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7. Seigo Ueda : The Mechanism of Solubilization of Water Insoluble Substances with Sodium Benzoate Derivatives. III.[*1] Decrease of Activity Coefficient of Water Insoluble Substances by Addition of Sodium Benzoate Derivatives in Aqueous Systems.

(*Product Development Laboratories, Sankyo Co., Ltd.*[*2])

It has previously been reported[*1] on the course of the serial studies on solubilization mechanism that the solubilization by sodium benzoates was not attributed in all to the complex formation between the added solubilizing agent and the water insoluble molecules to be solubilized. It has been suggested in the preceding paper of this series that increase of solubility might be partly attributed to decrease of the acitivity coefficient of the substances solubilized, which may be caused by addition of sodium benzoate derivatives.

Now, in this paper will be described the experimental evidences to prove decrease of the activity coefficient of the solubilized material in the aqueous systems studied.

Experimental

Materials

The water insoluble substances and sodium benzoates used here were same as described in the preceding papers. NaCl, Na_2SO_4, CH_3COONa and CH_3CH_2COONa were reagent grade chemicals and no further purifications were made.

Measurements of Visible Absorption Spectra

The spectra were obtained at 25±0.1° with a Hitachi automatic recording spectrophotometer (Model EPS). Each sample was prepared with 0.05 mole/L. phosphate buffer solution at pH 7.0.

Results and Discussion

Now, let us consider of the aqueous solution which contains a water insoluble substance of A and a sodium benzoate derivative of B. Assuming that the formation constant of the molecular complex of AB formed between A and B is K, and that the molar extinction coefficient of the complex AB at the apprepriate wave length to be chosen so that neither A nor B has any absorption, then the absorbance D observed at this wave length can be expressed by equation (1).

$$D=\epsilon(\mathrm{AB})=\frac{f_{\mathrm{A}}f_{\mathrm{B}}}{f_{\mathrm{AB}}}(\mathrm{A})(\mathrm{B}) \qquad (1)$$

In case where concentration of B is large enough to that of A, equation (1) can be reduced to equation (2).

$$D=\epsilon(\mathrm{AB})=\frac{\epsilon aK}{\frac{1}{b}\frac{f_{\mathrm{AB}}}{f_{\mathrm{A}}f_{\mathrm{B}}}+K} \qquad (2)$$

Here, (A) and (B) are the molar concentration of A and B in their free forms, respectively, and (AB) is the molar concentration of the complex formed in the system,

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[*2] Hiromachi, Sinagawa-ku, Tokyo (上田省吾).

a and b are the initial concentration of A and B, respectively. f is the molar activity coefficient in each species in the system. All experiments were carried out under this condition. Considerable changes in absorbance D were, in the first place, observed by addition of such electrolytes that do not seem to form complexes with either A or B. This can be considered as due to the change of the term $f_{AB}/f_A f_B$ in equation (2), which should be dependent only on the change of f_A because those of f_{AB}/f_B are supposed to be of negligible magnitude since B and AB are regarded as electrolytes.

In Table I, is shown the effect of various electrolytes on absorbance D at 410 mμ of the aqueous solution containing sodium p-aminosalicylate (NaPAS) and pyrazinamide (Py). The value D was more increased with addition of sodium sulfate, sodium chloride and sodium acetate in this order, and decreased with addition of sodium benzoate or sodium p-methylbenzoate. None of the electrolyte used here have been proved to form complex with Py nor NaPAS in aqueous system except sodium p-methylbenzoate

TABLE I. The Effects of Various Electrolytes on the Absorbance D of the Aqueous Solution Containing Pyrazinamide and NaPAS (pH 7.0 at 25° 410 mμ)

Py (mol./L.)		2.03×10^{-2}		4.06×10^{-2}		2.03×10^{-2}		4.06×10^{-2}	
NaPAS (mol./L.)		1.0		1.0		0.5		0.5	
Electrolyte	Concentration of electrolyte (mol./L.)	D	D/D_0	D	D/D_0	D	D/D_0	D	D/D_0
——		$0.350=D_0$		$0.685=D_0$		$0.210=D_0$		$0.433=D_0$	
NaCl	0.5	0.355	1.01	0.724	1.06	0.213	1.01	0.451	1.04
	1.0	0.361	1.03	0.742	1.08	0.217	1.03	0.454	1.05
Na_2SO_4	0.5	0.397	1.14	0.793	1.16	0.246	1.17	0.513	1.19
	1.0	0.454	1.30	0.893	1.30	0.326	1.55	0.596	1.38
CH_3COONa	0.5	0.369	1.05	0.728	1.06	0.231	1.10	0.461	1.06
	1.0	0.377	1.08	0.746	1.08	0.232	1.10	0.483	1.12
C_2H_5COONa	0.5	0.369	1.05	0.717	1.05	0.225	1.07	0.466	1.08
	1.0	0.372	1.06	0.729	1.06	0.227	1.08	0.475	1.09
C_6H_5COONa	0.5	0.334	0.96	0.640	0.94	0.188	0.90	0.402	0.93
	1.0	0.322	0.92	0.601	0.88	0.180	0.86	0.354	0.82
p-$CH_3C_6H_4COONa$	0.5	0.304	0.87	0.605	0.88	0.174	0.83	0.358	0.83

TABLE II. The Effects of Various Electrolytes on the Absorbance D of the Aqueous Solution Containing Pyrazinamide and NaSAL (pH 7.0 at 25° 362 mμ)

Py (mol./L.)		2.03×10^{-2}		4.06×10^{-2}		2.03×10^{-2}		4.06×10^{-2}	
NaSAL (mol./L.)		1.0		1.0		0.5		0.5	
Electrolyte	Concentration of electrolyte (mol./L.)	D	D/D_0	D	D/D_0	D	D/D_0	D	D/D_0
——		$0.088=D_0$		$0.153=D_0$		$0.053=D_0$		$0.102=D_0$	
NaCl	0.5	0.093	1.06	0.154	1.01	0.048	0.91	0.113	1.02
	1.0	0.098	1.11	0.163	1.07	0.056	1.06	0.114	1.09
Na_2SO_4	0.5	0.107	1.21	0.188	1.23	0.072	1.36	0.124	1.22
	1.0	0.145	1.65	0.231	1.51	0.092	1.74	0.154	1.56
CH_3COONa	0.5	0.093	1.06	0.160	1.05	0.061	1.15	0.101	1.08
	1.0	0.099	1.12	0.177	1.16	0.073	1.38	0.124	1.22
C_2H_5COONa	0.5	0.091	1.03	0.167	1.09	0.058	1.10	0.113	1.09
	1.0	0.096	1.09	0.186	1.21	0.065	1.23	0.116	1.14
C_6H_5COONa	0.5	0.080	0.80	0.146	0.95	0.045	0.85	0.095	0.88
	1.0	0.052	0.59	0.135	0.88	0.027	0.51	0.084	0.70
p-$CH_3C_6H_4COONa$	0.5	0.058	0.66	0.133	0.87	0.032	0.61	0.086	0.74

whose formation constant was found to be not zero but very small. Table I shows that changes of D/D_0 are strongly dependent on the salt concentration and most remarkable changes were found in the cases of sodium sulfate and sodium benzoate.

When sodium salicylate (NaSAL) was used instead of NaPAS as a solubilizing agent, almost same tendency was observed on the salt effect as in case of NaPAS, the results being shown in Table II. Thus, the effect of sodium sulfate or sodium benzoate on both of NaPAS-Py and NaSAL-Py systems tended to increase with decrease of the concentration of the solubilizing agents. It may, therefore, be concluded that the change of D by addition of electrolytes such as sodium chloride or sodium sulfate is not attributed to the change of f_B. Because, if so, the electrolyte effect would increase with increase of the concentration of NaPAS or NaSAL. The same experiments were carried out for the other insoluble substances than Py and the results were shown in Table III to VI.

TABLE III. The Effects of Various Electrolytes on the Absorbance D of the Aqueous Solution Containing 2-Acetamidotropone and NaPAS (pH 7.0 at 25° 400 mμ)

2-Acetamidotropone (mol./L.)		3.08×10^{-3}		6.15×10^{-3}		3.08×10^{-3}		6.15×10^{-3}	
NaPAS (mol./L.)		1.0		1.0		0.5		0.5	
Electrolyte	Concentration of electrolyte (mol./L.)	D	D/D_0	D	D/D_0	D	D/D_0	D	D/D_0
——		$0.368=D_0$		$0.748=D_0$		$0.274=D_0$		$0.546=D_0$	
NaCl	0.5	0.395	1.07	0.771	1.03	0.273	1.00	0.570	1.04
	1.0	0.394	1.07	0.771	1.03	0.283	1.03	0.592	1.08
Na_2SO_4	0.5	0.412	1.12	0.856	1.14	0.314	1.14	0.641	1.14
	1.0	0.447	1.21	0.924	1.23	0.339	1.24	0.735	1.23
CH_3COONa	0.5	0.383	1.04	0.790	1.06	0.276	1.01	0.583	1.04
	1.0	0.392	1.07	0.799	1.07	0.278	1.02	0.611	1.07
C_2H_5COONa	0.5	0.423	1.15	0.809	1.08	0.290	1.06	0.609	1.10
	1.0	0.442	1.20	0.821	1.10	0.296	1.08	0.623	1.13
C_6H_5COONa	0.5	0.345	0.94	0.663	0.89	0.219	0.80	0.478	0.88
	1.0	0.281	0.76	0.604	0.81	0.168	0.61	0.396	0.73
p-$CH_3C_6H_4COONa$	0.5	0.310	0.84	0.626	0.84	0.199	0.73	0.424	0.80

TABLE IV. The Effects of Various Electrolytes on the Absorbance D of the Aqueous Solution Containing 2-Acetamidotropone and NaSAL (pH 7.0 at 25° 406 mμ)

2-Acetamidotropone (mol./L.)		3.08×10^{-3}		6.15×10^{-3}		3.08×10^{-3}		6.15×10^{-3}	
NaSAL (mol./L.)		1.0		1.0		0.5		0.5	
Electrolyte	Concentration of electrolyte (mol./L.)	D	D/D_0	D	D/D_0	D	D/D_0	D	D/D_0
——		$0.342=D_0$		$0.629=D_0$		$0.210=D_0$		$0.408=D_0$	
NaCl	0.5	0.364	1.06	0.709	1.13	0.224	1.07	0.448	1.10
	1.0	0.402	1.18	0.740	1.18	0.241	1.15	0.462	1.13
Na_2SO_4	0.5	0.408	1.19	0.759	1.21	0.265	1.26	0.483	1.18
	1.0	0.461	1.35	0.881	1.40	0.302	1.44	0.591	1.45
CH_3COONa	0.5	0.366	1.07	0.703	1.12	0.232	1.10	0.427	1.05
	1.0	0.393	1.15	0.735	1.17	0.239	1.14	0.455	1.11
C_2H_5COONa	0.5	0.376	1.10	0.728	1.16	0.211	1.01	0.444	1.09
	1.0	0.398	1.16	0.733	1.17	0.251	1.20	0.466	1.14
C_6H_5COONa	0.5	0.330	0.97	0.585	0.93	0.189	0.90	0.355	0.81
	1.0	0.305	0.89	0.573	0.91	0.168	0.80	0.340	0.83
p-$CH_3C_6H_4COONa$	0.5	0.283	0.83	0.527	0.84	0.152	0.73	0.309	0.16

Table V. The Effects of Various Electrolytes on the Absorbance *D* of the Aqueous Solution Containing Cycloheptimidazol-2(1*H*)-one and NaPAS (pH 7.0 at 25° 454 mμ)

Cycloheptimidazol-2(1*H*)-one(mol./L.)		1.03×10^{-2}		2.06×10^{-2}		1.03×10^{-2}		2.06×10^{-2}	
NaPAS (mol./L.)		1.0		1.0		0.5		0.5	
Electrolyte	Concentration of electrolyte (mol./L.)	D	D/D_0	D	D/D_0	D	D/D_0	D	D/D_0
——		$0.400=D_0$		$0.791=D_0$		$0.303=D_0$		$0.601=D_0$	
NaCl	0.5	0.396	0.99	0.764	0.97	0.312	1.04	0.616	1.02
	1.0	0.386	0.97	0.790	1.00	0.309	1.02	0.617	1.02
Na_2SO_4	0.5	0.425	1.06	0.839	1.06	0.343	1.13	0.678	1.13
	1.0	0.444	1.11	0.884	1.12	0.366	1.21	0.737	1.23
CH_3COONa	0.5	0.392	0.98	0.786	0.99	0.306	1.01	0.616	1.02
	1.0	0.391	0.98	0.783	0.99	0.310	1.02	0.621	1.03
C_2H_5COONa	0.5	0.387	0.97	0.768	0.97	0.304	1.00	0.598	0.99
	1.0	0.370	0.93	0.773	0.98	0.298	0.98	0.602	1.00
C_6H_5COONa	0.5	0.346	0.87	0.688	0.87	0.251	0.83	0.495	0.83
	1.0	0.297	0.75	0.604	0.76	0.207	0.69	0.411	0.68
p-$CH_3C_6H_4COONa$	0.5	0.295	0.74	0.600	0.76	0.195	0.64	0.429	0.72

Table VI. The Effects of Various Electrolytes on the Absorbance *D* of the Aqueous Solution Containing Cycloheptimidazol-2(1*H*)-one and NaSAL (pH 7.0 at 25° 410 mμ)

Cycloheptimidazol-2(1*H*)-one(mol./L.)		1.03×10^{-2}		2.06×10^{-2}		1.03×10^{-2}		2.06×10^{-2}	
NaSAL (mol./L.)		1.0		1.0		0.5		0.5	
Electrolyte	Concentration of electrolyte (mol./L.)	D	D/D_0	D	D/D_0	D	D/D_0	D	D/D_0
——		$0.258=D_0$		$0.469=D_0$		$0.180=D_0$		$0.306=D_0$	
NaCl	0.5	0.272	1.05	0.470	1.01	0.191	1.06	0.338	1.04
	1.0	0.271	1.05	0.475	1.01	0.198	1.10	0.347	1.08
Na_2SO_4	0.5	0.289	1.12	0.517	1.10	0.215	1.19	0.365	1.15
	1.0	0.347	1.35	0.575	1.23	0.258	1.43	0.415	1.36
CH_3COONa	0.5	0.273	1.06	0.469	1.00	0.199	1.11	0.326	1.06
	1.0	0.279	1.08	0.473	1.01	0.202	1.12	0.342	1.08
C_2H_5COONa	0.5	0.267	1.04	0.472	1.01	0.194	1.08	0.326	1.05
	1.0	0.269	1.05	0.479	1.02	0.198	1.10	0.342	1.07
C_6H_5COONa	0.5	0.242	0.94	0.450	0.96	0.170	0.95	0.301	0.96
	1.0	0.208	0.81	0.416	0.89	0.121	0.67	0.258	0.85
p-$CH_2C_6H_5COONa$	0.5	0.212	0.82	0.402	0.86	0.127	0.71	0.263	0.85

The changes of *D* observed are almost alike as in case of Py-NaPAS system except for a few cases. The remarkable difference in the salt effect between Py-NaPAS and cycloheptimidazol-2(1*H*)-one-NaPAS was observed. Thus, *D* value increased for the former system and decreased or unchanged for the latter by addition of sodium acetate. This also supports that the change of *D* may be brought about by the change of f_A. If not so, tendency of the change of *D* should be common for both systems, because the concentration of NaPAS is the same for the both systems.

Now, let us consider the solubility changes caused by the electrolyte added, shown in Table VII.

Table VII. Solubilities of Various Water Insoluble Substances into Aqueous Solution Containing an Electrolyte (pH 7.0 at 25° (mol./L.))

Electrolyte (mol./L.)	Pyrazinamide	2-Acetamidotropone	Cycloheptimidazol-2(1*H*)-one
——	0.132	0.051	0.044
NaCl (1.0)	0.114	0.033	0.049
Na_2SO_4 (1.0)	0.057	0.022	0.028
CH_3COONa (1.0)	0.096	0.029	0.043
C_2H_5COONa (1.0)	0.101	0.032	0.051
C_6H_5COONa (1.0)	0.247	0.200	0.267
p-$CH_3C_6H_4COONa$ (0.5)	0.270	0.270	0.439

These electrolytes are not thought to form complex with these water insoluble substances. Then, if the activity coefficient of water insoluble substance only varied with the concentration of the electrolyte added, the relation between the activity f and the solubility S should be represented equation (3), which can be derived by the thermodynamic relation,[1]

$$f/f_0 = S_0/S \tag{3}$$

where f_0, f, S_0, and S represent activity coefficients of a water insoluble substance in aqueous solution and in electrolyte solution and solubilities of the water insoluble substance in water and in the electrolyte solution, respectively. Table VII shows that addition of sodium benzoate caused the solubility increase while addition of sodium sulfate or sodium chloride caused the solubility decrease. This may correspond to the f-decrease for the former case and to the f-increase for the latter cases. These results coincide well with those as expected from the data of D value changes shown in Table I to VI.

It was taken account of, furthermore, that the complexes formed in the system do not seem to change in their nature by addition of salt such as sodium chloride, since the molar extinction coefficient of the complex estimated from the Benesi-Hildebrand method did not change by addition of the electrolytes as shown in Table VIII.

Table VIII. Effects of Various Electrolytes on the Molar Extinction Coefficient ϵ of Complexes

Complex / Electrolyte (mol./L.)	Pyrazinamide-NaPAS ϵ_{410}	2-Acetamidotropone-NaPAS ϵ_{420}	Cycloheptimidazol-2(1*H*)-one-NaPAS ϵ_{430}
——	21.5	143	162
NaCl (1.0)	21.3	145	163
Na_2SO_4 (1.0)	21.2	147	168
CH_3COONa (1.0)	22.0	140	160
C_2H_5COONa (1.0)	21.3	142	162
C_6H_5COONa (1.0)	21.9	141	163
p-$CH_3C_6H_5COONa$ (0.5)	22.0	141	163

It may, therefore, be concluded the change of D values by salt addition are arised from the change of f_A caused by salt addition.

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[1] F. A. Long, *et al.*: Chem. Rers., **52**, 119 (1952).

Now, let us consider the case of the addition of sodium salicylate (NaSAL) as electrolyte, which was proved to form the complex with water insoluble substances, into the system of Py–NaPAS. The absorbance D observed at wave length 400 mμ is expressed by equation (4), for Py–NaPAS and Py–NaPAS–NaSAL systems, because individual solutions of these component and mixed solutions consisted of Na–PAS–NaSAL or Py–NaSAL did not show any absorption there at all,

$$D=\epsilon(\mathrm{PyP}) \tag{4}$$

where ϵ and (PyP) are molar extinction coefficient and molar concentration of Py–NaPAS complex, respectively. The stoichiometric relations in the system of Py, NaPAS and NaSAL are shown by equation (5),

$$\frac{f_{(\mathrm{PyP})}}{f_{\mathrm{Py}}f_{\mathrm{P}}}\frac{(\mathrm{PyP})}{(\mathrm{Py})(\mathrm{P})}=K \qquad \frac{f_{(\mathrm{PyS})}}{f_{\mathrm{Py}}f_{\mathrm{S}}}\frac{(\mathrm{PyS})}{(\mathrm{Py})(\mathrm{S})}=K' \tag{5}$$

$$\mathrm{Py}=(\mathrm{Py})+(\mathrm{PyP})+(\mathrm{PyS})$$

where (PyS), (PyP), (Py), (P) and (S) represent the molar concentration of Py–NaSAL complex, Py–NaPAS complex, pyrazinamide, NaPAS and NaSAL, respectively, and f represents the molar activity coefficient of the each species in the system. Supposing the concentrations of each component are chosen so as to be Py<NaPAS and Py<NaSAL, equation (6) can be derived from the equation (4) and the equation (5).

$$D=\epsilon(\mathrm{PyP})=\frac{\mathrm{PyP}K}{\dfrac{f_{\mathrm{PyP}}}{f_{\mathrm{Py}}f_{\mathrm{P}}}+\mathrm{P}K+\dfrac{f_{\mathrm{S}}f_{\mathrm{PyP}}}{f_{\mathrm{P}}f_{\mathrm{PyS}}}\mathrm{S}K'} \tag{6}$$

where Py, P and S represent the total concentration of Py, NaPAS and NaSAL added, respectively. Now, assuming all the f values to be equal to unity let us evaluate the D values from equation (6). The calculated values thus obtained, shown in Table IX, are always smaller than the observed values.

Table IX. Effects of Sodium *o*-, *m*- or *p*-Hydroxybenzoate on the Absorbance of Aqueous Solutions Containing a Water Insoluble Substance and NaPAS (pH 7.0 at 25°)

System containing a water insoluble substance and NaPAS		—	*o*-OH sodium-benzoate		*m*-OH sodium-benzoate		*p*-OH sodium-benzoate	
			0.3	0.5	0.3	0.5	0.3	0.5
Py 4.06×10⁻² mol./L. NaPAS 0.5 mol./L.	D^{400}_{obs}	0.423	0.363	0.343	0.404	0.358	0.413	0.360
	D^{400}_{Calcd}		0.395	0.356	0.402	0.388	0.402	0.388
	$\dfrac{D_{\mathrm{obs}}}{D_{\mathrm{Calcd}}}$		0.95	0.97	1.00	0.92	1.02	0.93
2-Acetamidotropone 6.15×10⁻³ mol./L. NaPAS 0.5 mol./L.	D^{420}_{obs}	0.410	0.228	0.193	0.358	0.338	0.350	0.330
	D^{420}_{Calcd}		0.242	0.200	0.390	0.378	0.367	0.342
	$\dfrac{D_{\mathrm{obs}}}{D_{\mathrm{Calcd}}}$		0.94	0.97	0.94	0.89	0.95	0.96
Cycloheptimidazol-2(1*H*)-one 6.85×10⁻³ mol./L. NaPAS 0.5 mol./L.	D^{426}_{obs}	0.788	0.593	0.534	0.690	0.640	0.652	0.593
	D^{426}_{Calcd}		0.635	0.572	0.709	0.665	0.700	0.650
	$\dfrac{D_{\mathrm{obs}}}{D_{\mathrm{Calcd}}}$		0.94	0.94	0.89	0.96	0.93	0.91
1-Benzylcycloheptimidazol-2(1*H*)-one 1.06×10⁻³ mol./L. NaPAS 0.5 mol./L.	D^{402}_{obs}	0.680	0.471	0.405	0.542	0.485	0.567	0.484
	D^{402}_{Calcd}		0.557	0.505	0.617	0.579	0.599	0.554
	$\dfrac{D_{\mathrm{obs}}}{D_{\mathrm{Calcd}}}$		0.85	0.80	0.88	0.84	0.95	0.87

As a matter of fact, f_P/f_{PyP}, f_S/f_P and f_{PyP}/f_{PyS} are reasonably considered to be unity, and as a result, these descrepancy should be concluded to be arised from the assumption of unity of f_{Py}. Thus, f_{Py} should be less than unity for the case of addition of NaSAL. As well as for the case of Py, the activity coefficient of other water insoluble substances used in the present study can be also considered to be decreased by addition of *o*-, *m*- or *p*-hydroxybenzoates as shown in Table Ⅸ. It is important to note that the ratio of $D_{obs.}/D_{calcd.}$ of each water insoluble substance are almost common to the position isomer of sodium hydroxybenzoate, and that this ratio is characteristic of the kind of water insoluble substances used, as shown in Table Ⅸ. This must be a strong support for the assumption that the change of D by addition of sodium hydroxybenzoate does depend only on the change of f_A. Thus, addition of sodium benzoate derivatives decrease the activity coefficient of water insoluble substances in aqueous solution so that the increase of solubility of the water insoluble substances is observed, even if no complex formation is observed.

It is concluded by these facts that solubilizing ability of sodium benzoate derivatives on the water insoluble substances can be deduced to two main reasons. One is the complex formation between sodium benzoate derivatives and water insoluble substances and the other is the salting in effect of sodium benzoate derivatives, that is decreasing of activity coefficient of water insoluble substances by addition of sodium benzoate derivatives.

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Summary

In the previous reports, it was suggested that as the mechanism of the solubilization by sodium benzoate derivatives, another factor than complex formation between solubilizing and solubilized molecules had to be considered. In this paper, it was proved that the activity coefficients of water insoluble substances in aqueous solutions decreased by addition of sodium benzoate derivatives. It was concluded that the mechanism of the solubilization by sodium benzoate derivatives composed of the two main factors, one of which was complex formation between solubilizied and solubilizing molecules and the other of which was the salting in effect of sodium benzoate derivatives.

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