Summary

The interactions between eight water insoluble substances and sodium benzoate derivatives in aqueous solutions were studied spectrophotometrically. It was found that the water insoluble substance used formed one to one molecular complex with sodium benzoate derivative in aqueous system. The formation constants of the complexes were determined at 25° and 60°, with which the enthalpy change ΔH and the entropy change ΔS of complex formation were obtained. As a result, it was suggested that the driving force of the complex formation would be due to charge transfer force or hydrogen bonding.

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6. Seigo Ueda : The Mechanism of Solubilization of Water Insoluble Substances with Sodium Benzoate Derivatives. II.[*1] Solubilities of Water Insoluble Substances in Aqueous Sodium Benzoates Solutions.

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In the previous paper,[*1] it was reported that various water insoluble substances formed molecular complexes with sodium benzoates in aqueous systems. The water insoluble substances cited there were all solubilized with sodium benzoates to various extents.

In this paper, the results of the solubility-measurements of the water insoluble substances in the aqueous solutions containing the sodium benzoates were described and some discussions were made on solubilizing mechanism.

Experimental

Materials

Water insoluble substances and sodium benzoate derivatives used in this paper were the same as described in the Part I of this serial studies.

Solubility Measurement

The solutions of sodium benzoates were prepared with 0.05 mol./L. phosphate buffered solution of pH 7.0. The concentrations were adjusted to 0.5 and 1.0 mol./L. with each solubilizing agents. An excess amounts of water insoluble substances was sealed in a ca. 5 ml. ampoule with about 4 ml. of the sodium benzoates solution prepared above and was agitated at 25°±0.1° for 8 hr. After solubility equilibrium thus obtained, excess amout of the crystal was filtered off. The filtrate was diluted with the phosphate buffered solvent and its UV absorbance D was measured by a Hitachi Model DU spectrophotometer at the wave length indicated in Table I, referring to the solubilizing solvent used in respective cases.

The solubilities were determined from the D values compared with $E^{1\%}_{1\,\mathrm{cm}}$s listed in Table I, since it is reasonably conceivable that a spectral change due to molecular complex formation between a solubilizing and a solubilized agent is completely negligible in such diluted solutions as in the present experimental conditions.

[*1] Part I : This Bulletin, **14**, 22 (1966).

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Table I. $E^{1\%}_{1\,\mathrm{cm}}$s of the Water Insoluble Substances in Aqueous Solutions pH 7.0

Water insoluble substances	Wave length (mμ)	$E^{1\%}_{1\,\mathrm{cm}}$
Riboflavine	450	270
Pyrazinamide	269	655
2-Aminotropone	394	842
2-Acetamidotropone	358	518
2-Benzamidotropone	365	500
Cyclohepta[*b*]pyrrol-2(1*H*)-one	408	604
Cycloheptimidazol-2(1*H*)-one	383	467
1-Benzylcycloheptimidazol-2(1*H*)-one	378	283

Table II. Solubilities of Water Insoluble Substances in Aqueous Sodium Benzoates Solutions

Sodium benzoate derivatives	Concentration of sodium benzoate **deriv.** (mol./L.)	Solubilities (mol./L.) at 25° pH 7.0							
		Riboflavine	Pyrazinamide	2-Aminotropone	2-Acetamidotropone	2-Benzamidotropone	Cyclohepta[*b*]pyrrol-2(1*H*)-one	Cycloheptimidazol-2(1*H*)-one	1-Benzylcycloheptimidazol-2(1*H*)-one
H_2O		3.5×10^{-4}	1.32×10^{-1}	1.71×10^{-1}	5.1×10^{-2}	2.2×10^{-4}	3.56×10^{-2}	4.4×10^{-2}	2.64×10^{-3}
Sodium benzoate	0.5	1.5×10^{-3}	1.82×10^{-1}	2.8×10^{-1}	1.08×10^{-1}	4.8×10^{-4}	1.1×10^{-1}	1.30×10^{-1}	1.06×10^{-2}
	1.0	4.5×10^{-3}	2.46×10^{-1}	4.95×10^{-1}	2.00×10^{-1}	1.2×10^{-3}	2.5×10^{-1}	2.67×10^{-1}	3.37×10^{-2}
p-CH_3	0.5	4.57×10^{-3}	2.09×10^{-1}	3.55×10^{-1}	1.29×10^{-1}	6.0×10^{-4}	8.2×10^{-2}	2.0×10^{-1}	1.65×10^{-2}
	1.0	1.15×10^{-2}	2.70×10^{-1}	6.90×10^{-1}	2.72×10^{-1}	1.95×10^{-3}	2.8×10^{-1}	4.39×10^{-1}	5.93×10^{-2}
o-NH_2	0.5	4.31×10^{-3}	1.81×10^{-1}	2.74×10^{-1}	1.02×10^{-1}	4.8×10^{-4}	1.01×10^{-1}	1.48×10^{-1}	1.31×10^{-2}
	1.0	8.87×10^{-3}	2.47×10^{-1}	4.50×10^{-1}	1.93×10^{-1}	9.1×10^{-4}	2.7×10^{-1}	3.10×10^{-1}	3.71×10^{-2}
m-NH_2	0.5	3.65×10^{-3}	1.81×10^{-1}	2.64×10^{-1}	9.34×10^{-2}	4.5×10^{-4}	1.0×10^{-1}	1.61×10^{-1}	1.14×10^{-2}
	1.0	8.17×10^{-3}	2.27×10^{-1}	3.74×10^{-1}	1.51×10^{-1}	8.0×10^{-4}	2.23×10^{-1}	3.10×10^{-1}	2.57×10^{-2}
p-NH_2	0.5	4.33×10^{-3}	1.58×10^{-1}	2.58×10^{-1}	9.9×10^{-2}	4.2×10^{-4}	1.05×10^{-1}	1.60×10^{-1}	1.06×10^{-2}
	1.0	1.09×10^{-2}	1.93×10^{-1}	3.88×10^{-1}	1.55×10^{-1}	7.4×10^{-4}	2.30×10^{-1}	3.24×10^{-1}	2.33×10^{-2}
o-OH	0.5	1.3×10^{-2}	2.65×10^{-1}	4.26×10^{-1}	2.10×10^{-1}	1.25×10^{-3}	1.15×10^{-1}	2.63×10^{-1}	3.2×10^{-2}
	1.0	2.8×10^{-2}	4.35×10^{-1}	9.60×10^{-1}	4.65×10^{-1}	5.3×10^{-3}	5.1×10^{-1}	5.14×10^{-1}	1.81×10^{-1}
m-OH	0.5	5.0×10^{-3}	2.12×10^{-1}	3.14×10^{-1}	1.30×10^{-1}	6.0×10^{-4}	5.4×10^{-2}	2.21×10^{-1}	1.72×10^{-2}
	1.0	1.47×10^{-2}	3.00×10^{-1}	5.43×10^{-1}	2.53×10^{-1}	1.36×10^{-3}	ppt.	5.64×10^{-1}	5.38×10^{-2}
p-OH	0.5	6.25×10^{-3}	2.17×10^{-1}	3.23×10^{-1}	1.43×10^{-1}	6.7×10^{-4}	5.7×10^{-2}	2.17×10^{-1}	1.84×10^{-2}
	1.0	2.16×10^{-2}	3.09×10^{-1}	5.73×10^{-1}	2.75×10^{-1}	1.45×10^{-3}	ppt.	5.3×10^{-1}	5.39×10^{-2}
NaPAS	0.5	1.06×10^{-2}	2.17×10^{-1}	4.07×10^{-1}	2.08×10^{-1}	1.3×10^{-3}	1.0×10^{-1}	2.96×10^{-1}	3.77×10^{-2}
	1.0	3.76×10^{-2}	3.52×10^{-1}	7.02×10^{-1}	4.06×10^{-1}	3.4×10^{-3}	4.0×10^{-1}	6.33×10^{-1}	1.30×10^{-1}

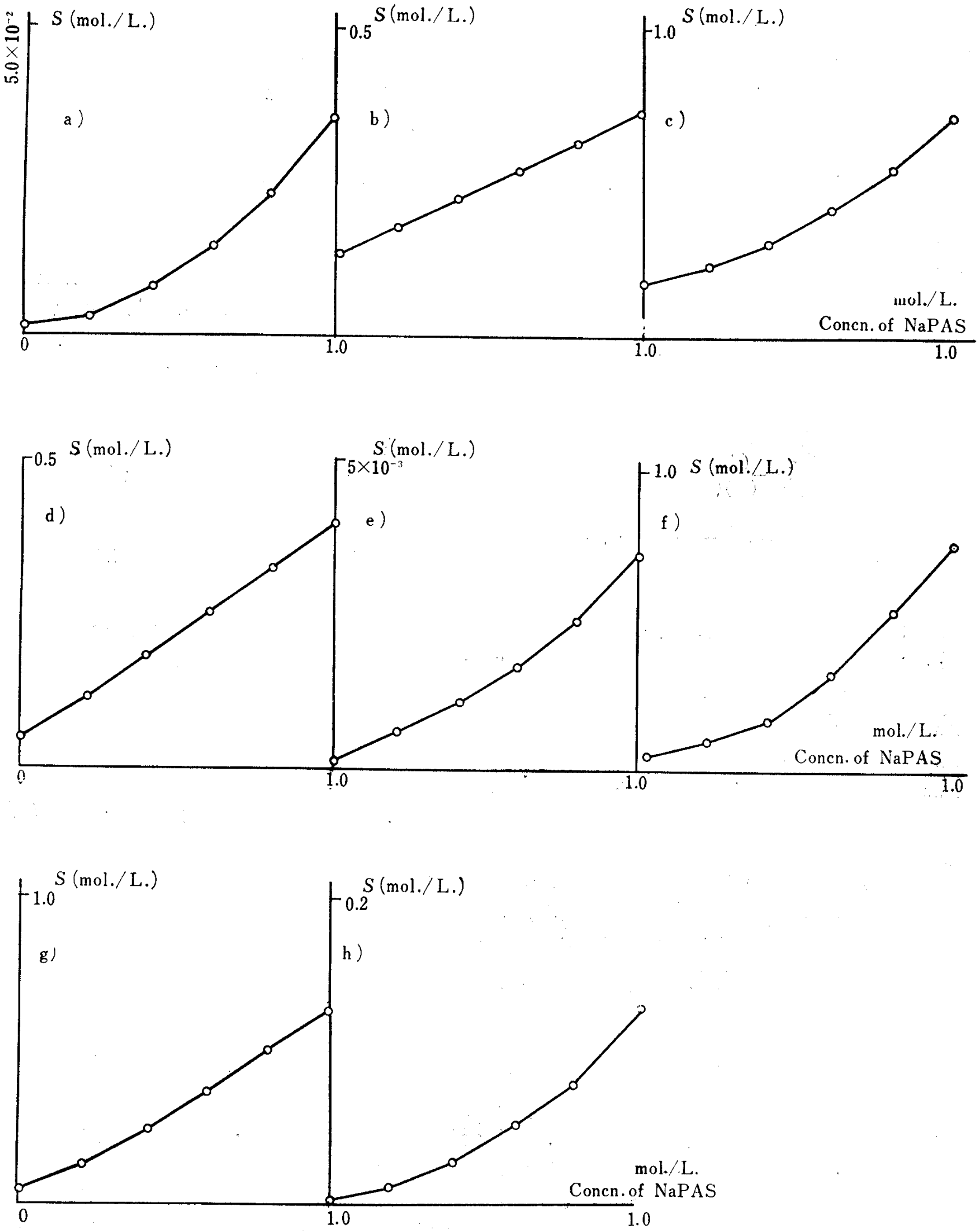

Fig. 1. Solubilities of Water Insoluble Substances in NaPAS Aqueous Solutions at 25° pH 7.0

a) Riboflavine
b) Pyrazinamide
c) 2-Aminotropone
d) 2-Acetamidotropone
e) 2-Benzamidotropone
f) Cyclohepta[*b*]pyrrol-2(1*H*)-one
g) Cycloheptimidazol-2(1*H*)-one
h) 1-Benzylcycloheptimidazol-2(1*H*)-one

Results and Discussion

The solubilities of the water insoluble substances in the solubilizing solvents were shown in Table II. These data show, in the first place, that any of sodium benzoates exhibit solubilizing ability to considerable extent to each of the substances concerned in these experiments. The observed solubility-increases were not always linearly dependent on the concentration of the solubilizing agents, convex curves to the tangential line being obtained in most cases as shown in Fig. 1.

It was previously reported that water insoluble substances and sodium benzoate derivatives formed one to one complex in aqueous solutions whose formation constants were determined in various combination system. Using these formation constant the amounts of the complex formed in solutions were calculated as follows. Namely they can be calculated by equation (2) which is derived from equation (1) supposing all activity coefficients to be unity.

$$K=\frac{f_{AB}}{f_A f_B}\frac{(AB)}{(A)(B)}\doteq\frac{(AB)}{(A)(B)} \qquad (1)$$

$$(AB)=\frac{[(S+c)K+1]-\sqrt{[(S+c)K+1]^2-4K^2Sc}}{2K} \qquad (2)$$

(A) : molar concentration of water insoluble substance in free form.
(B) : molar concentration of sodium benzoates in free form.
(AB) : molar concentration of complex.
f_A : molar activity coefficient of water insoluble substance.
f_B : molar activity coefficient of sodium benzoates.
f_{AB} : molar activity coefficient of complex.
$S=(A)+(AB)$: solubility (mol./L.) of water insoluble substance in c mol./L. solution of sodium benzoates.
c : molar concentration of sodium benzoates added.
K : formation constant of complex (L./mol.).
(where, by definition, c equals (B) and (AB).)

In case of $c \gg (AB)$, (AB) may be calculated by equation (3).

$$(AB)=\frac{cSK}{1+cK} \qquad (3)$$

Then, (A), which is concentration of solubilized substance in free form in the solution, can obtained as $S-(AB)$, listed in Table III～X.

These data led us to an important conclusion that it is not entirely due to complex formation that solubilities were increased by addition of the solubilizer, since $(A)/S_0$ (S_0 is the solubility without solubilizing agent) were always found larger than unity. (If complex formation act all part of solubilization, $(A)/S_0$ would be unity.) Let us consider, for example, the cases of sodium benzoate and *p*-methylbenzoate. These two derivatives do not form complexes with most of the water insoluble substances. Their formation constants, even if not zero, are rather small compared with other sodium benzoates. The solubilizing ability of these two derivatives, however, were shown to be considerably large. Then, other factor should be considered beside complex formation.

Hereupon, two important facts should be reminded; one is that activity coefficients of the non-electrolytes are decreased by addition of some electrolytes in aqueous

Table III. The Calculated Amounts of Complex and Free Form of Riboflavine in Solubilized Systems

Sodium benzoate derivatives	Concentration of sodium benzoate derivative (mol./L.)	K_{25} (L./mol.)	S (mol./L.)	(AB) (mol./L.)	(A) (mol./L.)	(A)/(S_0)
H_2O			$3.5 \times 10^{-4} = S_0$			
Sodium benzoate	0.5	3.4	1.5×10^{-3}	9.40×10^{-4}	5.6×10^{-4}	1.6
	1.0		4.5×10^{-3}	3.60×10^{-3}	9.2×10^{-4}	2.6
p-CH_3	0.5	5.0	4.57×10^{-3}	3.30×10^{-3}	1.3×10^{-3}	3.7
	1.0		1.15×10^{-2}	9.6×10^{-3}	1.9×10^{-3}	5.4
o-NH_2	0.5	3.3	4.31×10^{-3}	2.7×10^{-3}	1.62×10^{-3}	4.6
	1.0		8.87×10^{-3}	6.8×10^{-3}	2.07×10^{-3}	5.9
m-NH_2	0.5	2.4	3.65×10^{-3}	2.0×10^{-3}	1.65×10^{-3}	4.7
	1.0		8.17×10^{-3}	5.76×10^{-3}	2.41×10^{-3}	6.9
p-NH_2	0.5	6.8	4.33×10^{-3}	3.45×10^{-3}	9.8×10^{-4}	2.2
	1.0		1.09×10^{-2}	9.55×10^{-3}	1.35×10^{-3}	3.8
o-OH	0.5	7.3	1.30×10^{-2}	1.02×10^{-2}	2.8×10^{-3}	8.0
	1.0		2.80×10^{-2}	2.46×10^{-2}	3.4×10^{-3}	9.7
m-OH	0.5	2.8	5.00×10^{-3}	2.92×10^{-3}	2.08×10^{-3}	5.9
	1.0		1.47×10^{-2}	1.09×10^{-2}	3.80×10^{-3}	10.9
p-OH	0.5	4.6	6.25×10^{-3}	4.35×10^{-3}	1.90×10^{-3}	5.4
	1.0		2.16×10^{-2}	1.78×10^{-2}	3.80×10^{-3}	10.9
NaPAS	0.5	10.7	1.06×10^{-2}	8.92×10^{-3}	1.68×10^{-3}	4.8
	1.0		3.76×10^{-2}	3.44×10^{-2}	3.20×10^{-3}	9.2

K_{25}: The formation constants of complexes formed between riboflavine and sodium benzoate derivatives in aqueous solution at 25°(L./mol.).

S: Solubilities of riboflavine in Sodium benzoates aqueous solutions at 25°(mol./L.).

(AB): The calculated amounts of complexes formed between riboflavine and sodium benzoate derivatives (mol./L.).

(A): The calculated amounts of free form of riboflavine (mol./L.).

S_0: Solubility of riboflavine in water at 25°(mol./L.).

Table IV. The Calculated Amounts of Complex and Free Form of Pyrazinamide in Solubilized Systems

Sodium benzoate derivatives	Concentration of sodium benzoate derivative (mol./L.)	K_{25} (L./mol.)	S (mol./L.)	(AB) (mol./L.)	(A) (mol./L.)	(A)/(S_0)
H_2O			$1.32 \times 10^{-1} = S_0$			
Sodium benzoate	0.5		1.82×10^{-1}		1.82×10^{-1}	1.4
	1.0		2.46×10^{-1}		2.46×10^{-1}	1.9
p-CH_3	0.5	0.38	2.09×10^{-1}	3.2×10^{-2}	1.77×10^{-1}	1.3
	1.0		2.70×10^{-1}	7.0×10^{-2}	2.00×10^{-1}	1.5
o-NH_2	0.5	0.26	1.81×10^{-1}	2.1×10^{-2}	1.59×10^{-1}	1.2
	1.0		2.47×10^{-1}	4.7×10^{-2}	2.00×10^{-1}	1.5
m-NH_2	0.5	0.26	1.81×10^{-1}	2.1×10^{-2}	1.59×10^{-1}	1.2
	1.0		2.27×10^{-1}	4.6×10^{-2}	2.01×10^{-1}	1.5

p-NH_2	0.5	0.22	1.58×10^{-1}	1.1×10^{-2}	1.47×10^{-1}	1.1
	1.0		1.93×10^{-1}	3.4×10^{-2}	1.59×10^{-1}	1.2
o-OH	0.5	0.44	2.65×10^{-1}	4.2×10^{-2}	2.23×10^{-1}	1.7
	1.0		4.35×10^{-1}	1.18×10^{-1}	3.17×10^{-1}	2.4
m-OH	0.5	0.25	2.12×10^{-1}	1.6×10^{-2}	1.96×10^{-1}	1.5
	1.0		3.00×10^{-1}	6.0×10^{-2}	2.40×10^{-1}	1.8
p-OH	0.5	0.25	2.17×10^{-1}	1.8×10^{-2}	1.99×10^{-1}	1.5
	1.0		3.09×10^{-1}	6.0×10^{-2}	2.49×10^{-1}	1.9
NaPAS	0.5	0.78	2.17×10^{-1}	5.7×10^{-2}	1.60×10^{-1}	1.2
	1.0		3.52×10^{-1}	1.40×10^{-1}	2.12×10^{-1}	1.6

K_{25}: The formation constant of complexes formed between pyrazinamide and sodium benzoate derivatives in aqueous solution at 25°(L./mol.).
S: Solubilities of pyrazinamide in sodium benzoate aqueous solutions at 25°(mol./L.).
(AB): The calculated amounts of complexes formed between pyrazinamide and sodium benzoate derivatives (mol./L.).
(A): The calculated amounts of free form of pyrazinamide (mol./L.).
S_0: Solubility of pyrazinamide in water at 25°(mol./L.).

Table V. The Calculated Amounts of Complex and Free Form of 2-Aminotropone in Solubilized Systems at 25°

Sodium benzoate derivatives	Concentration of sodium benzoate derivative (mol./L.)	K_{25} (L./mol.)	S (mol./L.)	(AB) (mol./L.)	(A) (mol./L.)	(A)/(S_0)
H_2O			$1.71\times10^{-1}=S_0$			
Sodium benzoate	0.5		2.8×10^{-1}		2.8×10^{-1}	1.6
	1.0		4.95×10^{-1}		4.95×10^{-1}	2.9
p-CH_3	0.5	0.2	3.55×10^{-1}	3.2×10^{-2}	3.23×10^{-1}	1.9
	1.0		6.90×10^{-1}	1.15×10^{-1}	5.75×10^{-1}	3.4
o-NH_2	0.5	0.17	2.74×10^{-1}	2.1×10^{-2}	2.53×10^{-1}	1.5
	1.0		4.50×10^{-1}	6.5×10^{-2}	3.85×10^{-1}	2.3
m-NH_2	0.5	0.3	2.64×10^{-1}	3.4×10^{-2}	2.30×10^{-1}	1.3
	1.0		3.74×10^{-1}	8.6×10^{-2}	2.88×10^{-1}	1.7
p-NH_2	0.5	0.4	2.58×10^{-1}	4.3×10^{-2}	2.15×10^{-1}	1.3
	1.0		3.88×10^{-1}	1.11×10^{-1}	2.77×10^{-1}	1.6
o-OH	0.5	0.66	4.26×10^{-1}	1.05×10^{-1}	3.21×10^{-1}	1.9
	1.0		9.60×10^{-1}	3.80×10^{-1}	5.80×10^{-1}	3.4
m-OH	0.5	0.3	3.14×10^{-1}	4.1×10^{-2}	2.73×10^{-1}	1.6
	1.0		5.43×10^{-1}	1.25×10^{-1}	4.18×10^{-1}	2.4
p-OH	0.5	0.3	3.23×10^{-1}	4.2×10^{-2}	2.81×10^{-1}	1.6
	1.0		5.73×10^{-1}	1.32×10^{-1}	4.11×10^{-1}	2.4
NaPAS	0.5	0.9	4.07×10^{-1}	1.06×10^{-1}	3.01×10^{-1}	1.8
	1.0		7.02×10^{-1}	2.78×10^{-1}	4.24×10^{-7}	2.5

K_{25}: The formation constants of complexes formed between 2-aminotropone and sodium benzoate derivatives in aqueous solutions at 25°(L./mol.).
S: Solubilities of 2-aminotropone in sodium benzoates aqueous solutions at 25°(mol./L.).
(AB): The calculated amounts of complexes formed between 2-aminotropone and sodium benzoate derivatives (mol./L.).
(A): The calculated amounts of free form of 2-aminotropone (mol./L.).
S_0: Solubility of 2-aminotropone in water 25°(mol./L.).

Table VI. The Calculated Amounts of Complex and Free Form of 2-Acetamidotropone in Solubilized Systems at 25°

Sodium benzoate derivatives	Concentration of sodium benzoate derivative (mol./L.)	K_{25} (L./mol.)	S (mol./L.)	(AB) (mol./L.)	(A) (mol./L.)	(A)/(S_0)
H_2O			$5.1\ \times10^{-2}=S_0$			
Sodium benzoate	0.5	0.06	1.08×10^{-1}	$3.0\ \times10^{-3}$	1.05×10^{-1}	2.1
	1.0		2.00×10^{-1}	$1.1\ \times10^{-2}$	1.89×10^{-1}	3.7
p-CH_3	0.5	0.35	1.29×10^{-1}	$1.7\ \times10^{-2}$	1.12×10^{-1}	2.2
	1.0		2.72×10^{-1}	$6.3\ \times10^{-2}$	2.09×10^{-1}	4.1
o-NH_2	0.5	0.56	1.02×10^{-1}	$2.2\ \times10^{-2}$	$8.0\ \times10^{-2}$	1.6
	1.0		1.93×10^{-1}	$5.2\ \times10^{-2}$	1.41×10^{-1}	2.8
m-NH_2	0.5	0.30	9.34×10^{-2}	$1.2\ \times10^{-2}$	$8.1\ \times10^{-2}$	1.6
	1.0		1.53×10^{-1}	$3.3\ \times10^{-2}$	1.18×10^{-1}	2.3
p-NH_2	0.5	0.50	$9.9\ \times10^{-2}$	$1.9\ \times10^{-2}$	$8.0\ \times10^{-2}$	1.6
	1.0		1.55×10^{-1}	$5.0\ \times10^{-2}$	1.05×10^{-1}	2.1
o-OH	0.5	1.75	2.10×10^{-1}	$8.9\ \times10^{-2}$	1.21×10^{-1}	2.4
	1.0		4.65×10^{-1}	$2.6\ \times10^{-1}$	2.05×10^{-1}	4.0
m-OH	0.5	0.31	1.30×10^{-1}	$1.7\ \times10^{-2}$	1.13×10^{-1}	2.2
	1.0		2.53×10^{-1}	$5.8\ \times10^{-2}$	1.95×10^{-1}	3.8
p-OH	0.5	0.73	1.43×10^{-1}	$1.8\ \times10^{-2}$	1.25×10^{-1}	2.5
	1.0		2.75×10^{-1}	1.10×10^{-1}	1.65×10^{-1}	3.2
NaPAS	0.5	1.7	2.08×10^{-1}	$8.5\ \times10^{-2}$	1.23×10^{-1}	2.4
	1.0		4.06×10^{-1}	2.32×10^{-1}	1.74×10^{-1}	3.4

K_{25}: The formation constants of complex formed between 2-acetamidotropone and sodium benzoate derivatives in aqueous solutions at 25°(L./mol.).

S: Solubilities of 2-acetamidotropone in sodium benzoates aqueous solutions at 25°(mol./L.).

(AB): The calculated amounts of complexes formed between 2-acetamidotropone and sodium benzoate derivatives (mol./L.).

(A): The calculated amounts of free form of 2-acetamidotropone (mol./L.).

S_0: Solubility of 2-acetamidotropone in water 25°(mol./L.).

Table VII. The Calculated Amounts of Complex and Free Form of 2-Benzamidotropone in Solubilized Systems at 25°

Sodium benzoate derivatives	Concentration of sodium benzoate derivative (mol./L.)	K_{25} (L./mol.)	S (mol./L.)	(AB) (mol./L.)	(A) (mol./L.)	(A)/(S_0)
H_2O			$2.2\ \times10^{-4}=S_0$			
Sodium benzoate	0.5	0.75	$4.8\ \times10^{-4}$	1.31×10^{-4}	3.49×10^{-4}	1.6
	1.0		$1.2\ \times10^{-3}$	5.15×10^{-4}	6.85×10^{-4}	3.1
p-CH_3	0.5	0.74	$6.0\ \times10^{-4}$	1.61×10^{-4}	4.38×10^{-4}	2.0
	1.0		1.95×10^{-3}	8.28×10^{-4}	1.12×10^{-3}	5.1
o-NH_2	0.5	0.87	$4.8\ \times10^{-4}$	1.46×10^{-4}	3.34×10^{-4}	1.6
	1.0		$9.1\ \times10^{-4}$	4.23×10^{-4}	4.87×10^{-4}	2.2
m-NH_2	0.5	0.96	$4.5\ \times10^{-4}$	1.46×10^{-4}	3.04×10^{-4}	1.4
	1.0		$8.0\ \times10^{-4}$	3.92×10^{-4}	4.08×10^{-4}	1.9

p-NH$_2$	0.5	1.4	4.2×10^{-4}	1.73×10^{-4}	2.47×10^{-4}	1.2
	1.0		7.4×10^{-4}	4.32×10^{-4}	3.08×10^{-4}	1.4
o-OH	0.5	2.2	1.25×10^{-3}	6.55×10^{-4}	5.95×10^{-4}	2.7
	1.0		5.30×10^{-3}	3.65×10^{-3}	1.65×10^{-3}	7.5
m-OH	0.5	1.42	6.0×10^{-4}	2.49×10^{-4}	3.51×10^{-4}	1.6
	1.0		1.36×10^{-3}	7.98×10^{-4}	5.62×10^{-4}	2.6
p-OH	0.5	2.4	6.7×10^{-4}	3.65×10^{-4}	3.05×10^{-4}	1.4
	1.0		1.45×10^{-3}	1.025×10^{-3}	4.25×10^{-4}	1.9
NaPAS	0.5	2.2	1.30×10^{-3}	6.82×10^{-4}	6.18×10^{-4}	2.8
	1.0		3.40×10^{-3}	2.34×10^{-3}	1.06×10^{-3}	4.8

K_{25}: The formation constants of complex formed between 2-benzamidotropone and sodium benzoate derivatives in aqueous solutions at 25°(L./mol.).

S: Solubilites of 2-benzamidotropone in sodium benzoates aqueous solutions at 25°(mol./L.).

(AB): The calculated amounts of complexes formed between 2-benzamidotropone and sodium benzoate derivatives (mol./L.).

(A): The calculated amounts of free form of 2-benzamidotropone (mol./L.).

S_0: Solubility of 2-benzamidotropone in water at 25°(mol./L.).

TABLE VIII. The Calculated Amounts of Complex and Free Form of Cyclohepta[*b*]pyrrol-2(1*H*)-one in Solubilized Systems

Sodium benzoate derivatives	Concentration of sodium benzoate derivative (mol./L.)	K_{25} (L./mol.)	S (mol./L.)	(AB) (mol./L.)	(A) (mol./L.)	(A)/(S_0)
H$_2$O			$3.56\times10^{-2}=S_0$			
Sodium benzoate	0.5	0.09	1.1×10^{-1}	9.0×10^{-3}	1.01×10^{-1}	2.8
	1.0		2.5×10^{-1}	2.1×10^{-2}	2.29×10^{-1}	6.4
p-CH$_3$	0.5	0.33	8.2×10^{-2}	9.0×10^{-3}	7.3×10^{-2}	2.1
	1.0		2.8×10^{-1}	2.0×10^{-2}	2.6×10^{-1}	7.3
o-NH$_2$	0.5	0.91	1.01×10^{-1}	3.1×10^{-2}	7.0×10^{-2}	2.0
	1.0		2.7×10^{-1}	1.19×10^{-1}	1.51×10^{-1}	4.1
m-NH$_2$	0.5	0.88	1.0×10^{-1}	2.8×10^{-2}	7.2×10^{-2}	2.0
	1.0		2.23×10^{-1}	9.8×10^{-2}	1.25×10^{-1}	3.5
p-NH$_2$	0.5	1.04	1.05×10^{-1}	3.1×10^{-2}	7.4×10^{-2}	2.1
	1.0		2.30×10^{-1}	1.08×10^{-1}	1.22×10^{-1}	3.4
o-OH	0.5	2.4	2.37×10^{-1}	1.15×10^{-1}	1.22×10^{-1}	3.4
	1.0		8.97×10^{-1}	5.10×10^{-1}	4.87×10^{-1}	14.0
m-OH	0.5	1.3	1.47×10^{-1}	5.4×10^{-2}	9.3×10^{-2}	2.6
	1.0		1.95×10^{-1}	—	—	—
p-OH	0.5	1.3	1.63×10^{-1}	5.7×10^{-2}	1.06×10^{-2}	3.0
	1.0		1.07×10^{-1}	—	—	—
NaPAS	0.5	2.0	2.0×10^{-1}	1.0×10^{-1}	1.0×10^{-1}	2.8
	1.0		7.44×10^{-1}	4.0×10^{-1}	3.44×10^{-1}	9.7

K_{25}: The formation constants of complex formed between cyclohepta[*b*]pyrrol-2(1*H*)-one and sodium benzoate derivatives in aqueous solutions at 25°(L./mol.).

S: Solubilities of cyclohepta[*b*]pyrrol-2(1*H*)-one in sodium benzoate derivatives aqueous solutions at 25°(mol./L.).

(AB): The calculated amounts of complexes formed between cyclohepta[*b*]pyrrol-2(1*H*)-one and sodium benzoate derivatives (mol./L.).

(A): The calculated amounts of free form of cyclohepta[*b*]pyrrol-2(1*H*)-one (mol./L.).

S_0: Solubility of cyclohepta[*b*]pyrrol-2(1*H*)-one in water 25°(mol./L.).

Table IX. The Calculated Amounts of Complex and Free Form of Cycloheptimidazol-2(1*H*)-one in Solubilized Systems

Sodium benzoate derivatives	Concentration of sodium benzoate derivative (mol./L.)	K_{25} (L./mol.)	S (mol./L.)	(AB) (mol./L.)	(A) (mol./L.)	(A)/(S_0)
H_2O			$4.4\times10^{-2}=S_0$			
Sodium benzoate	0.5	0.17	1.30×10^{-1}	1.0×10^{-2}	1.2×10^{-1}	2.7
	1.0		2.67×10^{-1}	3.9×10^{-2}	2.28×10^{-1}	5.2
p-CH_3	0.5	0.25	2.0×10^{-1}	2.2×10^{-2}	1.78×10^{-1}	4.1
	1.0		4.39×10^{-1}	8.5×10^{-2}	3.54×10^{-1}	8.1
o-NH_2	0.5	0.44	1.48×10^{-1}	5.6×10^{-2}	9.2×10^{-2}	2.1
	1.0		3.10×10^{-1}	1.7×10^{-1}	1.4×10^{-1}	3.2
m-NH_2	0.5	0.87	1.61×10^{-1}	4.3×10^{-2}	1.18×10^{-1}	2.6
	1.0		3.10×10^{-1}	1.32×10^{-1}	1.78×10^{-1}	4.1
p-NH_2	0.5	1.81	1.60×10^{-1}	7.5×10^{-2}	8.5×10^{-2}	1.9
	1.0		3.24×10^{-1}	1.91×10^{-1}	1.33×10^{-1}	3.0
o-OH	0.5	1.57	2.63×10^{-1}	1.02×10^{-1}	1.61×10^{-1}	3.7
	1.0		5.14×10^{-1}	2.74×10^{-1}	2.4×10^{-1}	5.5
m-OH	0.5	0.87	2.21×10^{-1}	6.0×10^{-2}	1.61×10^{-1}	3.7
	1.0		5.64×10^{-1}	2.30×10^{-1}	3.34×10^{-1}	7.6
p-OH	0.5	0.98	2.17×10^{-1}	6.3×10^{-2}	1.54×10^{-1}	3.5
	1.0		5.30×10^{-1}	2.30×10^{-1}	3.0×10^{-1}	6.8
NaPAS	0.5	2.7	2.96×10^{-1}	1.45×10^{-1}	1.51×10^{-1}	3.4
	1.0		6.33×10^{-1}	3.92×10^{-1}	2.41×10^{-1}	5.5

K_{25}: The formation constants of complex formed between cycloheptimidazol-2(1*H*)-one and sodium benzoate derivatives in aqueous solutions at 25°(L./mol.).

S: Solubilities of cycloheptimidazol-2(1*H*)-one in sodium benzoate derivatives aqueous solutions at 25°(mol./L.).

(AB): The calculated amounts of complexes formed between cycloheptimidazol-2(1*H*)-one and sodium benzoate derivatives (mol./L.).

(A): The calculated amounts of free form of cycloheptimidazol-2(1*H*)-one (mol./L.).

S_0: Solubility of cycloheptimidazol-2(1*H*)-one in water at 25°(mol./L.).

Table X. The Calculated Amounts of Complex and Free Form of 1-Benzylcycloheptimidazol-2(1*H*)-one in Solubilized Systems

Sodium benzoate derivatives	Concentration of sodium benzoate derivative (mol./L.)	K_{25} (L./mol.)	S (mol./L.)	(AB) (mol./L.)	(A) (mol./L.)	(A)/(S_0)
H_2O			$2.64\times10^{-3}=S_0$			
Sodium benzoate	0.5	0.29	1.06×10^{-2}	1.34×10^{-3}	9.26×10^{-3}	3.5
	1.0		3.37×10^{-2}	7.57×10^{-3}	2.61×10^{-2}	9.9
p-CH_3	0.5	0.42	1.65×10^{-2}	2.86×10^{-3}	1.36×10^{-2}	5.2
	1.0		5.93×10^{-2}	2.47×10^{-2}	3.46×10^{-2}	13.0
o-NH_2	0.5	1.07	1.31×10^{-2}	4.56×10^{-3}	8.54×10^{-3}	3.2
	1.0		3.71×10^{-2}	1.92×10^{-2}	1.79×10^{-2}	6.8
m-NH_2	0.5	1.11	1.14×10^{-2}	4.07×10^{-3}	7.33×10^{-3}	2.8
	1.0		2.57×10^{-2}	1.35×10^{-2}	1.22×10^{-2}	4.6

p-NH$_2$	0.5	1.05	1.06×10^{-2}	3.65×10^{-3}	6.95×10^{-3}	2.6
	1.0		2.33×10^{-2}	1.19×10^{-2}	1.14×10^{-2}	4.3
o-OH	0.5	2.15	$3.2\ \times10^{-2}$	1.66×10^{-2}	1.54×10^{-2}	5.8
	1.0		1.81×10^{-1}	1.23×10^{-1}	$5.8\ \times10^{-2}$	22.0
m-OH	0.5	0.87	1.72×10^{-2}	5.21×10^{-3}	1.20×10^{-2}	4.6
	1.0		5.38×10^{-2}	2.51×10^{-2}	2.87×10^{-2}	10.8
p-OH	0.5	1.16	1.84×10^{-2}	6.75×10^{-3}	1.165×10^{-2}	4.4
	1.0		5.39×10^{-2}	$2.9\ \times10^{-2}$	2.49×10^{-2}	9.4
NaPAS	0.5	3.1	3.77×10^{-2}	2.29×10^{-2}	1.48×10^{-2}	5.6
	1.0		1.30×10^{-1}	9.83×10^{-2}	3.17×10^{-2}	12.0

K_{25}: The formation constants of complex formed between 1-benzylcycloheptimidazol-2(1*H*)-one and sodium benzoate derivatives in aqueous solutions at 25°(L./mol.).
S: Solubilities of 1-benzylcycloheptimidazol-2(1*H*)-one in sodium benzoate derivatives aqueous solutions at 25°(mol./L.).
(AB): The calculated amounts of complexes formed between 1-benzylcycloheptimidazol-2(1*H*)-one and sodium benzoate derivatives (mol./L.).
(A): The calculated amounts of free form of 1-benzylcycloheptimidazol-2(1*H*)-one (mol./L.).
S_0: Solubility of 1-benzylcycloheptimidazol-2(1*H*)-one in water at 25°(mol./L.).

solution and the other is that solubility change is, in general, governed by equation (4), which is derived thermodynamically.[1]

$$S/S_0=f_0/f \tag{4}$$

S: solubility of the non-electrolyte in electrolyte aqueous solution.
S_0: solubility of the non-electrolyte in water.
f: activity coefficient of non-electrolyte in electrolyte aqueous solution.
f_0: activity coefficient of non-electrolyte in water.

Therefore, decrease of activity coefficient result in increase of solubility. This phenomenon is well known as the salting in effect. The important role of this salting in effect in solubilization might be suggested by the fact that no appreciable change in (A)/S_0 was found in each case of position isomers (*o*, *m*, *p*) of OH- and NH$_2$-benzoates which is well known to be characteristic feature in the salting in phenomenon.

It might be tentatively concluded that decrease of activity coefficient of water insoluble substances is responsible for solubility increase beside due to complex formation.

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Summary

The solubilities of the eight water insoluble substances in aqueous sodium benzoates solutions were determined. As a result of these measurement, it was found that any water insoluble substances were solubilized by sodium benzoate derivatives. Using the formation constants of the complexes, which were obtained by spectrophotometric measurements, the amounts of the complex in the water insoluble substance solubilized by sodium benzoate could be obtained. These amounts were found to be rather smaller than the solubility increase of the water insoluble substances. So, it was concluded that the other factor than complex formation should be considered as the mechanism of solubilization by sodium benzoate derivatives.

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