
C-2	33.8	61.3	135.2	136.2	137.8
C-3	11.4	45.3	153.4	152.5	153.5
C-4	50.9	76.3	121.2	120.9	121.4
C-5	46.3	72.9	125.0	124.3	123.8
C-6	25.8	55.1	141.7	142.5	140.0

Table 2 continued

HOPt					
H-2	22.6	23.3	8.33	8.26	8.36
H-4	24.4	25.2	7.18	7.16	7.31
H-5	24.0	24.7	7.43	7.45	7.26
H-6	22.9	23.4	8.14	8.20	8.15
O-H	27.5	28.4			9.9
C-2	34.5	58.3	137.4	139.1	137.8
C-3	15.5	45.5	152.8	151.3	153.5
C-4	55.9	78.6	120.0	119.8	121.4
C-5	49.5	73.8	125.2	124.4	123.8
C-6	29.9	55.5	141.1	141.8	140.0
MeOPc					
H-2	22.9	23.5	7.70	8.34	8.32
H-4	24.0	24.7	6.56	7.14	7.38
H-5	24.0	24.6	6.56	7.24	7.34
H-6	22.8	23.3	7.81	8.54	8.19
OCH_3	27.5	27.9	2.92	3.94	3.84
C-2	41.7	64.2	133.4	130.0	137.3
C-3	12.6	43.0	163.5	150.3	155.2
C-4	50.1	73.6	124.7	121.0	120.0
C-5	49.0	73.5	125.8	121.1	123.8
C-6	28.8	54.7	146.7	139.1	141.4
OCH_3	118.9	139.0	53.6	58.6	55.3
MeOPt					
H-2	22.6	23.3	8.53	8.48	8.32
H-4	24.3	25.0	6.98	6.90	7.38
H-5	23.9	24.6	7.34	7.27	7.34
H-6	22.9	23.4	8.25	8.39	8.19
OCH_3	27.6	28.1	3.97	4.02	3.84
C-2	31.2	56.1	140.0	141.2	137.3
C-3	12.2	42.7	157.5	154.7	155.2
C-4	60.9	82.1	112.6	115.0	120.0
C-5	49.2	73.8	123.4	123.4	123.8
C-6	29.9	55.6	141.2	141.7	141.4
OCH_3	119.8	139.8	58.3	56.9	55.3

with the experiment. The most striking is the lack of a linear correlation in the case of PON. Based of this data and having in mind that the DMSO-d_6 solution contains a tautomeric

mixture HOP(c,t) and PON, we can conclude that this prototropic equilibrium is clearly shifted towards 3-hydroxypyridine. Another evidence supporting this interpretation is supplied by a comparison of the calculated shielding constants of MeOP(c,t) and EtPB (no proton tautomers) with corresponding values of both 3-hydroxypyridine and 3-pyridone - the shielding of MeOP(c,t) are much closer to that of 3-hydroxypyridine while signals from EtPB follow closely those of PON.

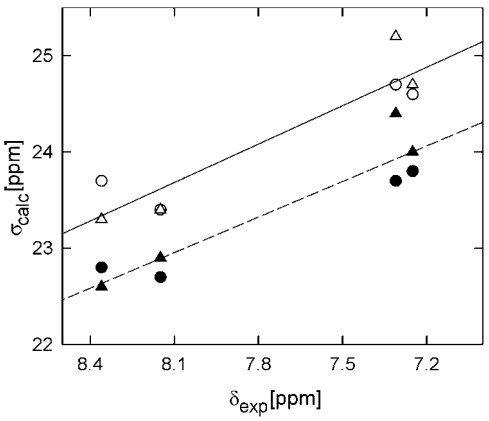

Fig. 2. Relationship between the computed ^{1}H screening constants (σ) and the experimental ^{1}H chemical shifts (δ) for HOPc (GIAO - o, IGLO – ●) and HOPt (GIAO – △, IGLO – ▲)

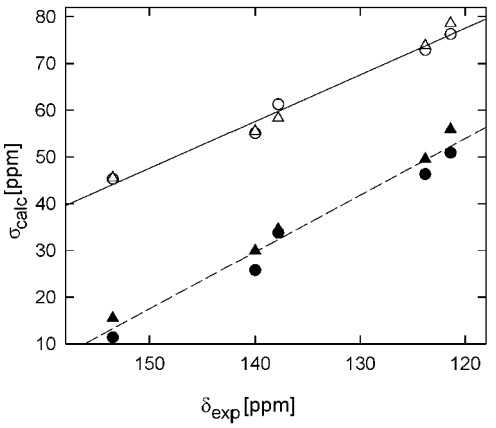

Fig. 3. Relationship between the computed ^{13}C screening constants (σ) and the experimental ^{13}C chemical shifts (δ) for HOPc (GIAO - o, IGLO – ●) and HOPt (GIAO – △, IGLO – ▲)

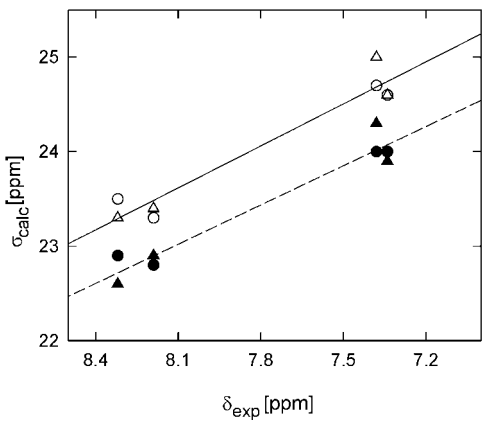

Fig. 4. Relationship between the computed ^{1}H screening constants (σ) and the experimental ^{1}H chemical shifts (δ) for MeOPc (GIAO - o, IGLO – ●) and MeOPt (GIAO – △, IGLO – ▲)

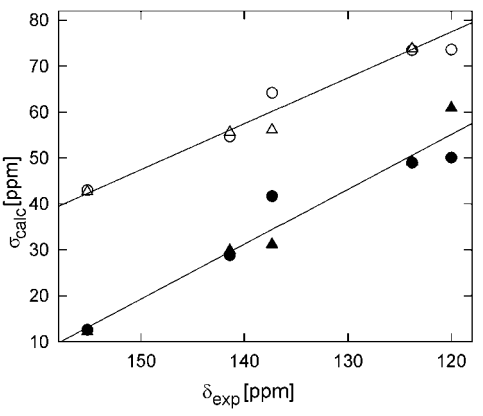

Fig. 5. Relationship between the computed ^{13}C screening constants (σ) and the experimental ^{13}C chemical shifts (δ) for MeOPc (GIAO - o, IGLO – ●) and MeOPt (GIAO – △, IGLO – ▲)

Table 3. Comparison of the IGLO and GIAO results for N-ethyl-3-oxypyridinium betaine (EtPB) and 3-pyridone (PON). The predicted IGLO and GIAO chemical shifts were computed from the linear equation $\delta_{exp} = A\ \sigma_{calc} + B$ with A and B determined from the fit to the experimental data

	Shielding constant, σ		Chemical shift, δ [ppm]		
Atom label	IGLO	GIAO	IGLO	GIAO	Exp.
EtPB					
H-2	24.3	25.1	7.21	7.34	7.47
H-4	24.1	25.0	7.42	7.41	6.92
H-5	23.9	24.9	7.63	7.54	7.28
H-6	24.7	25.5	6.78	6.85	7.43
CH_2	27.2	28.2	4.13	3.93	4.21
CH_3	29.6	30.3	1.58	1.68	1.44
C-2	36.0	61.5	134.4	136.5	133.4
C-3	0.3	32.6	169.6	167.5	169.1
C-4	33.0	59.7	137.3	138.4	132.4
C-5	44.8	71.2	125.7	126.1	126.9
C-6	58.6	84.8	112.1	111.5	120.8
CH_2	112.4	135.1	59.1	57.5	54.9
CH_3	156.2	173.1	15.9	16.6	16.6
PON					[9]
H-2	24.5	25.2	7.92	7.89	8.36
H-4	24.1	24.8	7.45	7.40	7.31
H-5	24.0	24.8	7.33	7.40	7.26
H-6	24.9	25.6	8.38	8.38	8.15
N-H	21.7	22.8			9.9
C-2	43.0	64.8	134.2	134.8	137.8
C-3	4.5	33.5	143.4	142.9	153.5
C-4	31.7	56.6	136.9	136.9	121.4
C-5	47.5	71.2	133.2	133.1	123.8
C-6	65.9	88.2	128.8	128.7	140.0

Table 3 contains new experimental NMR data for a betaine molecule (EtPB) listed together with the calculated ones. To our knowledge these are the first calculations of the NMR spectrum of a zwitterionic molecule. The ^{1}H and ^{13}C chemical shifts of pyridine ring of EtPB are very close to those in N-methyl-3-oxypyridinium betaine [9], although C(4) and C(6) are in the reversed order. The comparison shows that the predictive power of the

Table 4. Parameters of the linear regression equation describing the correlation between experimental ^{13}C and ^{1}H chemical shifts (ppm) and screening constants (ppm) computed by the IGLO/deMon and GIAO/B3LYP/6-31G(d,p) method for 3-hydroxypyridine (HOPc and HOPt), 3-methoxypyridine (MeOPc and MeOPt), N-ethyl-3-oxypyridinium betaine (EtPB) and N-H-3-oxypyridinium betaine (3-pyridone) (PON)

		A_C	B_C	r	ND	A_H	B_H	r	ND
HOPc	IGLO	–0.815	162.7	0.992	5	–0.952	29.915	0.975	4
	GIAO	–1.019	198.7	0.992	5	–0.839	27.974	0.933	4
HOPt	IGLO	–0.811	165.4	0.996	5	–0.641	22.819	0.974	4
	GIAO	–0.952	194.6	0.991	5	–0.576	21.685	0.962	4
MeOPc	IGLO	–1.034	176.5	0.995	6	–1.041	31.543	0.998	7
	GIAO	–0.955	191.3	0.998	6	–0.999	31.813	0.993	7
MeOPt	IGLO	–0.921	168.7	0.994	6	–0.911	29.107	0.992	7
	GIAO	–1.008	197.8	0.996	6	–0.929	30.128	0.988	7
EtPB	IGLO	–0.986	169.9	0.996	7	–1.062	33.013	0.985	9
	GIAO	–1.074	202.6	0.996	7	–1.085	34.553	0.987	9
PON	IGLO	–0.237	144.5	0.411	5	1.165	–20.615	0.845	4
	GIAO	–0.259	151.6	0.398	5	1.227	–23.035	0.829	4

theoretical methods applied to the betaine is similar to that for the regular derivative of the pyridine.

5. SUMMARY

Shielding constants, σ_{calc}, for 3-hydroxypyridine and its zwitterionic tautomer (3-pyridone), 3-methoxypyridine and N-ethyl-3-oxypyridinium betaine were calculated by GIAO B3LYP/6-31G(d,p) and IGLO deMon/NMR methods. Good linear correlations between the computed screening constants (σ_{calc}) and the experimental ^{1}H and ^{13}C chemical shifts (δ_{exp}) obtained for HOPc, HOPt, MeOPc, MeOPt and EtPB indicate that 3-hydroxypyridine is present in hydroxy-form in DMSO-d_6 and that the applied methods correctly reproduce chemical shifts for zwitterionic molecules. The lack of the correlation for 3-pyridone confirms the known fact that this species is absent in DMSO-d_6 solution, which shows that the approach presented in this paper can be used for determining the dominant tautomer.

The correlations between the calculated shielding constants and the experimental chemical shifts are better for carbon-13 than for proton. Both applied theoretical methods gave comparable chemical shifts for ^{13}C but for ^{1}H IGLO method yielded slightly better correlation with the experiment than GIAO.

Acknowledgement

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