

RAD: 14-40327- -2	FECHA: 2015-09-10 07:19:58
DEP: 2020 DIRECCION DE NUEVAS CREACIONES	EVE: 378 FASE NACIONAL INCLUIDO CAPITULO I
TRA: 11 PCT-PATENTE DE INVENCION CAPITULOS I Y II	FOLIOS: 7
ACT: 430 REQUERSOLICITA	

2020
Bogotá, D.C.,

Abogado(a)/Señor(a)
LUZ CLEMENCIA DE PÁEZ

Asunto:	Radicación:	14-40327- -2
	Trámite:	11
	Evento:	378
	Actuación:	430
	Oficio:	10605
	Folios:	7

Patente de Invención	X			Patente de Modelo de Utilidad	
Vía Nacional					
Vía PCT (Fase Nacional)	X	Capítulo I	X	Capítulo II	
No. Solicitud Internacional	PCT/US2012/048371				
Fecha de Presentación Internacional	26/07/2012				

Como resultado del examen de fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

Descripción:	Radicado No. 14-040327-00000-0000	26/febrero/2014
Reivindicaciones:	Radicado No. 14-040327-00000-0000	26/febrero/2014
Prioridad:	US 61/511, 867	26/julio/2011

Se acepta la reivindicación de prioridad porque ésta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

De acuerdo con lo establecido en el numeral 1.2.2.2 del capítulo primero del Título 10 de la Circular Única para efectos del examen de patentabilidad, se tendrá en cuenta la tasa pagada por el solicitante al momento de comenzar el examen para las reivindicaciones adicionales; esto es que cuando la solicitud contenga más de diez (10) reivindicaciones y no se haya pagado la tasa complementaria, sólo se estudiarán las cubiertas por la tasa pagada. En el presente caso, se tiene en

cuenta la totalidad del capítulo reivindicatorio (Radicado No. 14-040327-00000-0000) para el examen de patentabilidad.

Título de la solicitud: “MÉTODOS PARA AISLAR ÁCIDOS 4-CLORO-2-FLUORO-3-FENILBORÓNICOS SUSTITUIDOS” (modificado en el Fl. 259).

El problema planteado en esta solicitud consiste en la necesidad de suministrar métodos alternativos de aislamiento del ácido 4-cloro-2-fluoro-3-fenilborónico sustituido con un mejor rendimiento.

Para resolver este problema técnico la solicitud en estudio proporciona métodos para aislar dicho ácido que comprenden la reacción del ácido con una sal para formar una capa de solvente orgánico miscible en agua y una capa de agua. Igualmente propone un método en donde se agrega una sal a una mezcla de acetonitrilo/agua que comprende el ácido. De igual forma la solicitud propone un método para sintetizar y aislar el ácido 4-cloro-2-fluoro-3-fenilborónico sustituido.

El objeto de la presente solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C07B63/00; C07C43/205; C07F5/02.

4. De la solicitud de patente

Reivindicaciones (Art 30 D 486, Art 22 PCT)

La reivindicación 1 utiliza expresiones que no limitan el alcance de la solicitud tales como “un solvente orgánico”, “sustituido con una sal”, dichas expresiones abarcan un ilimitado número de agentes y le restan claridad y concisión a la solicitud. De igual forma, la descripción y los ejemplos presentados por la solicitante no son representativos del ilimitado alcance reclamado, especialmente por el hecho de no limitar las sales que se forman ya que es conocido por la persona versada en la materia que cada forma salina posee propiedades fisicoquímicas diferentes entre las que se encuentra la solubilidad del producto, por lo cual no es posible afirmar que cualquier forma salina que reaccione con la mezcla de agua y solvente orgánico permita obtener una mayor rendimiento luego de la recuperación con respecto a los métodos conocidos en el arte previo. Lo anterior también aplica para la reivindicación 4.

La reivindicación 1 no es coherente con la descripción ya que indica que la mezcla de PBA/agua/solvente orgánico se hace reaccionar con una sal, sin embargo no se especifica que se debe lograr una solución saturada de sal para lograr el “salting out” de la mezcla, lo cual es esencial para lograr los resultados que se pretenden mediante el proceso actualmente reivindicado según se encuentra establecido en la descripción de la presente solicitud.

La reivindicación 3 no divulga una forma preferida de la invención y tan solo repite el contenido de la materia divulgada en la reivindicación 1 por lo cual se considera redundante.

La reivindicación 16 carece de claridad ya que habla de utilizar el ácido 4-cloro-2-fluoro-3-metoxifenilborónico en acetonitrilo, sin embargo no se comprende cómo va a ser utilizado dicho compuesto o para qué va a ser utilizado.

La reivindicación 17 caracteriza el derivado de ácido 4-cloro-2-fluoro-3-fenilborónico sustituido, por un proceso de producción del mismo, esta caracterización no es aceptada ya que un producto debe caracterizarse por sus elementos técnicos esenciales, que en este caso corresponden al nombre químico

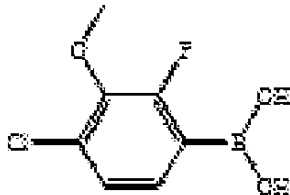
de la molécula o mediante su estructura química. En consecuencia, la caracterización de un producto por su proceso de síntesis no será considerada en el examen de patentabilidad.

5. Determinación del Estado de la Técnica

El estado de la técnica se determinó con base en la fecha de presentación de la solicitud de prioridad: 26 de julio de 2011, y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Ítem	Documento	Título	Fecha de Publicación
D1	US7,611,647	Process for the selective deprotonation and functionalization of 1-fluoro-2-substituted-3-chlorobenzenes	3/11/2009
D2	J. Am. Chem. Soc., 1933, 55(11)pp4430-4440	The "Salting-out" and "Salting-in" of Weak Acids. I. The Activity Coefficients of the Molecules of Ortho, Meta and Para Chlorobenzoic Acids in Aqueous Salt Solutions	1933

D1¹ divulga un proceso de reacción aislamiento del siguiente compuesto (Ejemplo 3):



D2² enseña la adición de sal a una mezcla de líquidos con la finalidad de lograr un efecto de "salting out". La anterioridad indica que frente a ciertas fuerzas iónicas, las moléculas de agua en la fase acuosa no son capaces de soportar las cargas de los dos iones y el PBA lo que da lugar a la separación de la sustancia menos soluble.

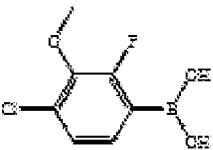
6. Examen de Patentabilidad (Art 14 D486)

Novedad (Art. 16 D 486)

La reivindicación 17 reclama un derivado de ácido 4-cloro-2-fluoro-3-fenilborónico sustituido.

Comparación de las características técnicas esenciales, con las del estado de la técnica:

1[https://www.google.com/patents/US7611647?](https://www.google.com/patents/US7611647?dq=US7611647&hl=es&sa=X&ved=0CB0Q6AEwAGoVChMIjvvjtNHoxwIViJQeCh1-QQIo)
[https://pubs.acs.org/doi/abs/10.1021/ja01338a016?](https://pubs.acs.org/doi/abs/10.1021/ja01338a016?journalCode=jacsat&quickLinkVolume=55&quickLinkPage=4430&selectedTab=citation&volume=55)

Características esenciales	D1
Un derivado de ácido 4-cloro-2-fluoro-3-fenilborónico sustituido.	Derivados de metoxi PBA  (ejemplos)

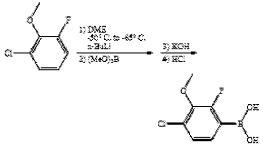
La materia reclamada mediante la reivindicación 17 ha sido anticipada por la divulgación contenida en el documento D1 el cual da a conocer derivados de metoxi PBA (ver ejemplos). En consecuencia la reivindicación 17 carece del requisito de novedad.

Nivel inventivo (Art18 D486)

La reivindicación 1 consiste en un método para aislar un ácido 4-cloro-2-fluoro-3-fenilborónico sustituido.

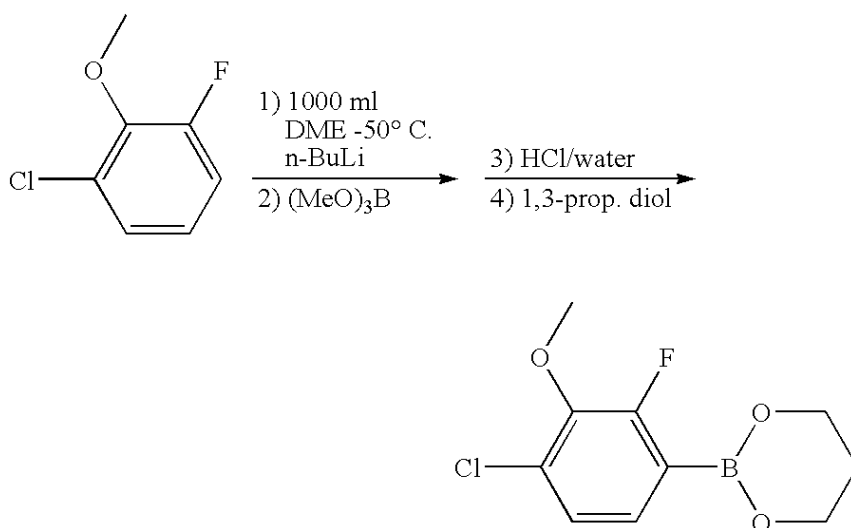
La reivindicación 11 reclama un método para sintetizar y aislar el ácido 4-cloro-2-fluoro-3-metoxifenilborónico.

Comparación de las características técnicas esenciales, con las del estado de la técnica:

Características esenciales	D1	D2
Reiv. 1 Un método para aislar un ácido 4-cloro-2-fluoro-3-fenilborónico sustituido que comprende: Hacer reaccionar una mezcla de agua, un solvente orgánico miscible en agua y un ácido 4-cloro-2-fluoro-3-fenilborónico sustituido con una sal para formar una capa de solvente orgánico miscible en agua y una capa de agua; Separar el ácido 4-cloro-2-fluoro-3-fenilborónico sustituido en la capa de solvente orgánico miscible en agua; y Separar la capa de solvente miscible en agua que comprende ácido 4-cloro-2-fluoro-3-fenilborónico sustituido de la capa de agua.	Un método para aislar derivados de ácido 4-cloro-2-fluoro-3-fenilborónico que consiste en Mezclar la capa acuosa que comprende ácido 4-cloro-2-fluoro-3-fenilborónico con acetonitrilo y posteriormente acidificar adicionando gotas de ácido clorhídrico 6M. La capa acuosa es extraída con acetonitrilo adicional. El producto total recuperado generó un rendimiento de 80.3%.	Describe el paso de adicionar sal a una mezcla acuosa el cual es conocido como “salting out” (Pág. 4431).
Reiv. 11 Un método para sintetizar y aislar el ácido 4-cloro-2-fluoro-3-fenilborónico que comprende: Hacer reaccionar 2-cloro-6-fluoroanisol (2,6-CFA, por sus siglas en inglés) con n-butilitio para formar un derivado litiado de 2,6-CFA; Hacer reaccionar el litiado de 2,6-CFA con B(OCH₃)₃ para formar un éster de ácido borónico de 2,6-CFA; Hacer reaccionar el éster de ácido borónico de 2,6-CFA con hidróxido de sodio acuoso para formar una sal de sodio del ácido borónico 2,6-CFA;	Un método de síntesis para el ácido 4-cloro-2-fluoro-3-metoxifenilborónico:  Donde una solución de hidróxido de potasio es adicionado a la mezcla de reacción, la capa acuosa es bañada tres veces con	

Hacer reaccionar la sal de sodio del ácido borónico de 2,6-CFA con ácido clorhídrico acuoso para formar una solución de ácido 4-cloro-2-fluoro-3-metoxifenil borónico; Agregar acetonitrilo a la solución de ácido 4-cloro-fluoro-3-metoxifenilborónico para formar una mezcla de acetonitrilo, agua y ácido 4-cloro-2-fluoro-3-metoxifenilborónico; Agregar una sal a la mezcla de acetonitrilo, agua y ácido 4-cloro-2-fluoro-3-metoxifenilborónico para formar una capa de acetonitrilo y una capa de agua; y Separar la capa de acetonitrilo y la capa de agua.	ter-butil-metil éter (2 veces) para remover el 2-cloro-6-fluoroanisol. La capa acuosa es luego transferida a un Erlenmeyer y diluida con acetonitrilo y cidificada con gotas de ácido clorhídrico. La capa acuosa fue extraída con acetonitrilo adicional.	
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El documento D1 se considera el estado de la técnica cercano a las invenciones definidas en las reivindicaciones 1 y 11 porque enseña el siguiente esquema de reacción:



Donde una solución de hidróxido de potasio en agua es adicionada a la mezcla de reacción. La mezcla fue secada por 60 minutos, y luego es transferida a un embudo de separación donde las fases fueron posteriormente separadas. La capa acuosa fue lavada con terbutil metil éter para remover el 2-cloro-6-fluoroanisol que no reaccionó. La capa acuosa fue luego transferida a un Erlenmeyer y diluida con acetonitrilo, acidificada mediante la adición de gotas de una solución 6M de ácido clorhídrico. Posteriormente, la capa orgánica fue separada y la capa acuosa fue lavada con acetonitrilo adicional y las dos capas orgánicas adicionales se mezclaron con la primera. El producto total recuperado de la solución de acetonitrilo fue de 9.85g lo que representa un rendimiento de 80.3% de rendimiento.

La diferencia entre la invención, definida en las reivindicaciones y el proceso de D1 consiste en que la anterioridad no adiciona sal a la mezcla acuosa de PBA/acetonitrilo/agua.

Estas diferencias no parecen conceder un efecto técnico inesperado o una ventaja sorprendente ya que esta técnica para mejorar la recuperación de un producto y aumentar el rendimiento es ampliamente conocida.

El problema técnico objetivo de esta solicitud consiste en la necesidad de un proceso de síntesis y extracción alternativo para los derivados de PBA.

Sin embargo, el documento D2 enseña que a una determinada fuerza iónica, las moléculas de agua en la fase acuosa no son suficientemente capaces de soportar las cargas de los dos iones y del PBA. El resultado es la separación del soluto menos soluble, el cual es en este caso el PBA (Pág. 4431). El documento especifica que en una solución de un agente no iónico en agua, los dipolos del agua se organizan alrededor de la molécula dependiendo de las propiedades polares de la misma. Cuando un electrolito es adicionado a la solución, debido a la hidratación de los iones, hay menos agua disponible para la saturación de la sustancia no iónica, por lo que se espera un “salting-out” de la molécula que no es iónica.

En consecuencia, el la persona del oficio normalmente versada en la materia, incluiría una sal a la mezcla PBA/agua/ acetonitrilo como lo enseña el documento D2 en el procedimiento de síntesis y aislamiento divulgado en el documento D1 con la expectativa razonable de inducir un “salting out” para el PBA en solución mucho más eficiente permitiendo un mayor rendimiento y a su vez con un mayor grado de pureza. Por lo cual el objeto de los procesos de las reivindicaciones 1 y 11 se considera obvio.

De manera que la solución propuesta por esta solicitud en las reivindicaciones 1 y 11 y en las reivindicaciones dependientes 2 a 10 y 12 a 16 es obvia y no tiene nivel inventivo.

7. Conclusión

Los requisitos de Patentabilidad de la presente solicitud están afectados así:

Ítem	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO2007134876	1 – 16 17	Nivel inventivo Novedad
D2	WO2004089988	1 – 16	Nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir del día siguiente de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante de sesenta (60) días para dar respuesta a este requerimiento y presentarla por escrito.

Finalmente, se le recuerda al solicitante que si como respuesta a este requerimiento llegara a modificar el capítulo reivindicatorio y éste contenga más de diez (10) reivindicaciones, no pagará la tasa de modificación voluntaria pero sí la correspondiente al pago por reivindicación adicional.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (c)

El anterior requerimiento fue notificado por fijación en lista, de fecha 2015-09-15

Elaboró: Emilse Cano Urrego
Revisó: Rubiela Pacanchique Vargas

method which yields their determination of K seems to approach a much smaller limiting value than the simple mass action extrapolation in both cases.

In view of the failure of the theory to account for the conductance of sodium amide and the uncertainty of the treatment of potassium amide it would be useless to calculate ion sizes. If the underlying notions of the theory are at all justified it is certain, however, that the amide ion is exceedingly small. It may be that the unusual properties that have been found are specific for the amide ion but it seems more likely that they will prove rather to be characteristic of small ions in general.

V. Summary

The electrical conductance of sodium and potassium amide has been measured in liquid ammonia solution up to concentrations of 36,000 and 52,000 liters, respectively. The data for sodium amide deviate from the theory of Fuoss and Kraus as well as from the simple mass action theory. The agreement is better in the case of potassium amide but is not as good as might be desired. The results indicate that the specific properties of extremely small ions are important in the case of these electrolytes.

CAMBRIDGE, MASSACHUSETTS

RECEIVED JUNE 20, 1933

PUBLISHED NOVEMBER 7, 1933

[CONTRIBUTION FROM THE LABORATORY OF PHYSICAL CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

The "Salting-out" and "Salting-in" of Weak Acids. I. The Activity Coefficients of the Molecules of Ortho, Meta and Para Chlorobenzoic Acids in Aqueous Salt Solutions¹

BY ARTHUR OSOL AND MARTIN KILPATRICK

In general the solubility of a non-electrolyte is increased or decreased by the addition of an electrolyte, but the effect is not independent of the solvent salt. The results may be expressed by the equation

$$\log S_0/S = \log f \quad (1)$$

where S_0 is the solubility at zero ion concentration, S the solubility in the salt solution and f the activity coefficient of the non-electrolyte. It has been found that the equation

$$\log f = kC \quad (2)$$

C being the concentration of electrolyte in moles per liter and k a constant, holds over a wide range of concentration. The constant k is known as the "salting-out" constant. Provided a correction is made for the part

(1) Abstracted from the dissertation of Arthur Osol presented April 1, 1933, to the Faculty of the Graduate School of the University of Pennsylvania in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Paper presented in part before the Washington meeting of the American Chemical Society, March, 1933.

present as ions, equation (2) is applicable to weak electrolytes also. In most of the early work on acids this correction was neglected, or improperly made, with the result that (2) did not hold.² It has been mentioned that for a given non-electrolyte the effect depends upon the solvent salt. It is also true that in general, for a given solvent salt, the effect depends upon the saturating non-electrolyte.³ The "salting-out" constant k generally increases with decrease in the polar properties of the non-electrolyte. This is the basis of the theory of Debye.⁴

The theory of Debye does not explain how certain salts "salt-out" a specified non-electrolyte while others salt it in. An explanation has been offered by Krulyt and Robinson.⁵

The point of view of Krulyt and Robinson is briefly as follows. In a solution of a non-electrolyte in water, the water dipoles are arranged about a molecule of non-electrolyte with their positive or negative end toward the non-electrolyte depending upon the polar properties of the latter. When an electrolyte is added to the solution, due to the hydration of the ions less water is available to the saturating non-electrolyte and on this basis alone "salting-out" of the non-electrolyte is expected. There is, however, a counteracting effect. Its polar nature determines whether the molecule of non-electrolyte attracts cations or anions. About the attracted ions water molecules are arranged in a manner opposite to the arrangement about the non-electrolyte and the result of the approach of the ion to the molecule of non-electrolyte is a packing in of water molecules about the molecules of non-electrolyte, *i. e.*, "salting-in." The effectiveness of the specified ion depends according to Krulyt and Robinson upon its degree of hydration. The non-electrolyte is "salted-out" if the first effect predominates and *vice versa*.

This paper concerns the solubility of molecular ortho, meta and para-chlorobenzoic acids in various salt solutions and compares the "salting-out" constants obtained with those found for benzoic acid.

Experimental Part

The experimental method was that of Chase and Kilpatrick.² In order to minimize the correction for the part present as ions, buffer solutions were used throughout the work.

The chlorobenzoic acids were purified by recrystallization from alcohol. They melted sharply at 139, 154 and 235° for the ortho, meta and para acids, respectively. The criterion of purity was constancy of solubility upon repeated treatment of the solid with water. Titrations were carried out in an atmosphere of nitrogen with carbonate

(2) Chase and Kilpatrick, *THIS JOURNAL*, **53**, 2589 (1931).

(3) Randall and Failey, *Chem. Rev.*, **4**, 291 (1927).

(4) Debye and McAulay, *Physik. Z.*, **26**, 22 (1925); Scatchard, *THIS JOURNAL*, **47**, 2069 (1925); *Chem. Rev.*, **3**, 383 (1927); Debye, *Z. physik. Chem.* (Cohen Festband), 56 (1927). For further references and a complete discussion see Falkenhagen, "Elektrolyte," S. Hirzel, Leipzig, 1933, p. 138-152.

(5) Krulyt and Robinson, *Proc. Acad. Amsterdam*, **29**, 1244 (1926). See also the very recent paper of P. M. Gross, *Chem. Rev.*, **13**, 91 (1933).

free sodium hydroxide. Weight burets were employed. When necessary the salts were purified by recrystallization.

The total solubility of *o*-chlorobenzoic acid in water was found to be 0.01362 mole per liter. Correction for the part present as ions was made by multiplying the K_c/K_a ratio⁶ for benzoic acid given by Chase and Kilpatrick by K_a for *o*-chlorobenzoic acid (1.28×10^{-3}) and applying the mass law to the K_c thus found to obtain the hydrogen-ion concentration. The corresponding solubility of the molecular acid is 0.00986 mole per liter. In a similar manner the total solubilities of meta and para chlorobenzoic acids were found to be 0.00246 and 0.000435 and the corresponding molecular solubilities 0.00191 and 0.000275. Table I gives the solubilities of the acids in dilute solutions of sodium salts of the acids.

TABLE I
SOLUBILITIES OF CHLOROBENZOIC ACIDS IN SOLUTIONS OF THEIR SODIUM SALTS
o-Chlorobenzoic Acid

Sodium <i>o</i> -chloro- benzoate mole/liter	Density, ^a g. per cc.	Total acid mole per liter	H ₃ O ⁺ , mole per liter	Molecular acid, mole per liter	$f = \frac{0.00990}{C_{oHClB}}$
0.01	0.997	0.01131	0.00135	0.00996	0.994
.02	.999	.01085	.00080	.01005	.985
.05	1.002	.01059	.00035	.01024	.967
.0962	1.003	.01075	.00021	.01054	.939
.20	1.011	.01135	.00012	.01123	.882
<i>m</i> -Chlorobenzoic Acid					
Sodium <i>m</i> -chloro- benzoate					$f = \frac{0.00191}{C_{mHClB}}$
0.00212	0.997	0.00206	0.00014	0.00192	0.995
<i>p</i> -Chlorobenzoic Acid					
Sodium <i>p</i> -chloro- benzoate					$f = \frac{0.000275}{C_{pHClB}}$
0.000342	0.997	0.000343	0.000065	0.000278	0.989

^a The densities are given so that other workers can express the results in molality if that is preferred.

These results will be discussed in connection with the experiments on "salting-in." They are put in at this point to give the magnitude of the corrections in the experiments with the other salts given in Tables II to XI. It might be mentioned that the value for the solubility of *o*-chlorobenzoic acid at zero ion concentration, 0.00990 was obtained by the method of least squares for all the "salting-out" experiments (see Figs. 1 and 2). For *m*- and *p*-chlorobenzoic acids the corresponding values are 0.00191 and 0.000275.

Table II gives the results with potassium chloride. The values in column four were obtained as before with correction for the "salting-in" of the sodium salt.

The slopes of the potassium chloride lines in Figs. 1, 2 and 3 are equivalent to values of $k = 0.139, 0.142, 0.138$, respectively. The corresponding value for benzoic acid is 0.138.²

(6) K_c represents the classical, K_a the thermodynamic, dissociation constant.

TABLE II

SOLUBILITIES OF CHLOROBENZOIC ACIDS
IN POTASSIUM CHLORIDE SOLUTIONS

KCl moles per liter	Density, g. per cc.	Total acid, mole per liter	Mol. acid, mole per liter	"Salt- ing- out" con- stant
<i>o</i> -Chlorobenzoic Acid				
Solutions	0.01	molar in sodium salt.		
Correction = -0.00007				
0.1	1.002	0.01137	0.00961	0.128
.3	1.012	.01086	.00905	.130
.5	1.021	.01014	.00843	.139
1.0	1.042	.00861	.00719	.139
2.0	1.087	.00607	.00515	.142
<i>m</i> -Chlorobenzoic Acid				
Solutions	0.00212	molar in sodium salt.		
Correction = -0.00001				
0.2	1.007	0.00199	0.00179	0.147
.5	1.020	.00183	.00163	.136
.75	1.031	.00167	.00149	.143
1.0	1.042	.00158	.00141	.133
1.5	1.064	.00127	.00114	.148
<i>p</i> -Chlorobenzoic Acid				
Solutions	0.000342	molar in sodium salt.		
Correction = -0.000003				
0.5	1.020	0.000331	0.000238	0.129
1.0	1.041	.000273	.000197	.146
1.5	1.063	.000235	.000172	.136
2.0	1.086	.000206	.000153	.128
2.5	1.107	.000156	.000118	.147

TABLE III

SOLUBILITIES OF CHLOROBENZOIC ACIDS IN
SODIUM CHLORIDE SOLUTIONS

NaCl moles per liter	Density, g. per cc.	Total acid, mole per liter	Mol. acid, mole per liter	"Salt- ing- out" con- stant
o-Chlorobenzoic Acid				
Solutions	0.01 molar	in sodium salt.		
	Correction = -0.00007			
0.2	1.005	0.01094	0.00915	0.171
.5	1.017	.00966	.00801	.182
2.0	1.076	.00498	.00422	.185
Solutions	0.02 molar	in sodium salt.		
	Correction = -0.00013			
0.5	1.018	0.00907	0.00806	0.179
1.0	1.039	.00739	.00658	.178
m-Chlorobenzoic Acid				
Solutions	0.00212 molar	in sodium salt.		
	Correction = -0.00001			
0.5	1.017	0.00174	0.00155	0.180
.75	1.027	.00156	.00140	.180
1.0	1.039	.00139	.00124	.187
2.0	1.076	.00094	.00085	.176

Table III gives the results with sodium chloride. Here and in all other cases the hydrogen-ion concentrations were calculated by combining the thermodynamic dissociation constant with the K_c/K_a ratios for each concentration of each salt as determined by Kilpatrick and Riesch by a catalytic method.⁷ It seems reasonable to assume that the K_c/K_a ratios for the substituted benzoic acids are little different from the ratio for benzoic acid, in the given salt solution.⁸

Here and in Table IV it is shown that changing the buffer ratio makes no appreciable difference in the "salting-out" constant. In fact a comparison of the results for benzoic acid between buffered and unbuffered solutions showed that when proper corrections were applied the "salting-out" constants were the same in both cases. Studies in buffer solutions render the hydrogen-ion correction more certain.

The slopes of the lines for sodium chloride in Figs. 1 and 2 are 0.182 and

(7) Kilpatrick and Riesch, unpublished results.

(8) Larsson and Adell, *Z. physik. Chem.*, **167**, 342 (1931).

0.180. Berry² as well as Güntelberg and Schiödt⁹ find 0.176 for benzoic acid at 20°, while Larsson¹⁰ gives 0.177 at 18° and from the results of

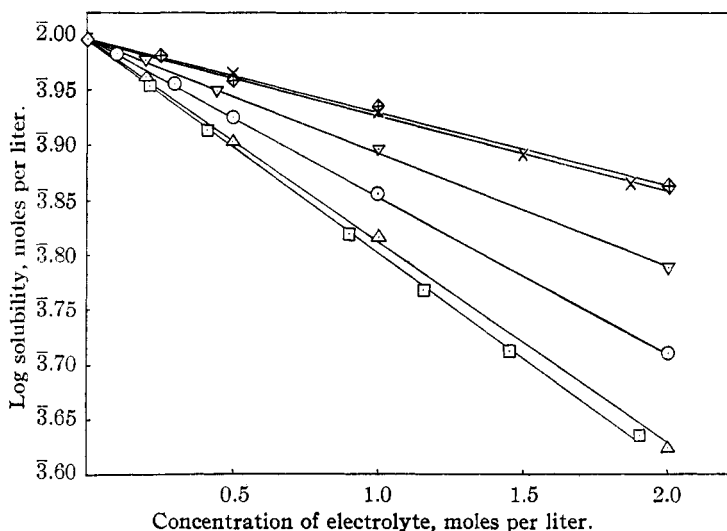


Fig. 1.—Solubilities of molecular *o*-chlorobenzoic acid in salt solutions: ×, NaClO₄; ∇, KBr; ○, KCl; △, NaCl; □, LiCl; ⊕, CsCl.

Kolthoff and Bosch¹¹ for benzoic acid at 25° values ranging from 0.181 to 0.199 are calculated.

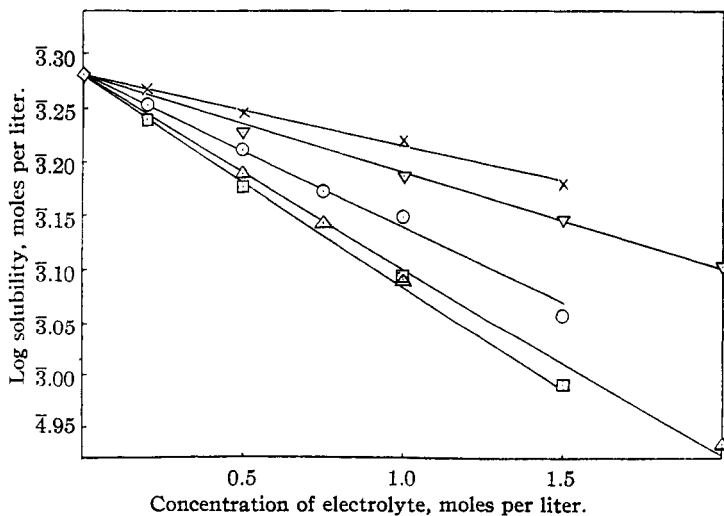


Fig. 2.—Solubilities of molecular *m*-chlorobenzoic acid in salt solutions: ×, NaClO₄; ○, KCl; △, NaCl; ∇, KBr; □, LiCl.

(9) Güntelberg and Schiödt, *Z. physik. Chem.*, **135**, 393 (1928).

(10) Larsson, *ibid.*, **153A**, 299 (1931).

(11) Kolthoff and Bosch, *J. Phys. Chem.*, **36**, 1685 (1932)..

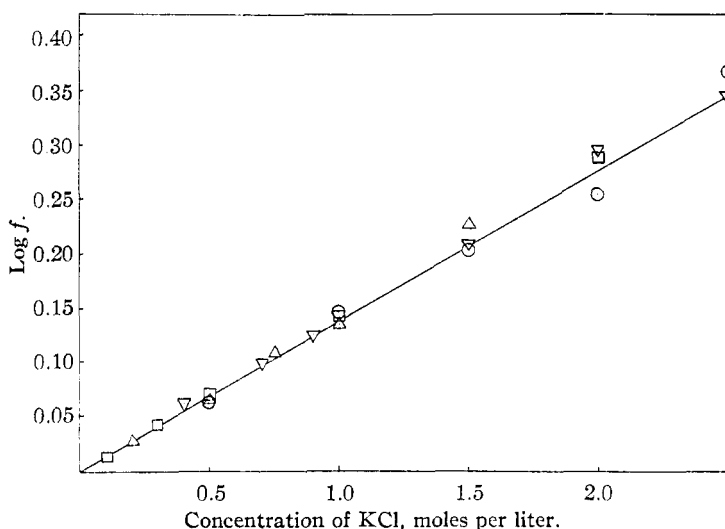


Fig. 3.—Activity coefficients of molecular benzoic, ortho, meta and para-chlorobenzoic acid in KCl solutions: ∇ , benzoic; $\triangle$, *m*-chlorobenzoic; $\square$, *o*-chlorobenzoic; $\circ$, *p*-chlorobenzoic.

TABLE IV

SOLUBILITIES OF CHLOROBENZOIC ACIDS
IN LITHIUM CHLORIDE SOLUTIONS

LiCl moles per liter	Density, g. per cc.	Total acid, mole per liter	Mol. acid, mole per liter	"Salt- ing- out" con- stant
<i>o</i> -Chlorobenzoic Acid				
Solutions 0.01 molar in sodium salt. Correction = -0.00007				
0.988	1.022	0.00797	0.00642	0.190
1.157	1.026	.00731	.00588	.195
1.458	1.032	.00645	.00518	.193
1.905	1.045	.00529	.00433	.189
Solutions 0.02 molar in sodium salt. Correction = -0.00013				
0.213	1.004	0.01018	0.00902	0.190
.415	1.007	.00939	.00822	.194
.901	1.020	.00763	.00665	.192
<i>m</i> -Chlorobenzoic Acid				
Solutions 0.00212 molar in sodium salt. Correction = -0.00001				
0.2	1.003	0.00196	0.00174	0.207
.5	1.009	.00172	.00151	.200
1.0	1.021	.00143	.00125	.185
1.5	1.034	.00112	.00098	.192

TABLE V

SOLUBILITIES OF CHLOROBENZOIC ACIDS
IN POTASSIUM BROMIDE SOLUTIONS

KBr moles per liter	Density, g. per cc.	Total acid, mole per liter	Mol. acid, mole per liter	"Salt- ing- out" con- stant
<i>o</i> -Chlorobenzoic Acid				
Solutions 0.01 molar in sodium salt. Correction = -0.00007				
0.2	1.017	0.01132	0.00949	0.091
.45	1.036	.01071	.00892	.100
1.0	1.083	.00943	.00789	.099
2.0	1.165	.00722	.00615	.103
<i>m</i> -Chlorobenzoic Acid				
Solutions 0.00212 molar in sodium salt Correction = -0.00001				
0.5	1.037	0.00190	0.00169	0.106
1.0	1.079	.00172	.00154	.093
1.5	1.121	.00156	.00140	.089
2.0	1.164	.00140	.00127	.089

The slopes of the lithium chloride lines in Figs. 1 and 2 are 0.193 and 0.193. Larsson finds for benzoic acid 0.192, while Kolthoff and Bosch give $\log f$ values from which constants may be obtained ranging from 0.186 to 0.213.

The slopes of the potassium bromide lines in Figs. 1 and 2 are 0.099 and 0.090. Larsson, reporting the solubilities of benzoic acid in three solutions, finds "salting-in" at the lowest concentration and gives the average value of k for the two others to be 0.070. Kolthoff and Bosch report activity coefficients which may be calculated to k values between 0.107 and 0.120. Haeseler's results are more complete and when corrected for the dissociated part give an average value of 0.113¹² at 25°.

TABLE VI

SOLUBILITIES OF CHLOROBENZOIC ACIDS
IN SODIUM PERCHLORATE SOLUTIONS

NaClO ₄ moles per liter	Density, g. per cc.	Total acid, mole per liter	Mol. acid, mole per liter	"Salt- ing- out" con- stant
<i>o</i> -Chlorobenzoic Acid				
Solutions 0.01 molar in sodium salt. Correction = -0.00007				
0.25	1.016	0.01152	0.00962	0.050
.50	1.038	.01096	.00922	.061
1.00	1.076	.00995	.00852	.065
1.50	1.113	.00895	.00781	.068
1.87	1.142	.00834	.00737	.068
<i>m</i> -Chlorobenzoic Acid				
Solutions 0.00212 molar in sodium salt. Correction = -0.00001				
0.2	1.012	0.00206	0.00185	0.064
.5	1.037	.00197	.00176	.067
1.0	1.075	.00183	.00166	.061
1.5	1.112	.00166	.00151	.069

TABLE VII

SOLUBILITIES OF CHLOROBENZOIC AND
BENZOIC ACIDS IN CESIUM CHLORIDE
SOLUTIONS

CsCl moles per liter	Density, g. per cc.	Total acid, mole per liter	Mol. acid, mole per liter	"Salt- ing- out" con- stant
<i>o</i> -Chlorobenzoic Acid				
Solutions 0.01 molar in sodium salt. Correction = -0.00007				
0.25	1.030	0.01134	0.00950	0.071
.50	1.062	.01094	.00910	.074
1.00	1.124	.01015	.00851	.066
2.00	1.245	.00854	.00730	.066
Benzoic Acid				
Solutions 0.01 molar in sodium salt. Correction = -0.0001				
0.2	1.024	0.0256	0.0252	0.108
.5	1.062	.0242	.0238	.093
1.0	1.124	.0223	.0220	.081

Here k for the sodium perchlorate lines is 0.065 in both Fig. 1 and Fig. 2. Larsson's value for benzoic acid at 18° is 0.050, while the results of Kolthoff and Bosch may be calculated to k values ranging from 0.051 to 0.080.

The slope of the cesium chloride line in Fig. 1 is 0.067. The two values given by Larsson for benzoic acid are "salting-in" constants indicating an increased solubility of molecular benzoic acid in solutions of cesium chloride. His calculations for k in 0.5 and 1.0 molar solutions are -0.008 and -0.009, respectively, at 18°. As this is the only case found in which there is a definite difference between the k values for *o*-chlorobenzoic acid and benzoic acid, solubility determinations were carried out with benzoic

(12) Haeseler. Dissertation, Columbia University, 1929.

acid in cesium chloride solutions at 25°. These values are given in the second part of Table VII.

The "salting-out" constant is 0.092, slightly higher than the values for *o*-chlorobenzoic acid and not in agreement with the values of Larsson for benzoic acid. The explanation is offered that while the activity coefficients seem to be independent of temperature for the case of marked decrease in solubility, this is not the case where the "salting-in" effect is playing a more important role.

In Figs. 1 and 2 it is seen that for the chlorides the order of decreasing solubility is as expected from the ion sizes, the greater effect being due to the smaller ion, *i. e.*, $\text{Li} > \text{Na} > \text{K} > \text{Cs}$. For the anions, however, in accordance with the theory one would expect that if the cations "salt-out" the anions would "salt-in" and although in this case the predominant effect is still "salting-out," a comparison of potassium bromide with potassium chloride and sodium perchlorate with sodium chloride shows this effect. We shall now turn to salts which definitely "salt-in" the chlorobenzoic acids.

"Salting-In" of Chlorobenzoic Acids.—The "salting-in" effect of sodium *o*-chlorobenzoate on *o*-chlorobenzoic acid has already been cited in Table I. A similar effect in the case of benzoic acid with sodium benzoate has been interpreted by Kolthoff and Bosch to be attributable to the formation of anions of double molecules of benzoic acid. The chief reason for not accepting compound formation as a general explanation is that potassium benzoate "salts-in" benzene and nitrobenzene, while potassium chloride "salts-out" these substances.¹³ A definite case of a general "salting-in" effect which must be attributed to the polar structure of the non-electrolyte is the "salting-in" of trinitrotriamminecobalt by potassium chloride.¹⁴

Table VIII gives the results for *o*- and *m*-chlorobenzoic acids and benzoic acid in sodium benzenesulfonate solutions.

The results indicate that equation (2) no longer holds. The k values are not the same as those found by Larsson. For benzoic acid in 0.01 molar buffer solutions containing 0.2, 0.5 and 1.0 mole of sodium benzenesulfonate, Larsson obtains k values of -0.134 , -0.117 and -0.120 (at 18°).

Table IX gives the results of solubility determinations of benzoic and *o*-chlorobenzoic acids in sodium *p*-toluenesulfonate solutions.

From Tables VIII and IX it is seen that the activity coefficient is apparently dependent on the buffer ratio. Table X gives the results with sodium β -naphthalenesulfonate as the solvent salt. Due to the slight solubility of this salt the results could not be extended above 0.2 molar.

(13) Private communication from P. M. Gross—from the Master's thesis of A. Whitenfish with J. H. Saylor and P. M. Gross.

(14) Brönsted, Delbanco and Volqvartz, *Z. physik. Chem.*, **162A**, 129 (1932).

TABLE VIII

SOLUBILITIES OF CHLOROBENZOIC AND BENZOIC ACIDS IN SODIUM BENZENE-SULFONATE SOLUTIONS

Sodium benzene-sulfonate moles/liter	Density, g. per cc.	Total acid, mole per liter	Mol. acid moles per liter	"Salt-ing-out" constant
<i>o</i> -Chlorobenzoic Acid				
Solutions 0.01 molar in sodium salt. Correction = -0.00007				
0.2	1.011	0.01248	0.01045	-0.116
.5	1.032	.01381	.01164	-.140
.7	1.048	.01506	.01286	-.162
1.0	1.068	.01728	.01523	-.187
Solutions 0.05 molar in sodium salt. Correction = -0.00033				
0.5	1.033	0.01285	0.01199	-0.166
1.0	1.070	.01671	.01588	-.205
<i>m</i> -Chlorobenzoic Acid				
Solutions 0.00212 molar in sodium salt. Correction = -0.00001				
0.2	1.010	0.00226	0.00202	-0.122
.5	1.031	.00250	.00225	-.138
1.0	1.067	.00310	.00285	-.174
Benzoic Acid				
Solutions 0.01 molar in sodium salt. Correction = -0.0001				
0.1	1.005	0.0274	0.0270	-0.079
.2	1.011	.0280	.0276	-.089
.5	1.033	.0308	.0304	-.120
1.0	1.068	.0393	.0389	-.167
Solutions 0.05 molar in sodium salt. Correction = -0.0005				
0.2	1.013	0.0284	0.0278	-0.100
.5	1.034	.0313	.0307	-.128
1.0	1.071	.0417	.0411	-.190

TABLE IX

SOLUBILITIES OF *o*-CHLOROBENZOIC AND BENZOIC ACIDS IN SODIUM *p*-TOLUENE-SULFONATE SOLUTIONS

Sodium <i>p</i> -toluene-sulfonate moles/liter	Density, g. per cc.	Total acid, mole per liter	Mol. acid, mole per liter	"Salt-ing-out" constant
<i>o</i> -Chlorobenzoic Acid				
Solutions 0.01 molar in sodium salt. Correction = -0.00007				
0.2	1.011	0.01334	0.01130	-0.287
.5	1.032	.01668	.01447	-.329
.7	1.048	.01980	.01754	-.355
1.0	1.066	.02715	.02483	-.399
Solutions 0.05 molar in sodium salt. Correction = -0.00033				
0.2	1.015	0.01248	0.01166	-0.355
.3	1.022	.01364	.01276	-.367
.5	1.035	.01636	.01549	-.389
.7	1.048	.01964	.01877	-.397
1.0	1.069	.02721	.02630	-.425
Benzoic Acid				
Solutions 0.01 molar in sodium salt. Correction = -0.0001				
0.2	1.014	0.0305	0.0301	-0.278
.5	1.035	.0378	.0373	-.298
1.0	1.066	.0620	.0616	-.366

Discussion

A general survey of the results with any of the acids indicates that for the same weak acid some salts "salt-out" while others "salt-in." In general, it would appear that for the carboxylic acids investigated, the anion of the solvent salt has very little if any "salting-out" effect, but rather that its general effect is to increase the solubility. This is interpreted to mean that the molecules of weak acid are oriented about the anion.

A comparison of the activity coefficients of the chlorobenzoic acids

TABLE X
SOLUBILITIES OF *o*-CHLOROBENZOIC AND BENZOIC ACIDS IN SODIUM β -NAPHTHALENE-SULFONATE SOLUTIONS

Sodium β -naphthalene sulfonate moles/liter	Density, g. per cc.	Total acid, mole per liter	Mol. acid, mole per liter	"Salting-out" constant
<i>o</i> -Chlorobenzoic Acid				
Solutions 0.01 molar in sodium salt.			Correction = -0.00007	
0.10	1.005	0.01382	0.01176	-0.747
.15	1.008	.01513	.01285	- .757
.20	1.010	.01693	.01432	- .802
Benzoic Acid				
Solutions 0.01 molar in sodium salt.			Correction = -0.0001	
0.10	1.005	0.0313	0.0309	-0.670
.20	1.013	.0385	.0380	- .784

with benzoic acid is of particular interest in that the molecular solubility of the most soluble acid (benzoic) is approximately ninety-five times greater than the least soluble acid (*p*-chlorobenzoic) and the dissociation constant of the strongest acid (*o*-chlorobenzoic) is approximately twenty times greater than the weakest acid (benzoic). Table XI gives a summary of the "salting-out" constants for the different acids.

TABLE XI
THE "SALTING-OUT" CONSTANTS FOR BENZOIC AND ORTHO-, META- AND PARA-CHLOROBENZOIC ACIDS

Salt	Benzoic	<i>o</i> -Chlorobenzoic	<i>m</i> -Chlorobenzoic	<i>p</i> -Chlorobenzoic
NaClO ₄	0.060 ^a	0.065	0.065	..
CsCl	.092 ^b	.067	..	..
KBr	.108 ^c	.099	.090	..
KCl	.138 ^d	.139	.142	0.138
NaCl	.177 ^e	.182	.180	..
LiCl	.192 ^f	.193	.193	.

^a Average value from Kolthoff and Bosch.

^b Larsson gives -0.009 and -0.008 at 18°. See Table VII.

^c Calculated from Haeseler's results (corrected).

^d From the results of Chase and Kilpatrick.

^{e, f} From Larsson.

From the table it is seen that in cases of "salting-out" the constant is practically the same for all four acids, that is, the activity coefficients of each acid are the same at the same concentration of a given salt. This is illustrated graphically for the case of potassium chloride as solvent salt in Fig. 3. Evidently this is a case in which a highly polar carboxyl group plays the predominating role in the "salting-in" process and the substitution of a chlorine atom in the phenyl group is without effect on the activity coefficient.

Summary

From determinations of the total solubility of the monochlorobenzoic acids in aqueous salt solutions the molecular solubilities and the activity coefficients have been obtained.

For the same weak acid some salts "salt-out" and others "salt-in." An explanation has been offered based on the work of Kruyt and Robinson.

The activity coefficients of the molecules of the monochlorobenzoic and benzoic acids are the same at corresponding concentrations of the same salt.

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The "Salting-out" and "Salting-in" of Weak Acids. II. The Activity Coefficients of the Molecules of Ortho, Meta and Para-Hydroxybenzoic Acids in Aqueous Salt Solutions¹

BY ARTHUR OSOL AND MARTIN KILPATRICK

In the preceding paper it was shown that for the monochlorobenzoic acids the activity coefficients of the molecular part of these acids were the same at corresponding concentrations of the same salt. The present paper deals with the activity coefficients of ortho, meta and para-hydroxybenzoic acids.

Experimental Part

The experimental method was essentially the same as that given in the preceding paper. The acids were purified by recrystallization and melted at 159, 201 and 214° for the ortho, meta and para acids, respectively. The total solubilities were 0.01598, 0.0706 and 0.0451 mole per liter, from which the molecular solubilities at zero ion concentration, calculated from the K_a and K_c/K_a ratios as before, were found to be 0.01217, 0.0683 and 0.0440 mole per liter for the ortho, meta and para-hydroxy acids, respectively. The corrections for the buffer salts are given in each table. Table I gives the results in potassium chloride solutions.

From Table I it is evident that the activity coefficients are not the same for the three acids as in the case of the monochloro substituted acids. The "salting-out" constants decrease in the order ortho ($k = 0.122$), meta ($k = 0.115$), para ($k = 0.095$) as compared with benzoic acid ($k = 0.138$). Table II gives the results with sodium chloride.

The slope of the line for *o*-hydroxybenzoic acid in sodium chloride solutions in Fig. 1 is 0.172 as compared with 0.177 for benzoic acid.

(1) Abstracted from the dissertation of Arthur Osol presented April 1, 1933, to the Faculty of the Graduate School of the University of Pennsylvania in partial fulfillment of the requirements for the degree of Doctor of Philosophy. Paper presented in part before the Washington meeting of the American Chemical Society, March, 1933.