[Chem. Pharm. Bull.
11 (9) 1123 ~ 1133]

UDC 615-07 : 541.123 : 536.4

184. Keiji Sekiguchi, Keiji Ito, and Yoshiko Nakamori : Studies on the Method of Thermal Analysis of Organic Medicinals. IV.*1,*2 Double Melting Point of Organic Binary Mixtures.

(*Faculty of Pharmaceutical Sciences, School of Medicine, Hokkaido University**3)

In visual thermal analysis, it often happens that a binary mixture liquefies completely at a temperature considerably below its melting point. Consequently, the mixture will exhibit two melting points. This phenomenon which is named by Sekiguchi, one of the authors the double melting point of a binary mixture, is observed in a system in which one or more compounds are formed. If proper distinction between the two melting points is not made, an inconclusive or an erroneous phase diagram will be obtained.

Although a great many organic systems have been investigated by the thaw-melt method, it seems strange for the authors that there was no systematic study concerning the phenomenon. In the preceding papers of this series, a modified thaw-melt method was proposed and the importance of sample preparation was explained. Besides, the meaning and the use of the double thaw point were thoroughly discussed. In this communication, the authors investigate the conditions of occurrence of the double melting phenomenon on five kinds of binary systems, and suggest its application to the detection of molecular compound.

Experimental

Materials——Pure isonicotinamide was supplied by Prof. Z. Tamura of the University of Tokyo, and was used without further purification. The rest of the component substances were all recrystallized twice from suitable solvents.

Sample Preparation——The evaporated and the fused mixture were prepared by the procedures reported in the previous paper. For the former, Me_2CO or MeOH was used as solvent.

Apparatus and Measurement

Visual Thermal Analysis——A modified melting point apparatus equipped with a stirring device by air bubbles was used. The thaw and melting points were determined with or without stirring by a thin glass rod. The rate of heating near these points was usually adjusted to 1.0~3.0°/min. The discrimination of the kind of primary crystals was done as far as possible with a lens of three magnification.

Differential Thermal Analysis——A simple differential thermal analyser was set up and used by modifying the one reported by Inoue.1) The temperature difference between the sample and the standard substance was detected by the difference of resistance between two thermisters inserted into each of them, and measured in terms of the deflection of the micro-ammeter. The temperature of the standard or of the heating bath was read directly with a Hg-thermometer immersed in the middle and in the same depth of both cells. Finely powdered KCl obtainhd by freeze-drying was used as the standard substance. The specific surface of the particles was found to be 2.5~2.8 m^2./g. by the gas adsorption analysis.2)

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*1 This work was presented at the Hokkaido Branch Meeting of Pharmaceutical Society of Japan, March 3, 1962.

*2 Part III. K. Sekiguchi, Y. Ueda, Y. Nakamori : This Bulletin, **11**, 1108 (1963).

*3 Kita-12-jo, Nishi-5-chome, Sapporo, Hokkaido, Japan (関口慶二, 伊藤圭二, 中森良子).

1) M. Inoue, T. Saito : Yakugaku Zasshi, **80**, 694 (1960).

2) A water solution containing potassium chloride less than the cryohydric composition was freeze-dried. The product is felt like a face powder, and found to be an excellent standard substance for the differential thermal analysis. Since potassium chloride has a cubic structure and its density is equal to 1.989, the mean particle size is calculated 1.1~1.2 μ. The authors express their great gratitude to Dr. H. Negoro and Dr. E. Nakajima of Sankyo Co., Ltd. for determining surface area.

An enamelled iron vessel containing 1 L. liquid paraffine was used as a heating bath. Heating was done at a rate of 1.5°/min. by an immersion electric heater. The DTA-curve was obtained by plotting the temperature of the bath along the horizontal axis and the deflection of the micro-ammeter which corresponds to the temperature difference between both cells along the vertical axis. An improved semimicro DTA apparatus of this type which permits direct viewing of the sample and is very suitable for the analysis of organic materials will be reported in detail in the next paper.

Results and Discussion

Aminopyrine/Barbital System (Fig. 1, Table I)——In this well-known system,[3] the metastable or the first melting points were realized chiefly when stirring was not applied. These points occupy their position on the upper extension of liquidus, and are limited up to about 42% of barbital. They were observed more easily by rapid heating, though some excess values were obtained. The peritectic reaction which had suspended occurred rapidly by agitation of the metastable liquid. If the liquid was maintained at a temperature a little above the first melting point, growth of primary crystals was clearly observed. The submerged maximum could not be determined inspite of repeated trials using both isolated compound and samples of the same composition. When the analysis was done with the evaporated mixtures, more reproducible results could be obtained. Samples prepared by fusion containing barbital more than the composition

Table I. Aminopyrine/Barbital System

Barbit. (%)	Evaporated mixt. (°C)			Fused mixt. (°C)			
	t.p.	m.p.		t.p.	m.p.		
0.0	107.6	108.2		107.8		108.4	
5.8	95.7	104.2					
9.9	95.5	101.1					
13.3	95.5	98.4					
16.0	95.3	96.2		92.8～93.5	95.4		
21.3	95.3	103.8					
24.9	95.5	107.7		93.0～93.9	106.7		
30.0	95.4	112.2		93.5～94.0	111.7		
32.0	95.5	113.4		93.3～94.3	113.0		
34.0	95.6	114.8		92.5～94.0	114.3,	(115.6),[a]	119.1
35.9	95.6	(115.6)[d] →	124.5	93.5～94.5	115.5,	(116.0),	125.2
38.0	96.2	(116.5) →	130.5	ca. 88, 93.5		(116.4) →	132.7
40.0	103～107	(117.8) →	136.0	ca. 87	117.7,	(117.8) →	136.4
40.8	107.4		137.3				
41.8	109.0～111.7		139.8	87		(119.0)[b] →	139.8
44.0	112.4		142.4	107～111			143.0
44.3[c]	112.5		142.7				142.2
49.8	112.5		151.8	87			151.5
59.8	112.2		165.4	109.8～110.5			165.2
69.7	112.3		173.3	110.5			172.4
79.7	112.5		179.6				
89.6	112.5		184.7				
94.2	115～120		186.5				
100.0	188.0		189.5	187.8			189.7

a) These values in the brackets were obtained without stirring.
b) A trace of primary crystals still remained at the bottom of the melting point capillary.
c) t.p. and m.p. of the molecular compound isolated from water.
d) The arrows mean that the samples once melt at the former temperature, then separate out new crystals and again melt at the latter temperature.

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[3] H. Reinboldt, M. Kircheisen: Arch. Pharm., **263**, 513 (1925).

of the transition point sometimes exhibited the metastable eutectic points of about 87°. This is attributed to the fact that the reaction between the liquid and the primary crystals was suspended on cooling, and as a result, free aminopyrine as well as barbital remains in the solidified mass. The metastable eutectic points due to the same cause was observed more clearly with the system of aminopyrine and diallylbarbituric acid.*[2]

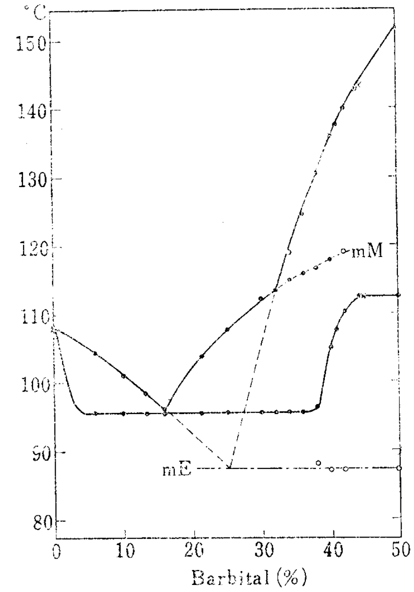

Fig. 1. Aminopyrine/Barbital System

Closed circles: Evaporated mixtures
Open circles: Fused mixtures
Crosses: Isolated molecular compound
mM Metastable melting points
mE Metastable eutectic points

Aminopyrine/Sulfisoxazole System (Figs. 2, 3, and 4, Table II)——The diagram reported by Kuroyanagi and Narikawa is the one of eutectic type.[4] However, the result obtained by us indicates that a one-to-one molecular compound with an incongruent melting point is formed between both components (Fig. 2). The mistake made by the previous authors is supposed to come from the incompleteness of sample preparation. The thaw point of 81.5° found by them is not a stable eutectic point but is a metastable one, since the extrapolations of liquidus starting from the melting points of aminopyrine and sulfisoxazole meet at a point of about 81.5°.

The most characteristic feature of this system is the fact that the submerged or the hypothetical maximum is actually observed. Both the isolated molecular compound and the sample having nearly the same composition exhibit two melting points at 118.5° and 145°. So far as the authors know, this is the first system that the existence of the submerged maximum is determined by the thaw-melt method. Practically, the determination of the maximum is done more easily, whereas the stable melting point of 145° is often overlooked, unless sufficient stirring is applied. The peak of solidus at the composition of combining ratio which is sometimes observed in other systems is another proof of suspended phase reaction.

The differential thermal analysis conducted with the molecular compound showed a single heat absorption due to the metastable melting (Fig. 3). No heat effects corresponding to the separation of solid sulfisoxazole and to the second melting point was shown in the curve. This indicates the limit of applicability of the differential method to binary systems. Although the sensitivity of the determination of thawing or polymorphic transition is superior to the thaw-melt method, the lack of agitation and the difficulty of visual observation of the sample mixture during measurement often lead

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[4] S. Kuroyanagi, M. Narikawa : Yakugaku Zasshi 73, 990 (1953).

to an erroneous result. For this reason, the authors believe that the modified thaw-melt method is more dependable than the differential method.

Light yellow crystals of molecular compound was isolated from water solution of both components (Fig. 4). *Anal.* Calcd. for $C_{24}H_{30}O_4N_6S$: C, 57.82; H, 6.07; N, 16.86. Found : C, 58.02; H, 5.99; N, 16.94.

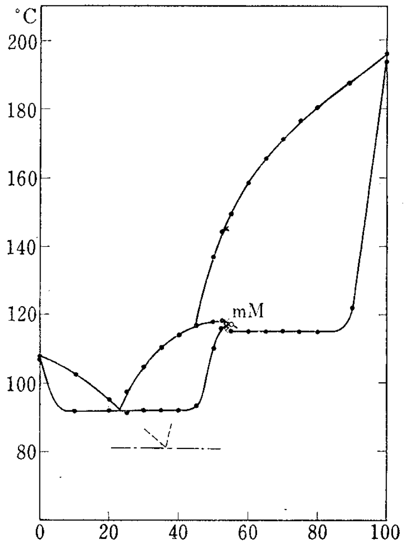

Fig. 2. Aminopyrine/Sulfisoxazole System

Closed circles: Evaporated mixtures
Open circles: Fused mixtures
Crosses: Isolated molecular compound
mM Metastable melting points

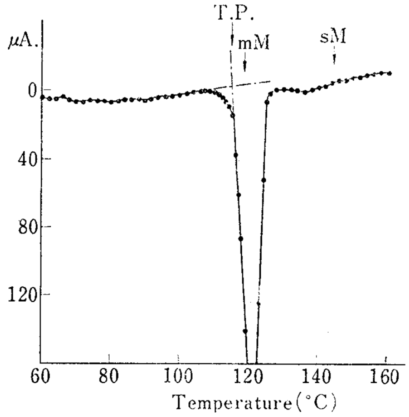

Fig. 3. DTA-curve of the Molecular Compound of Sulfisoxazole and Aminopyrine

T.P. Thaw point
mM Metastable melting point
sM Stable melting point
Sample amount 260 mg.
Heating rate 2.0°/min.

Table II. Aminopyrine/Sulfisoxazole System

SI[a] (%)	Evaporated mixt. (°C) t.p.	Evaporated mixt. (°C) m.p.	Fused mixt. (°C) t.p.	Fused mixt. (°C) m.p.	Primary crystals
0.0	107.6	108.2	107.8	108.4	
10.1	92.0	102.5		101.8	AM[b]
19.9	92.0	94.8	91~91.5	94.0	AM
25.0	91.5	97.7			MC[c]
30.1	92.0	104.6	89~91		MC
35.3	92.1	110.5	89.5~91	110.2	MC
40.1	92.0	114.0	91~92	114.0	MC
45.3	92.0~94.5	116.5			MC
50.0	108~112	118.0, 137.0			MC, SI[d]
52.5	116.0	118.5, 144.4	114~115	144.5	MC, SI
53.6[e]	115.2, 117.3	118.5, 145.1			MC, SI
55.1	115.5	149.8	112~113	117,[f] 148.3	MC, SI
60.1	115.2	158.7			SI
65.0	115.0	165.8			SI
69.8	115.2	171.2	112~113	170.6	SI
74.7	115.2	176.4			SI
80.2	115.0	180.5			SI
89.2	115~129	187.2			SI
100.0	194.3	196.0			

a) SI : Sulfisoxazole. *b*) AM : Aminopyrine. *c*) MC : Mol. Compd.
d) The first one corresponds to the crystals at the metastable melting point, and the second to those at the stable melting point.
e) t.p. and m.p. of the molecular compound isolated from water.
f) This value was obtained by rapid heating.

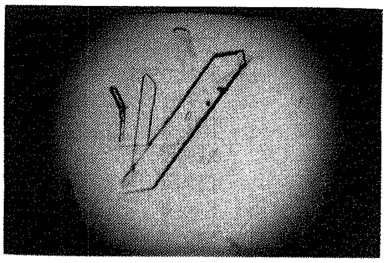

Fig. 4. Crystals of the Molecular Compound of Aminopyrine and Sulfisoxazole

Benzoic Acid/Isonicotinamide System (Figs. 5(A) and 5(B), Table Ⅲ)——This system is an example showing the application of the double melting point to the detection of molecular compound. At the beginning, thaw and melting points were determined with samples prepared by mixing components at every 10% intervals. Although it is evident from the diagram thus obtained (Fig. 5(A)) that a one-to-one compound with a congruent melting point is formed between components, the presence of a different compound would be supported by the following observations.

At first, the double melting point is noticed in samples containing the amide 20 and 30%. The metastable melting points were 141.5° and 146.3°, respectively. Secondly, the thaw point of the 40% sample was always measured at a constant temperature of 138°, whereas that of the 30% sample could not be determined as a definite point but was observed with a range between 130° and 137°.

In visual thermal analysis, the thaw point can be noticed only when the amount of liquid in a mixture becomes sufficient enough for the eye to permit direct observation. Therefore, in a system with an incongruently melting compound, the peritectic or meritectic liquefaction caused by a mixture having a composition a little more than that of the compound should be measured as a definite point, if the mixture was properly prepared. On the other hand, when the composition is a little less than the combining ratio, thawing due to eutectic fusion can hardly be observed as a point, since the proportion of the eutectic conglomerate in the mixture is very small. It is observed practically with a temperature range. From these findings, it is supposed that the second molecular compound with an incongruent melting point exists at a composition between 30 and 40%.

The presence of another compound having a combining ratio of one-to-two with respect to the acid and the amide was determined by more detailed experiments. The

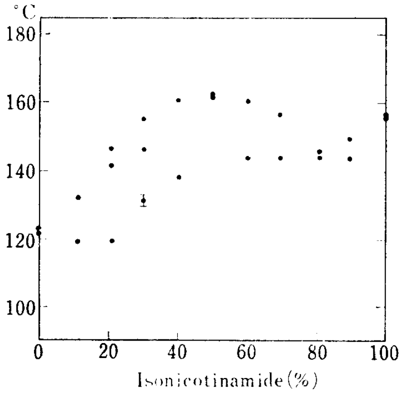

Fig. 5(A). Benzoic Acid/Isonicotinamide System

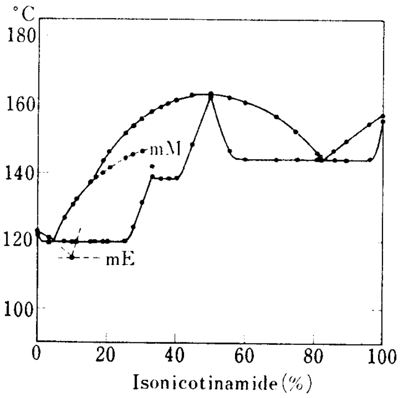

Fig. 5(B). Benzoic Acid/Isonicotinamide System

mM Metastable melting points
mE Metastable eutectic point

TABLE III. Benzoic Acid/Isonicotinamide System

INA[a] (%)	Evaporated mixt. (°C)		Fused mixt. (°C)	
	t.p.	m.p.	t.p.	m.p.
0.0	122.3	122.9	122.1	122.8
3.0	119.7	121.0	119.6	121.3
7.6	119.7	127.1	119.4	127.2
9.9	ca. 115,[b] 119.5	131.0	119.4	131.3
10.9	119.6	132.5	119.2	132.5
15.2	119.7	137.3	119.4	137.3
16.6	119.6	138.3	119.7	138.0
18.7	119.7	139.5, 143.4	119.7	139.5, 143.3
20.5	119.8	(141.5),[c] 146.5	119.4	141.5, 146.8
25.2	119.8	(144.4), 151.5	119~121	144.2, 151.1
27.5	122~126	(145.2), 153.6	123~128.5	(145.2), 153.2
29.8	130~133	(146.3), 155.5	134~137	(146.0), 155.8
32.9	138.8, 142.2	157.8	138.7, 141.0	157.6
35.7	138.1	159.0	138.2	159.0
37.6	138.2	159.8	138.1	160.0
40.0	138.2	160.9	138.3	161.5
44.6	147~150	162.5		
49.9	162.0	162.9	161.7	163.2
55.4	143~150	162.1	144~154	162.3
59.8	144.0	160.5	143.5	160.5
69.1	143.9	156.4	143.4	156.5
74.8	143.7	152.2		
81.0	143.9	145.8	143.3	145.5
81.8	143.7	144.8		
85.7	143.8	146.5		
89.3	143.8	149.5	143.5	149.6
95.8	143.8	154.4	144.1	154.5
100.0	155.3	156.9	155.2	157.2

a) INA : Isonicotinamide.
b) Metastable eutectic point between benzoic acid and the molecular compound of 1:1 ratio.
c) The values in the brackets were obtained without stirring.

metastable liquidus was realized from 19 to 30%. Moreover, different thaw points were observed with samples having the composition of the second compound. The higher value of 142° is attributed to the suspended peritectic reaction, as has been stated in the former system.

Nicotinamide/Sulfamerazine System (Figs. 6(A) and 6(B), Tables IV(A) and IV(B))——A molecular compound with an incongruent melting point is formed. Metastable melting points were observed on the lower extensions of either sides of liquidus. Three kinds of thaw point were obtained. The lowest one of 123~123.5° is clearly attributed to the metastable eutectic point. The middle one of 125~125.5° is due to the stable eutectic liquefaction between nicotinamide and the molecular compound. The highest is assigned to the peritectic point. Between the temperature of the metastable and of the stable liquidus, resolidification of samples prepared by fusion was comparatively easy.

When samples were prepared by the evaporation method, an excess amount of either nicotinamide or sulfamerazine was apt to be separated out as metastable primary crystals and the transformation of them into the molecular compound was delayed. Therefore, preparation of a sample in a stable equilibrium state was often difficult by this method. For example, the evaporated residue containing the sulfonamide 18.5% was found to be mainly composed of the spherites of the metastable eutectic conglomerate. However, the fused mixture of the same composition solidified in some cases, as a mixture of the compound and the stable eutectic.

Although the combining ratio of the molecular compound was reported by Kuroyanagi and Narikawa[4] as four-to-three with respect to the amide and the sulfonamide, it must be corrected to three-to-two as we have determined here. The ratio was also determined by isolating the molecular compound from acetone solution. *Anal.* Calcd. for $C_{40}H_{42}O_7N_{14}S_2$: C, 53.68; H, 4.73; N, 21.91. Found : C, 53.84; H, 4.85; N, 21.92.

When analyses were done with mixtures of both the isolated compound and the amide or the sulfonamide, only stable thaw and melting points were observed (Table IV (B)).

TABLE IV (A). Nicotinamide/Sulfamerazine System

SM[b] (%)	Evaporated mixt.[a] (°C) t.p.	Evaporated mixt.[a] (°C) m.p.	Fused mixt. (°C) t.p.	Fused mixt. (°C) m.p.
0.0			128.3	129.3
5.1	123.5	128.3(NA)[c]	123.1, 125.0	128.3(NA)[c]
10.0	123.3	126.0(NA)	123.3, 125.0	126.8(NA)
11.6	123.4	127.1	125.2	127.3
13.5	123.3	130.6(M)	123.1, 125.3	125.9, 129.8
14.9	123.2	124.7→132.4	123.3→125.5	124.6(NA), 131.8(M)
16.5			123.2→125.5	124.7, 134.2(M)
18.5	123.3	124.3→136.8	123.4, 125.5	123.5(NA), 136.5(M)
20.0	123.1	125.5	123.3→125.6	125.8→137.9(M)
21.5	123.5	141.0(M)	123.4, 125.6	130.5(SM)→139.6(M)
23.5	123.4	135.6(SM)	123.3→125.5	135.1(SM)→141.5(M)
25.0	123.2	139.5	123.2→125.4	137.8, 142.4
27.6	123.1	145.5	123.5, 125.4	143.7
30.0	123.3		123.0→125.0	148.0
34.1			123.1→125.5	154.4
36.0	123.3	159.0(SM)	123.5→125.4	158.0
37.8			123.1→125.3	160.5
40.1	123.3	164.7	123.1→125.3	164.4
44.7			123.0→125.6	170.0
50.2	123.7	177.0	123.3→125~127	176.8
55.1	123.4→126~140	184.5	123.4, 130~140	184.0
60.5	123.5	191.5	123.5, 141~145	190.5
65.1	123.3→143~144		144.0	196.0
68.5	123.5→145.0	201.2		
70.1	123.4→144.7		144.7	202.0
73.6	123.5→145.0	205.5	144.3	205.4
79.9	145.0	212.2	145.0	212.5
90.0			166~190	220.8
100.0			231.5	233.7

a) Acetone was used as solvent.
b) SM : Sulfamerazine.
c) Primary crystals observed; NA : Nicotinamide, M : Granular crystals of the molecular compound.

TABLE IV (B). Nicotinamide/Sulfamerazine System

SM (%)	Components	Physical mixt.[a] (°C) t.p.	Physical mixt.[a] (°C) m.p.
0.0		129.2	130.8
16.8	NA+SM	123.2	126, 135.5
29.2	NA+MC[b]	125.2	144.6
40.0	NA+SM	123.3	166.5
49.7	NA+MC	125.5	177.8
51.2	NA+MC	125.5~127.5	178.5
54.1	NA+MC	140~142	182.9
59.1	MC	145.5	188.5
64.4	MC+SM	144.4	195.6
100.0		234.2	235.3

a) Both component substances were mixed in an agate mortar.
b) MC : Isolated molecular compound.

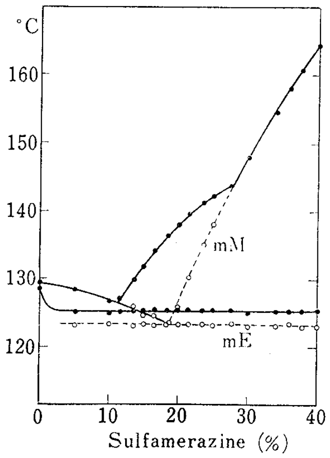

Fig. 6(A). Nicotinamide/Sulfamerazine System

Closed circles: Stable thaw and melting points of fused mixtures
Open circles: Metastable thaw and melting points of fused mixtures

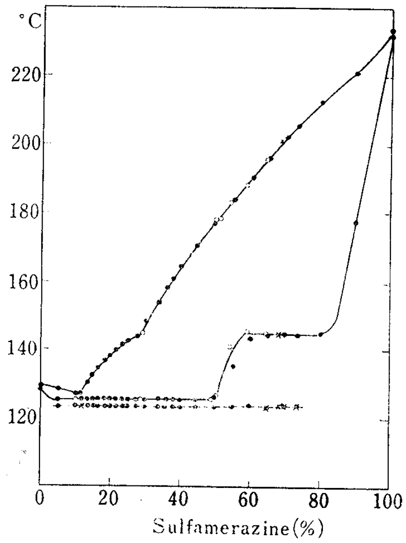

Fig. 6(B). Nicotinamide/Sulfamerazine System

Closed circles: Fused mixtures
Open circles: Isolated molecular compound, or its physical mixtures with nicotinamide or sulfamerazine
Crosses: Evaporated mixtures

Urea/N-Sulfanilyl-3,4-xylamide System (Figs. 7 and 8, Table V)——Since both component substances are not thermally stable and the molecular weight of the sulfonamide is about five times larger than that of urea, the combining ratio of the molecular compound could not be determined so easily as in usual systems; however, the diagram obtained by jointing the plotts of evaporated mixtures indicates clearly that the compound has an equimolar ratio of both components (Fig. 7). This was also confirmed by the isolation of the compound from several solvents, such as acetone, ethanol, ethanol-benzene mixture and n-propylalcohol (Fig. 8). *Anal.* Calcd. for $C_{16}H_{20}O_4N_4S$: C, 52.73; H, 5.53; N, 15.38. Found : C, 52.68; H, 5.63; N, 15.93.

With mere physical mixtures, the eutectic horizontal line extended too long by the reason described in the previous papar. Although the observation of milky suspension formed above this temperature suggests an interaction between both components, the melting points could not be measured reproducibly with these mixtures.

When samples were prepared by fusion, the phase diagram in a stable equilibrium could never be determined. Solidification of them on cooling was usually incomplete and they were apt to take a vitreous state. These incompletely solidified samples exhibit metastable melting points on the extrapolation of the left branch of liquidus, and the primary crystals of them were observed to be urea.

It must be noticed that the double melting point phenomenon in a mixture which is composed of both supercooled liquid and the crystals of easily solidified component suggest nothing about the existence of molecular compound. Such a metastable liquidus can be obtained with systems of eutectic type in which no compound formed, especially when the thermal analysis is conducted by the cooling curve method. However, in the heating procedure, if a completely solidified sample that contains no supercooled liquid exhibits double melting point as shown in the former system, it will serve as a strong evidence for the presence of molecular compound.

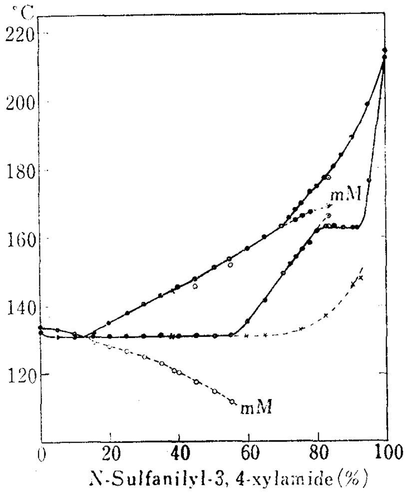

Fig. 7. Urea/N-Sulfanilyl-3,4-xylamide System

Closed circles: Evaporated mixtures
Open circles: Fused mixtures
Crosses: Physical mixtures
Double circles, Isolated molecular compound
mM Metastable melting points

Table V. Urea/N-Sulfanilyl-3,4-xylamide System

SX[b] (%)	Evaporated mixt.[a] (°C) t.p.	m.p.	Fused mixt. m.p. (°C)	Physical mixt. t.p. (°C)
0.0	132.8	133.6		132.7 (133.5)[d]
5.3	131.0	133.0 (U)[c]	132.3 (U)[c]	130
10.0	131.0	132.4 (U)	131 (U)	130
15.5	131.0	131.8 (M)	129.5 (U)	129.5
20.2	131.0	135.2 (M)	128 (U)	
24.9	131.0	187.8 (M)	126.5 (U)	130
30.2	131.0	139.8 (M)	125 (U)	130
35.1	131.0	142.5 (M)	123 (U)	
38.4[e]			121 (U)	131.0 (144.4)[d]
40.0	131.0	145.5 (M)	120.5 (U)	
45.2	131.0	147.5 (M)	118 (U), 145.5 (M)	130.5
50.5	131.0	151.2 (M)	115 (U)	131
55.2	131.5	153.5 (M)	112 (U), 152 (M)	131
59.7	134～137	156.5 (M)		131
65.0	139～144	160.0 (M)		131.5
70.0	148～151	163.0 (M)		
72.0	151～153	165.0		
74.0	152.5～152.6	164.5 (M), 167.5		
75.7	156～157	165.5 (M), 169.0 (SX)		133
78.1	157～158	167.0 (M), 173.0 (SX)		
80.1	160.5～162.5	174.5 (SX)		
82.5	162～164	177.0 (SX)		137
83.5[f]	163.0, 165.5	168.5 (M), 177.0 (SX)		
84.8	163.0	180.5 (SX)		
87.2	162.5	183.5 (SX)		
90.3	162.5	188.5 (SX)		146
91.3	162.5	191.0 (SX)		
92.5	162.5	193.5 (SX)		148
94.8	174～178	198 (SX)		
100.0				212.5 (214.5)[d]

a) Acetone with a small amount of methanol was used as solvent.
b) SX : N-Sulfanilyl-3,4-xylamide.
c) The primary crystals observed; U : Urea, M : Milky suspension of the molecular compound.
d) Melting points.
e) These values were obtained using the isolated compound and urea as components.
f) Isolated molecular compound.

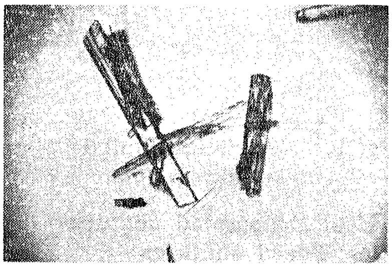

Fig. 8. Crystals of the Molecular Compound of Urea and N-Sulfanilyl-3,4-xylamide

Conclusion

As is seen in the results shown above, there are two kinds of double melting phenomenon in binary systems forming compounds. One of them is observed in such a mixture that it is in a metastable equilibrium state and contains no supercooled liquid. When transformation from the metastable to the stable state is delayed, it will melt at the temperature of the metastable melting point. Such a melting point is always shown on one or both of the extensions of liquidus branches starting from the melting point of both components. The metastable eutectic point is usually observed along with the metastable melting point. Because the rate of reaction is more rapid in liquid than in solid state, a new solid should be separated on further heating by the reaction of compound formation; consequently, complete fusion should again be observed at the melting point. However, in actual practice, the tendency of the transformation varies considerably with the kind of system. In some rare cases, the separation of crystals of a molecular compound needs so much time that the second melting point becomes difficult to be realized.

Although the double melting point of the first kind occurs in a system forming a compound either with a congruent[5] or an incongruent melting point, occurrence of the second type is limited to the system with an incongruently melting compound. Usually, the sample should be prepared in a stable equilibrium condition. The metastable eutectic point will therefore disappear. When metastable mixture is used, the metastable melting point of this kind will not be observed, unless complete transformation to the stable state takes place during heating.

In any event, it is clear that the occurrence of this phenomenone in a binary mixture is clearly due to the suspended phase reaction; accordingly, the nature of the mixture and the conditions of measurement have much influence on this phenomenon. Rapid heating is preferable for observing the metastable melting point, while the stable one is more easily observed by gradual heating. Agitation is also an important condition. If a mixture is heated without stirring, the first melting point will be more easily measured. However, when stirring is not applied, separation of a new solid phase which ought to occur on further heating is often hindered, and the second melting point will sometimes disappear. On the contrary, if the mixture is effectively stirred, complete fusion at the temperature of the metastable melting point will become difficult and only the stable melting point will be observed.

Since the third type of the phenomenon is observed in a mixture containing supercooled liquid, it is able to occur even in an eutectic system and the presence of a compound between components can not be indicated by it. However, because the thermal analysis by the thaw-melt method is usually conducted using completely solidified samples, confusion due to this type will be entirely neglected.

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5) As shown in the previous paper, the system of *p*-nitrophenol and 7-(2-hydroxyethyl)theophylline which was found to form a congruently melting compound is an example of this type.

When the heating process is adopted in the thermal analysis, the fourth type of the double melting is possible in a binary mixture, in which one or both of the components exist as polymorphic forms having lower melting points. Such a phenomenon will not be probable, and even if it occurs, it will be easily distinguished from the first two. In fact, the authors have not yet experienced the one of this type by the thaw-melt method, although they have analyzed about three hundred binary systems.

Accordingly, when two melting points were observed in a binary mixture, it is quite possible that a molecular compound is formed between both components. Also, the knowledge of this phenomenon will become a useful aid in constructing a correct phase diagram. Since the phenomenon is intimately related to the state of sample mixture, the importance of sample preparation must be more strongly emphasized.

The authors express their hearty gratitude to Prof. Dr. E. Ochiai and Prof. Dr. H. Nogami for their great interest and encouragement throughout this work. Also, the authors are indebted to Prof. Dr. Z. Tamura for the supply of the purified reagent, and to Mr. K. Narita, Mrs. K. Toma and Miss Y. Maeda for elementary analyses.

Summary

In order to improve the dependability of the thaw-melt method, the double melting point phenomenon which has hitherto been neglected or overlooked was investigated on five kinds of organic binary systems with one or two molecular compounds. The systems were those of aminopyrine and barbital, aminopyrine and sulfisoxazole, benzoic acid and isonicotinamide, nicotinamide and sulfamerazine, and urea and N-sulfanilyl-3,4-xylamide. The metastable or the first melting point occurs either by the delayed peritectic reaction in a stable mixture or by the suspended compound formation in a metastable mixture. In the former case, the metastable melting points appear on the upper extension of the middle branch of the stable liquidus. In the latter, they are observed on either or both of the extensions of the right and the left branch of liquidus. The occurrence of this phenomenon depends not only on the nature of the system but also on the conditions of measurement, such as agitation and heating rate. The submerged maximum which was thought to be hypothetical was clearly observed with the system of aminopyrine and sulfisoxazole and that of urea and N-sulfanilyl-3,4-xylamide. The isolated compound of the former was examined by the differential thermal analysis. Heat effect was noted only at the metastable melting point of this compound.

If the sample contains no supercooled liquid, the occurrence of double melting point in the heating procedure is actually limited to those cases described above. It will therefore, be very useful for the detection of molecular compound. Also the knowledge of this phenomenon will help to construct a correct phase diagram.

(Received March 12, 1963)