

**OLARTEMOURE**

OLARTE MOURE & ASOCIADOS LTDA.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Señores

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

DIVISIÓN DE NUEVAS CREACIONES

E. \_\_\_\_\_ S. \_\_\_\_\_ D. \_\_\_\_\_

Re: Expediente No. 05-102.549

Solicitud de patente de invención titulada: "COMPUESTOS HETEROCÍCLICOS  
INMUNOMODULADORES"

Solicitante: MEDIGENE LIMITED

Nuestra Ref.: P2005/000092

**RESPUESTA AL OFICIO No. 02717 NOTIFICADO POR FIJACIÓN EN LISTA No. 53,**  
**DE FECHA 18 DE FEBRERO DE 2011**  
**(TERCER EXAMEN DE FONDO)**

CARLOS R. OLARTE, mayor de edad y vecino de Bogotá, identificado tal como aparece al pie de mi firma, en mi carácter de apoderado de la sociedad solicitante, me permito manifestar lo siguiente ante el auto emanado por ese Despacho, dentro del plazo legal previsto en el artículo 45 de la Decisión 486, en los siguientes términos:

1. En primer lugar, con el ánimo de brindar mayor claridad a la materia reivindicada, me permito presentar un **Capítulo Reivindicatorio Modificado**, que reemplaza en su totalidad al Capítulo Reivindicatorio presentado en respuesta al segundo examen de fondo, de fecha 23 de octubre de 2009.

Así entonces, el Capítulo Reivindicatorio Modificado contiene los siguientes cambios:

- se han eliminado las Reivindicaciones 7, 8 y 10 a 12;
- se han introducido las limitaciones de las antiguas Reivindicaciones 3, 4 y 9 en la nueva Reivindicación 1, restringiendo así los significados de los radicales X, R<sub>1</sub> y R<sub>7</sub>;
- en la nueva Reivindicación 1 se ha limitado el significado de los radicales Alq y Q.

Valga anotar que las modificaciones efectuadas al Capítulo Reivindicatorio cumplen a cabalidad con lo estipulado en el Artículo 34 de la Decisión 486, ya que éstas de ninguna manera implican una ampliación de la protección correspondiente a la divulgación contenida en la solicitud inicial; éstas corresponden a una franca limitación a la materia inicialmente reivindicada

2. a- El Examinador insiste en que los hidratos reclamados en la presente invención no encuentran soporte en el Capítulo Descriptivo.

b- Como lo mencioné en mi respuesta al segundo examen de fondo, en el presente caso, los hidratos de los compuestos de la presente invención se refieren a dioles germinales que son obtenidos por hidratación de aldehídos y cetonas ( $R_2C=O + H_2O \leftrightarrow R_2C(OH)_2$ ) en una reacción denominada hidratación hidrolítica, claramente, formados debido a la presencia de un grupo carbonilo en la estructura.

En el presente caso, la Reivindicación 1 se refiere a compuestos de Fórmula I, que tienen un núcleo dihidropirazolocinolino, y por lo tanto, corresponden a compuestos que contienen un grupo cetona. Cuando las cetonas se encuentran en soluciones acuosas se presenta un equilibrio entre la cetona y su hidrato, que corresponde a un diol germinal, de acuerdo con la reacción explicada anteriormente, y como se muestra en un extracto de libro “March’s Advanced Organic Chemistry” (Anexo 1). Dichos hidratos de cetonas se forman por la adición de agua en la función cetona, dando como resultado un diol germinal.

Para referencia adicional del Examinador, adjunto a este memorial el artículo “Carbonilamines and germinal diols in aqueous environmental organic chemistry” (Anexo 2), en donde se explican a profundidad estos hidratos y su formación.

De acuerdo con la anterior explicación y la definición de dioles germinales, en el presente caso, el término “hidrato” no denota o se refiere a todos los posibles compuestos que pueden contener agua en forma de complejos acuosos, es decir aquellos que contienen agua en la forma H<sub>2</sub>O (por

# OLARTEMOURE

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ejemplo, monohidratos, dihidratos, pentahidratos y similares), sino a hidratos correspondientes a dioles germinales de fórmula general  $R_2(C(OH)_2)$ , formados por una reacción de hidratación hidrolítica. Teniendo en cuenta la estructura de los compuestos de Fórmula I, cualquier persona medianamente versada en la materia entenderá los límites y alcance de la presente invención en lo que respecta a los hidratos.

3. a- El Examinador insiste en que el Capítulo Reivindicatorio no es claro ni conciso. El Examinador señala que en la definición de Alq se ha incluido el grupo ciano, y que persisten términos generales y ambiguos como “carbociclo  $C_{3-12}$ ”, “carbociclo  $C_{3-8}$ ”, “alquileo  $C_{1-12}$ ”, “alquileo  $C_{2-12}$ ”, “alquileo  $C_{2-12}$ ” o “anillo heterocíclico de 5-7 átomos”, así como sustituyentes muy amplios, tales como  $R_4$  y X. Por último, el Examinador proporciona una tabla en la que define los sustituyentes  $R_1$ ,  $R_3$ ,  $R_4$ ,  $R_6$ ,  $R_7$  Q y X que se encontrarían ilustrados en los ejemplos del Capítulo Descriptivo, y sugiere limitar la materia reivindicada a una generalización razonable de los compuestos ejemplificados.

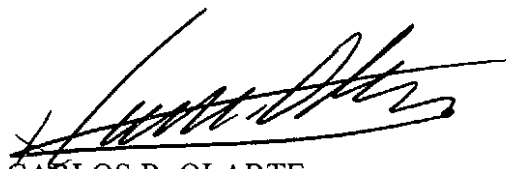
b- En primera medida, me permito señalar respetuosamente que la tabla proporcionada por el Examinador en su examen de fondo resulta algo confusa, ya que señala que el significado soportado por el Capítulo Descriptivo de  $R^6$  corresponde a un grupo  $-(Alq)_m-Q$  en donde  $m=0$ . Sin embargo, si los ejemplos ilustrados en el Capítulo Descriptivo ilustraran que el significado de “m” fuera exclusivamente 0, la columna bajo el título “Alq” no sería aplicable en la tabla realizada por el Examinador, ya que al “m” ser 0, el grupo “Alq” no existiría. De acuerdo con lo anterior, y según lo ilustrado en el Capítulo Descriptivo, se entiende que la tabla proporcionada por el Examinador proporciona soporte para “m” cuando es 0 o 1.

Aclarado lo anterior, considero superada la objeción de claridad, en tanto que el Capítulo Reivindicatorio de la presente invención se ha ajustado de manera que corresponde exactamente con la tabla proporcionada en el examen de fondo, es decir, se ha modificado el significado de los radicales  $R_1$ ,  $R_4$ ,  $R_6$ ,  $R_7$ , Alq, Q y X, según la amable sugerencia del Examinador.

Por último, agradezco la observación del Examinador respecto al término ciano en la definición del radical “Alq”. Dicho término fue eliminado del Capítulo Reivindicatorio Modificado adjunto.

4. Por todo lo anterior, considero que las objeciones presentadas por el Examinador en su examen de fondo No. 242 han sido resueltas y por consiguiente, solicito respetuosamente que el Despacho tenga por cumplidos los requisitos de patentabilidad y se proceda con la concesión de la patente.

Atentamente,



CARLOS R. OLARTE

C.C. No. 79.782.747 de Bogotá

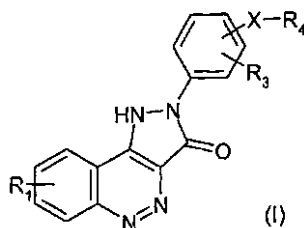
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Anexos:

- Capítulo Reivindicatorio Modificado;
- Anexo 1: Extracto del libro "*March's Advanced Organic Chemistry*". Smith M. y March J. Sexta Edición. Wiley-Interscience. A John Wiley & Sons Inc., publication. Páginas 2273 y 1261-1263.
- Anexo 2: Ubanski, Edward. "*Carbonilamines and germinal diols in aqueous environmental organic chemistry*". Journal of Chemical Education, vol. 77. Páginas 1644-1647. December 2000.

**CAPITULO REIVINDICATORIO MODIFICADO**  
**(Tercer Examen de Fondo)**

1. Un compuesto de la fórmula (I) o una sal o hidrato aceptable desde el punto de vista farmacéutico o veterinario del mismo:



caracterizado porque

$R_1$  representa independientemente H o F;

$R_3$  representa H;

$R_4$  representa  $-C(=O)NR_6R_7$  o  $-NHC(=O)NR_6R_7$  en donde:

$R_6$  representa un radical de la fórmula  $-(Alq)_m-Q$  en donde:

$m$  es 0 o 1;

Alq es:

alquileo  $C_1-C_9$  opcionalmente sustituido por uno o más grupos OH, oxo, F o ciano;

alquenileno  $C_3-C_{4,10}$  opcionalmente sustituido por uno o más grupos F;

-alquil  $C_{2-5}$ -O-alquilo  $C_{1-5,12}$  opcionalmente sustituido por uno o más grupos OH u oxo;

-alquil  $C_{2-4}$ -(O-alquil  $C_{1-2}$ )<sub>2</sub>;

-alquil  $C_{1-3}$ -S-alquilo  $C_{1-3}$ ;

-alquil  $C_2$ -NH-alquilo  $C_2$ ;

cicloalquileo  $C_{3-7}$  opcionalmente sustituido por uno o más grupos alquilo  $C_4$  u OH; y

fenileno opcionalmente sustituido por uno o más grupos F;

Q es H,  $-NH_2$ ,  $-N(\text{alquilo } C_{1-4})_2$ ,  $-N(\text{alquenilo } C_4)_2$ ,  $-NH\text{-alquilo } C_{1-5}$ ,  $-N(\text{alquileo } C_3)\text{cicloalquilo } C_5$ ,  $-NH\text{-ciclohexilo}$ ,  $-N\text{-metilciclohexilo}$ ,  $-NH\text{-fenilo}$ ,  $-N\text{-metilfenilo}$ ,  $-NH\text{-naftilo}$ ,  $-NH\text{-piperidinilo}$ ,  $-NH\text{-C(O)-O-bencilo}$ ,  $-NH\text{-C(O)-O-alquilo } C_{1,4}$ ,  $-N\text{-alquil } C_1\text{C(O)-O-alquilo } C_4$ ,  $-NH\text{-C(O)-O-bencilo}$ ,  $-\text{pirrolidin-1-ilo}$ ,  $-\text{piperazin-1-ilo}$ ,  $-\text{morfolin-4-ilo}$ ,  $-\text{tiomorfolin-4-ilo}$ ,  $\text{piperidin-1-ilo}$ ,  $\text{azepan-1-ilo}$ ,  $-\text{imidazolin-1-ilo}$ ; donde el  $NH\text{-piperidinilo}$  está opcionalmente sustituido por metilo, y los grupos  $-\text{pirrolidin-1-ilo}$ ,  $-\text{piperazin-1-ilo}$ ,  $-\text{morfolin-4-ilo}$ ,  $-\text{tiomorfolin-4-ilo}$ ,  $\text{piperidin-1-ilo}$ ,  $\text{azepan-1-ilo}$ ,  $-\text{imidazolin-1-ilo}$  están opcionalmente sustituidos por oxo, metilo, bencilo,  $-\text{C(O)-O-butilo}$ ,  $-\text{CF}_3$ ;

$R_7$  es H;

o  $R_6$  y  $R_7$ , junto con el átomo de N al que se encuentran unidos, forman un anillo piperidinilo o azepanilo, que se encuentra opcionalmente sustituido por uno o más grupos metilo;

X representa un enlace.

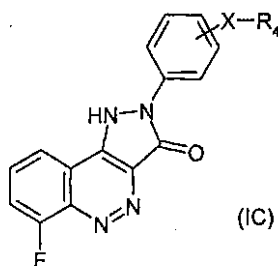
2. Un compuesto de conformidad con la Reivindicación 1, caracterizado porque el radical  $R_4X$ - está en la posición 4 del anillo de fenilo.

3. Un compuesto de conformidad con cualquiera de las reivindicaciones anteriores, caracterizado porque  $R_4$  representa  $-C(=O)NR^6R^7$ , en donde  $R^6$  y  $R^7$  son como se definiera en la Reivindicación 1.

4. Un compuesto de conformidad con cualquiera de las reivindicaciones anteriores, caracterizado porque  $R_4$  representa  $-NHC(=O)NR_7R_6$ , en donde  $R_6$  y  $R_7$  son como se definiera en la Reivindicación 1.

5. Un compuesto de conformidad con la Reivindicación 1, caracterizado porque  $R_1$  es F, en la posición 6 del sistema de anillos de 3-oxo-1,3-dihidro-2H-pirazolo[4,3-c]cinnolin-2-ilo.

6. Un compuesto de la fórmula (IC) o una sal o hidrato aceptable desde el punto de vista farmacéutico o veterinario del mismo:

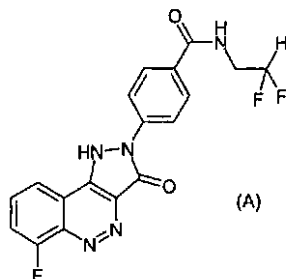


caracterizado porque X y  $R^4$  son como se especifica de conformidad con la Reivindicación 1.

7. Un compuesto de conformidad con la Reivindicación 6, caracterizado porque el radical  $R_4X$ - está en la posición 4 del anillo de fenilo.

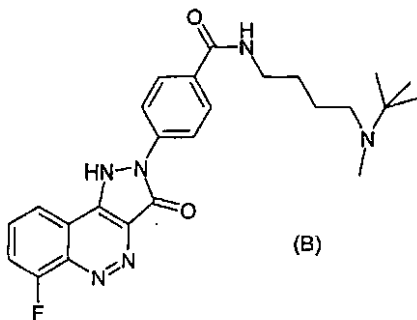
8. Un compuesto de conformidad con la Reivindicación 6 o la Reivindicación 7, caracterizado porque X es un enlace y  $R_4$  es  $-C(=O)NR_6R_7$ , en donde  $R_6$  y  $R_7$  son como se especifica en la Reivindicación 1.

9. El compuesto de conformidad con la Reivindicación 1 caracterizado porque es 4-(6-fluoro-3-oxo-1,3-dihidro-pirazolo[4,3-c]cinnolin-2-il)-N-(2,2-difluoro-etilil)-benzamida, de la fórmula (A):



o una sal o hidrato aceptable desde el punto de vista farmacéutico o veterinario del mismo.

10. El compuesto de conformidad con la Reivindicación 1 caracterizado porque es N-[3-(terc-butil-metil-amino)-butil]-4-(6-fluoro-3-oxo-1,3-dihidro-pirazolo[4,3-c]cinnolin-2-il)-benzamida, de la fórmula (B):



o una sal o hidrato aceptable desde el punto de vista farmacéutico o veterinario del mismo.

11. Una composición farmacéutica o veterinaria, caracterizada porque comprende un compuesto de conformidad con cualquiera de las Reivindicaciones 1 a 10, junto con un excipiente o portador

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# MARCH'S ADVANCED ORGANIC CHEMISTRY

REACTIONS, MECHANISMS,  
AND STRUCTURE

SIXTH EDITION

**Michael B. Smith**  
Professor of Chemistry

**Jerry March**  
Professor of Chemistry

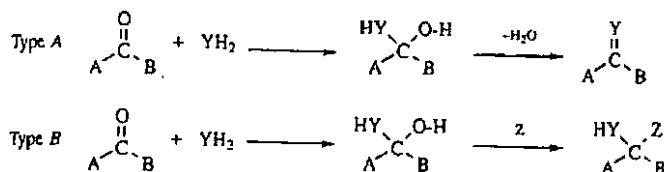


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## REACTIONS

Many of the reactions in this chapter are simple additions to carbon-hetero multiple bonds, with the reaction ending when the two groups have been added. But in many other cases subsequent reactions take place. We will meet a number of such reactions, but most are of two types:



In type A, the initially formed adduct loses water (or, in the case of addition to  $\text{C}=\text{NH}$ , ammonia, etc.), and the net result of the reaction is the substitution of  $\text{C}=\text{Y}$  for  $\text{C}=\text{O}$  (or  $\text{C}=\text{NH}$ , etc.). In type B, there is a rapid substitution, and the OH (or  $\text{NH}_2$ , etc.) is replaced by another group Z, which is often another YH moiety. This substitution is in most cases nucleophilic, since Y usually has an unshared pair and  $\text{S}_{\text{N}}1$  reactions occur very well on this type of compound (see p. 482), even when the leaving group is as poor as OH or  $\text{NH}_2$ . In this chapter, we will classify reactions according to what is initially adding to the carbon-hetero multiple bond, even if subsequent reactions take place so rapidly that it is not possible to isolate the initial adduct.

Most of the reactions considered in this chapter can be reversed. In many cases, we will consider the reverse reactions with the forward ones, in the same section. The reverse of some of the other reactions are considered in other chapters. In still other cases, one of the reactions in this chapter is the reverse of another (e.g., 16-2 and 16-13). For reactions that are reversible, the principle of microscopic reversibility (p. 309) applies.

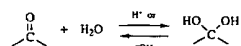
First, we will discuss reactions in which hydrogen or a metallic ion (or in one case phosphorus or sulfur) adds to the heteroatom and second reactions in which carbon adds to the heteroatom. Within each group, the reactions are classified by the nature of the nucleophile. Additions to isocyanides, which are different in character, follow. Acyl substitution reactions that proceed by the tetrahedral mechanism, which mostly involve derivatives of carboxylic acids, are treated at the end.

## REACTIONS IN WHICH HYDROGEN OR A METALLIC ION ADDS TO THE HETEROATOM

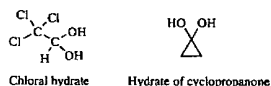
A. Attack by OH (Addition of  $\text{H}_2\text{O}$ )

## 16-1 The Addition of Water to Aldehydes and Ketones: Formation of Hydrates

## O-Hydro-C-hydroxy-addition



The adduct formed upon addition of water to an aldehyde or ketone is called a hydrate or gem-diol.<sup>36</sup> These compounds are usually stable only in water solution and decompose on distillation; that is, the equilibrium shifts back toward the carbonyl compound. The position of the equilibrium is greatly dependent on the structure of the hydrate. Thus, formaldehyde in water at 20°C exists 99.99% in the hydrated form, while for acetaldehyde this figure is 58%, and for acetone the hydrate concentration is negligible.<sup>37</sup> It has been found, by exchange with <sup>18</sup>O, that the reaction with acetone is quite rapid when catalyzed by acid or base, but the equilibrium lies on the side of acetone and water.<sup>38</sup> Since methyl, a +I group, inhibits hydrate formation, it may be expected that electron-attracting groups would have the opposite effect, and this is indeed the case. The hydrate of chloral (trichloroacetaldehyde)<sup>39</sup> is a stable crystalline substance. In order for it to revert to chloral, <sup>-</sup>OH or H<sub>2</sub>O must leave; this is made difficult by the electron-withdrawing character of the Cl<sub>3</sub>C group. Some other<sup>40</sup> polychlorinated and polyfluorinated



aldehydes and ketones<sup>41</sup> and α-keto aldehydes also form stable hydrates, as do cyclopropanones.<sup>42</sup> In the last case,<sup>43</sup> formation of the hydrate relieves some of the I strain (p. 399) of the parent ketone.

<sup>36</sup>For reviews, see Bell, R.P. *The Proton in Chemistry*, 2nd ed., Cornell University Press, Ithaca, NY, 1973, pp. 183–187; *Adv. Phys. Org. Chem.* **1966**, *4*, 1; Le Hénaff, P. *Bull. Soc. Chim. Fr.* **1947**, 4687.

<sup>37</sup>Bell, R.P.; Clunie, J.C. *Trans. Faraday Soc.* **1952**, *48*, 439. See also, Bell, R.P.; McDougall, A.O. *Trans. Faraday Soc.* **1960**, *56*, 1281.

<sup>38</sup>Cohn, M.; Urey, H.C. *J. Am. Chem. Soc.* **1938**, *60*, 679.

<sup>39</sup>For a review of chloral, see Lukitskii, F.I. *Chem. Rev.* **1975**, *75*, 259.

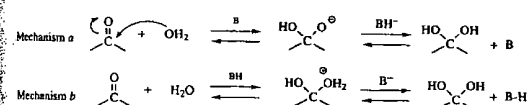
<sup>40</sup>For a discussion, see Schulman, E.M.; Bonner, O.D.; Schulman, D.R.; Laskovics, F.M. *J. Am. Chem. Soc.* **1976**, *98*, 3793.

<sup>41</sup>For a review of addition to fluorinated ketones, see Gambaryan, N.P.; Rokhlina, B.M.; Zeifman, V.Y.; Ching-Yun, C.; Krutyants, I.L. *Angew. Chem. Int. Ed.* **1966**, *5*, 947.

<sup>42</sup>For other examples, see Krois, D.; Lehner, H. *Monatsh. Chem.* **1982**, *113*, 1019.

<sup>43</sup>Turro, N.J.; Hammond, W.B. *J. Am. Chem. Soc.* **1967**, *89*, 1028; Schaafsma, S.E.; Steinberg, H.; Boer, T.J. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 651. For a review of cyclopropanone chemistry, see Wasserman, H.H.; Clark, G.M.; Turley, P.C. *Top. Curr. Chem.* **1974**, *47*, 73.

The reaction is subject to both general-acid and general-base catalysis; the following mechanisms can be written for basic (B) and acidic (BH) catalysis, respectively.<sup>44</sup>



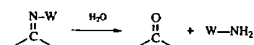
In mechanism a, as the H<sub>2</sub>O attacks, the base pulls off a proton, and the net result is addition of <sup>-</sup>OH. This can happen because the base is already hydrogen bonded to the H<sub>2</sub>O molecule before the attack. In mechanism b, because HB is already hydrogen bonded to the oxygen of the carbonyl group, it gives up a proton to the oxygen as the water attacks. In this way, B and HB accelerate the reaction even beyond the extent that they form <sup>-</sup>OH or H<sub>3</sub>O<sup>+</sup> by reaction with water. Reactions in which the catalyst donates a proton to the electrophilic reagent (in this case the aldehyde or ketone) in one direction and removes it in the other are called class c reactions. Reactions in which the catalyst does the same to the nucleophilic reagent are called class n reactions.<sup>45</sup> Thus the acid-catalyzed process here is a class c reaction, while the base catalyzed process is a class n reaction.

For the reaction between ketones and H<sub>2</sub>O<sub>2</sub>, see 17-37.

There are no OS references, but see OS VIII, 597, for the reverse reaction.

16-2 Hydrolysis of the Carbon-Nitrogen Double Bond<sup>46</sup>

Oxo-de-alkylimino-bisubstitution, and so on



Compounds containing carbon–nitrogen double bonds can be hydrolyzed to the corresponding aldehydes or ketones.<sup>47</sup> For imines (W = R or H) the hydrolysis is easy and can be carried out with water. When W = H, the imine is seldom stable enough for isolation, and in aqueous media hydrolysis usually occurs *in situ*, without isolation. The hydrolysis of Schiff bases (W = Ar) is more difficult and requires

<sup>46</sup>Bell, R.P.; Rand, M.H.; Wynne-Jones, K.M.A. *Trans. Faraday Soc.* **1956**, *52*, 1093; Pocker, Y. *Proc. Chem. Soc.* **1960**, 17; Sørensen, P.E.; Jencks, W.P. *J. Am. Chem. Soc.* **1987**, *109*, 4675. For a comprehensive treatment, see Lowry, T.H.; Richardson, K.S. *Mechanism and Theory in Organic Chemistry*, 3rd ed., Harper and Row, NY, **1987**, pp. 662–680. For a theoretical treatment see Wolfe, S.; Kim, C.-K.; Yang, K.; Weinberg, N.; Shi, Z. *J. Am. Chem. Soc.* **1995**, *117*, 4240.

<sup>47</sup>Jencks, W.P. *Acc. Chem. Res.* **1976**, *9*, 425.

<sup>48</sup>For a review, see Khoee, S.; Ruoho, A.E. *Org. Prep. Proceed. Int.* **2003**, *35*, 527.

<sup>49</sup>The proton affinities of imines have been determined, see Hammerum, S.; Sølting, T.I. *J. Am. Chem. Soc.* **1999**, *121*, 6002.



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**Carbinolamines and Geminal Diols in Aqueous  
Environmental Organic Chemistry**

Edward T. Urbansky

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# Carbinolamines and Geminal Diols in Aqueous Environmental Organic Chemistry<sup>†</sup>

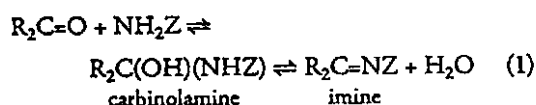
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The beginning environmental chemist or environmental scientist with a bachelor's degree most likely has taken one or two courses of organic chemistry. In general, the reactions and mechanisms studied will have been staged in organic solvents: ethers, alcohols, ketones, hydrocarbons, halogenated hydrocarbons, etc. While these solvents are sometimes encountered as discrete phases in environmental sites (e.g., dense nonaqueous phase liquids or DNAPLs), most environmental chemistry takes place in water or in its presence—very much unlike the conditions of a Grignard reaction, for example. The traditional organic chemistry sequence is not intended to prepare students for careers in environmental chemistry and may mislead them. What is generally true in an organic solvent may not apply at all in an aqueous solution. Both courses and texts tend to emphasize synthetic utility, and exercises are geared to promote synthesis reasoning. This approach has served organic chemists well, and no curriculum can cover every nuance. Thus, it falls to teachers of environmental chemistry to treat aqueous organic chemistry.

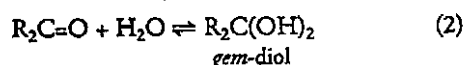
## Carbinolamines and Geminal Diols

*Carbinolamines* or *hemiaminals* form as intermediates in the reactions of aldehydes and ketones with ammonia and amines. For primary amines, this often leads to the formation of an imine (eq 1), the most stable of which are the Schiff bases (which usually have at least one aryl R or Z group).



Carbinolamines are presented only as short-lived reaction intermediates in the formation of imines (including oximes, hydrazones, and semicarbazones) (1–3). In fact, Fessenden and Fessenden refer to the carbinolamine only as “an unstable addition product” (2).

Geminal or *gem* diols form from a hydrolytic hydration reaction of aldehydes or ketones (usually with electronegative moieties on R), as shown in eq 2,



where R can be alkyl, aryl, or hydrogen and is often substituted, such as  $-CCl_3$ . In their coverage of aldehyde and ketone reactions, three popular sophomore-level organic chemistry textbooks discuss these species (1–3). Geminal diols are presented as novelties of organic chemistry, exceptions to the rule of stability of the C=O double bond. Each textbook presents

several examples with hydrolytic hydration reaction equilibrium constants (including the favorite example of a Mickey Finn), but Carey is the only one to solidly cover the kinetics of dehydration and hydration, including specific acid and base catalyses (3).

Considerably more discussion of substitution–addition reactions of aldehydes and ketones focuses on the products formed when alcohols act as nucleophiles to give hemiacetals, acetals, hemiketals, and ketals. In water, however, these compounds are usually hydrolyzed. In fact, 2,2-dimethoxypropane (acetone dimethyl ketal) is specifically used as a water scavenger (4). Other dialkyl ketals can also be used in this fashion. While acetals and ketals may serve as protecting groups during synthesis in organic solvents, they generally would not survive in aqueous solution. Consequently, much of this synthetically useful chemistry finds little applicability in environmental science.

It is unfortunate that the solvent is often not explicitly given in many of the reactions presented in sophomore organic chemistry textbooks, for it would be useful for students to see how infrequently water or water-containing solutions are used as solvents in synthesis. Although it may be argued that students realize this, it cannot be argued that they necessarily understand what would happen if water were to replace the solvent of choice. In environmental chemistry, on the other hand, water is the most common and most abundant solvent.

## Occurrence of Carbinolamines and Geminal Diols

### Evidence for Carbinolamines and Geminal Diols

Despite the oft-reported instability of carbinolamines, they are sufficiently stable to be observed by <sup>1</sup>H NMR spectrometry (5–10), and they have been observed by mass spectrometry (8, 10) as well. Furthermore, these intermediates can build up in sufficient quantity to alter reaction kinetics (9, 10). A substantial body of literature exists on carbinolamine formation (5–23), and it has been the focus of physical organic chemistry studies of the Hammond postulate (12, 15), a discussion of which is beyond the scope of this work. Although carbinolamines are generally not isolable from solution, some, for example, 2-[(acetamido)(hydroxo)methyl]-1-methylpyridinium iodide, have been isolated (17). Isolability should not be regarded as a criterion of stability, however, for many chemical species can exist only in solution.

Any aldehyde or ketone that can form a gem diol is more hydrophilic owing to increased hydrogen bonding and is more massive because a water molecule has been incorporated into its constitution. Under common conditions, the aldehydes are converted to the geminal diols: for example, 0.05 mol% CH<sub>2</sub>O, 99.95% H<sub>2</sub>C(OH)<sub>2</sub>; 43.5% CH<sub>3</sub>CHO, 56.5% CH<sub>3</sub>CH(OH)<sub>2</sub>; <0.01% CCl<sub>3</sub>CHO, >99.99% CCl<sub>3</sub>CH(OH)<sub>2</sub>; 58.5% CH<sub>3</sub>CH<sub>2</sub>CHO, 41.5% CH<sub>3</sub>CH<sub>2</sub>CH(OH)<sub>2</sub> (29). In

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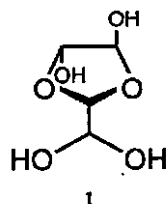
addition to the equilibria, the kinetics and mechanisms of the hydrolytic hydration of methanal (24–35) and other small aldehydes (36–38), including trichloroethanal, have been studied extensively.

### Naturally Occurring Species and Disinfection Byproducts

Several short-chain oxo-containing compounds are formed as ozonation byproducts (OBPs) from the disinfection of drinking water supplies (39, 40). Methanal is ubiquitous and results from natural processes, in addition to anthropogenic ones. Although the very low concentrations of the nonhalogenated compounds that occur in potable water supplies have not been implicated in any adverse health effects, they can serve as nutrients for microbes in the distribution system. Some chlorinated aldehydes and ketones are found as chlorination byproducts (CBPs), for instance, 2,2,2-trichloroethane-1,1-diol (39). There are two important consequences of the hydrophilicity associated with gem diol formation: lower volatility and reduced partitioning into organic solvents. Because these compounds are quantitated by extraction into organic solvents, such as *t*-butyl methyl ether (41, 42), this behavior raises the lower limit of detection relative to what would be expected for the aldehydes.

Nonetheless, these compounds remain sufficiently volatile that air-stripping (a treatment process used to purge volatile compounds from water) can remove them. On a laboratory scale, monoaldehydes of 1–4 carbons can be sparged away with a stream of argon or nitrogen gas. However, this process is not efficient and air-stripping methanal (methanediol) takes longer than would be predicted because of the hydrophilicity of the diol.

When two oxo groups are present, the process has minimal effect. Ethanedial (glyoxal) and 2-oxopropanal (methyl glyoxal or pyruvaldehyde) are not removed by sparging with an inert gas. Ethanedial actually exists as mixture of gem diols and cyclic ethers, such as ethane-1,1,2,2-tetraol,  $\text{CH}(\text{OH})_2\text{CH}(\text{OH})_2$ , or (4*S*,5*S*)-1,3-dioxo-2-dihydroxymethylcyclopentane-4,5-diol, **1** (43–45).



### Derivatization in Environmental Analytical Chemistry

Derivatives (hydrazones, oximes, and semicarbazones) are framed in terms of identification. Melting points and other properties of derivatives distinguish carbonyl compounds, and lab manuals tabulate these (46). In environmental chemistry, oximes and hydrazones are studied by quantitative instrumental techniques. Dinitrophenylhydrazone concentrations can be measured by liquid chromatography with UV detection (47), gravimetry (48, 49), or other techniques (49–51). In drinking water, *O*-(2,3,4,5,6-pentafluorobenzyl)oximes of carbonyl compounds are determined by gas chromatography with electron-capture detection (GC-ECD) (52–68). These include

the  $\alpha$ -oxocarboxylates, which occur as ozonation byproducts (39, 63–66, 70). *O*-(2,3,4,5,6-Pentafluorobenzyl)oxylamine derivatization has also been applied to determination of oxo compounds in other matrices (69).

Carbinolamines are intermediates in the formation of the derivatives; accordingly, their stability and lability influence derivatization. In water, the range of pH allows for varying protonation; consequently, derivatization rarely progresses to completion and perhaps cannot. Geminal diol formation, too, can interfere in this process. It is generally accepted that the initial nucleophilic attack of a derivatizing agent occurs at the carbonyl carbon as opposed to an  $\text{S}_{\text{N}}2$  process at a tetraligated gem diol (11–15). Tying up carbonyls as the unreactive gem diols therefore reduces the derivatization rate. The kinetics can be fairly complicated, with general acid- and base-assisted steps (10, 11–15). This may explain some of the problems in analyzing dihydroxopropanedioate (oxopropanedioate) (70). Because this species exists >99.9 mol% as the gem diol (71), the rate of derivatization should be reduced. A rapid equilibrium step or a reversible reaction must occur first. Either would reduce the concentration of the reactant, the 2-oxo species.

### Consequences and Conclusions

Any aqueous process whereby an aldehyde or ketone undergoes nucleophilic substitution can be expected to have some effects from the stability of carbinolamines and gem diols imparted by the water (72). As summarized above, a significant body of literature exists on the role of these compounds in aqueous organic chemistry. Nevertheless, carbinolamines are still commonly regarded as short-lived intermediates and gem diols as exceptions by sophomore organic chemistry textbooks (1–3), and thus students come to view them that way. In environmental applications, however, these species are ubiquitous and may dominate—or at least alter—the observable chemistry. For example, carbinolamines play key roles in the formation of cyanogen chloride from methanal and chloramine (10).

Even in the field of drinking water chemistry, these species have been largely ignored. No effort has been made to exploit carbinolamine reaction kinetics or imine formation in analytical chemistry, such as adding arylamines as catalysts or adjusting pH, based on past reports (14, 22, 73, 74). Such modifications could lead to improved analytical methods, with advantages in convenience (shorter time for oximation) or lower limits of detection and are worthy of exploration.

Four aldehydes dominate DBP studies: methanal, ethanal, ethanedial, and oxopropanal. Ethanal and oxopropanal experience some degree of hydration, but methanal and ethanedial are >99% hydrated in aqueous solution. Geminal diol stability usually decreases with increasing size of substituent and increases with increasing electronegativity of substituent moieties; practical consequences may be kinetic or thermodynamic. Stable gem diols and hemiaminals are readily found in environmental chemistry applications, but only graduate texts delve deeply into the behavior of these compounds (75–77). Ideally, future sophomore texts will include environmental application notes; for now, it is hoped that this work illuminates the significance of geminal diols and carbinolamines in aqueous environmental organic chemistry.

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