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## CONTENTS

- Andrew Gelling, John C. Jeffery, David C. Povey, Michael J. Went 349 Formation of Novel Bidentate and Crown Thioether Ligands *via* Dicobalt Alkyne Complexes
- Mark F. Beatty, Clive Jennings-White, Mitchell A. Avery 351 Stereocontrolled Synthesis of (2*S*, 3*S*, 8*S*, 9*S*)-3-Amino-9-methoxy-2,6,8-trimethyl-10-phenyldeca-4*E*,6*E*-dienoic Acid (ADDA),<sup>1</sup> the Characteristic Amino Acid of Microcystins and Nodularin
- José Barluenga, Miguel Tomás, Alfredo Ballesteros, Jian-She Kong, Santiago García Granda, Enrique Pérez-Carreño 353 A New Class of Fused 1,4-Diazepines: Synthesis of Substituted 8,8a-Dihydrofuro[2,3-*b*][1,4]diazepin-2-ones
- Jeffrey H. Byers, Thomas G. Gleason, Kyle S. Knight 354 Hexenyl Radical Cyclization *via* Phenyl Selenide Transfer
- Arunabha Datta, Ashok R. Saple, Ravindra Y. Kelkar 356 Effect of Zinc Incorporation on the Structure of the Catalyst Precursor (VO)<sub>2</sub>H<sub>4</sub>P<sub>2</sub>O<sub>9</sub>
- T. Stanley Cameron, Robert C. Haddon, Saba M. Mattar, Simon Parsons, Jack Passmore, Arthur P. Ramirez 358 The Synthesis, Characterization, X-Ray Crystal Structure and Solution ESR Spectrum of the Paramagnetic Solid, 4,5-Bis(trifluoromethyl)-1,2,3-trithiolium Hexafluoroarsenate: Implications for the Identity of '1,2-Dithiete' Cations (η<sup>5</sup>-C<sub>5</sub>H<sub>4</sub>SiMe<sub>3</sub>)<sub>3</sub>UH: The First Stable Organouranium(IV) Hydride
- Jean-Claude Berthet, Jean-François Le Maréchal, Michel Ephritikhine 360 Carboxy to Ketone Dimeric and Catemeric Hydrogen Bonding in a Keto Acid Phosphorane: X-Ray Structure of 6-Ethoxycarbonyl-5-oxo-6-(triphenylphosphoranylidene)hexanoic Acid
- Andrew D. Abell, John Trent, Ward T. Robinson 362 Tschernichite, the Mineral Analogue of Zeolite Beta
- Joseph V. Smith, Joseph J. Pluth, Russell C. Boggs, Donald G. Howard 363 A New Synthetic Route to Polyheteroarene-divinylbenzenes
- R. Galarini, A. Musco, R. Pontellini, A. Bolognesi, S. Destri, M. Catellani, M. Mascherpa, G. Zhuo 364 Syntheses of Linked Ruthenium and Osmium Carbonyl Clusters containing a Bridging Oxalato Ligand: X-Ray Structures of [(Os<sub>3</sub>(μ-H)(CO)<sub>10</sub>)<sub>2</sub>(C<sub>2</sub>O<sub>4</sub>)] and [(Ru<sub>5</sub>(μ-H)C(CO)<sub>14</sub>)<sub>2</sub>(C<sub>2</sub>O<sub>4</sub>)]
- Brian F. G. Johnson, Jack Lewis, Paul R. Raithby, Vijay P. Saharan, Wing Tak Wong 365 Reductive Aggregation of an Organorhenium Oxide: an Unusual Metal Chain Structure
- Wolfgang A. Herrmann, Rolf W. Albach, Joachim Behm 369 The Kinetics of the Quantitative, Symmetry Allowed, Reverse Electron Demand Cycloadditions of the Pseudo-1,3-Dipole SNS<sup>+</sup> with Alkynes and Nitriles; the Preparation and X-Ray Crystal Structures of NCCSNSCHAsF<sub>6</sub> and SNSNC-CNSNS(AsF<sub>6</sub>)<sub>2</sub>: the Precursor to a New Class of S<sub>2</sub>N<sub>2</sub>C-CN<sub>2</sub>S<sub>2</sub><sup>n+</sup> (n = 0,1,2) Bicyclics
- Simon Parsons, Jack Passmore, Melbourne J. Schriver, Peter S. White 372 From *N*-Nitroacetylproline to Leucylproline
- Sulur G. Manjunatha, Srinivasachari Rajappa 373 Rate-accelerating Metal Ion Effects on Decarboxylation of α-Keto Acids by a Thiazolium Ion bearing a Metal Binding Site
- Tatsuya Nabeshima, Kazuhiko Moriyama, Yumihiko Yano 375 The Formation of Aryltetralin Derivatives in the Photolysis of Two *trans*-Cinnamoyl Moieties at Both Ends of a Polyethylene Glycol Chain in the Presence of Lithium Perchlorate
- Masaru Kimura, Masahiko Shimoyama, Shiro Morosawa 376 Stereoselective Galactosyl Transfer to *cis*-Cyclohexa-3,5-diene-1,2-diol
- David H. G. Crout, David A. MacManus, Peter Critchley 378 The Stereocontrolled Claisen Rearrangement of Tertiary Allylic Sulphone Esters: Stereoselective Formation of Trisubstituted Double Bonds
- Alan H. Davidson, Nick Eggleton, Ian H. Wallace 380 Synthesis of a Novel Acceptor Substrate for a Mannosyl Transferase
- Sabine L. Flitsch, James P. Taylor, Nicholas J. Turner

- Luciano Lattuada, Emanuela Licandro, Stefano Maiorana, Antonio Papagni 437 2-Methyl-4-alkenyl-2,3-dihydrofurans by Cleavage of the Metal-Carbon Double Bond in  $\alpha,\beta$ -Unsaturated 2-Oxacyclopentylidene Pentacarbonyl Chromium Complexes
- Nicolaas J. R. van Elkema Hommes, Freidrich Bickelhaupt, Gerhard W. Klumpp 438 Dilithium Diphenylmethanediide; Generation, Redox Relationship with Lithium Chlorodiphenylmethanide, Implication with regard to Aggregation
- J. F. Bartoli, O. Brigaud, P. Battioni, D. Mansuy 440 Hydroxylation of Linear Alkanes Catalysed by Iron Porphyrins: Particular Efficacy and Regioselectivity of Perhalogenated Porphyrins
- Michel A. Petit, Marcel Bouvet, Didier Nakache 442 Electrosynthesis of a New Molecular Semiconductor: Lithium Naphthalocyanine Radical
- Masazo Niwa, Tetsu Yamamoto, Nobuyuki Higashi 444 pH-Responsive Plastic Optical Fibres Modified with Polyion Complexed Multibilayers Containing a Poly(methacrylic acid) Segment
- Stuart R. Batten, Bernard F. Hoskins, Richard Robson 445 3D Knitting Patterns. Two Independent, Interpenetrating Rutile-related Infinite Frameworks in the Structure of  $Zn[C(CN)_3]_2$
- Georg Süss-Fink, Meinhard Langenbahn, Helen Stoeckli-Evans, Dieter Naumann 447 Room-temperature Activation of Aliphatic C-H Bonds in Cyclohexane and Pentane by the System  $[Os_3(CO)_{11}(NCMe)]-Te(CF_3)_2$ : X-Ray Crystal Structure of  $[Os_3(CO)_{11}\{Te(C_6H_{11})_2\}]$

## AUTHOR INDEX

- Abell, Andrew D., 362  
Albach, Rolf W., 367  
Arai, T., 410  
Avery, Mitchell A., 351  
Ballesteros, Alfredo, 353  
Balm, Simon, 412  
Barco, Achille, 390  
Barluenga, José, 353  
Bartoli, J. F., 440  
Basile, Tiziana, 391  
Batten, Stuart R., 445  
Battersby, Alan R., 384  
Battioni, P., 440  
Baum, Marc M., 431  
Beatty, Mark F., 351  
Behm, Joachim, 367  
Belal, Arafa A., 402  
Benetti, Simonetta, 390  
Berscheid, Ralf, 414  
Berthet, Jean-Claude, 360  
Bickelhaupt, Freidrich, 438  
Boggs, Russell C., 363  
Bolognesi, A., 364  
Bouas-Laurent, Henri, 416  
Bouvet, Marcel, 442  
Brigaud, O., 440  
Brotin, Thierry, 416  
Byers, Jeffrey H., 354  
Cameron, T. Stanley, 358  
Cassidy, Mark A., 384  
Catellani, M., 364  
Chang, Kieyoung, 394  
Cheng, Chien-Hong, 423  
Coche-Guerente, Liliane, 386  
Collet, André, 435  
Conroy-Lewis, Fiona M., 388  
Consiglio, Giambattista, 421  
Critchley, Peter, 376  
Crockett, Nigel, 384  
Crout, David H. G., 376  
Cunningham, D., 432  
Datta, Arunabha, 356  
Davidson, Alan H., 378  
Denis, J. M., 403  
Dennis, T. John, 412  
Deronzier, Alain, 386  
Desiraju, Gautam R., 426  
Destri, S., 364  
Desvergne, Jean-Pierre, 416  
Disch, Raymond L., 411  
Domen, K., 410  
Drouin, Jacques, 435  
Eggleton, Nick, 378  
Ephritikhine, Michel, 360  
Fages, Frédéric, 416  
Fallis, Ian, 402  
Farrugia, Louis J., 402  
Flitsch, Sabine L., 380, 382  
Foote, Jefferson, 419  
Fujimoto, Takahiro, 428  
Galarini, R., 364  
Gallagher, J. F., 432  
Galland, Bruno, 386  
García Granda, Santiago, 353  
Gelling, Andrew, 349  
Gleason, Thomas G., 354  
Graham, Alan, 407  
Guillemin, J. C., 403  
Haddon, Robert C., 358  
Hara, Kenji, 408  
Hare, Jonathan P., 412  
Herrmann, Wolfgang A., 367  
Higashi, Nobuyuki, 444  
Higgins, T., 432  
Hoskins, Bernard F., 445  
Howard, Donald G., 363  
Jarvis, John, 419  
Jeffery, John C., 349  
Jennings-White, Clive, 351  
Johnson, Brian F. G., 365  
Kagabu, Shinzo, 408  
Kaneko, Chikara, 434  
Keeler, James, 419  
Kelkar, Ravindra Y., 356  
Kibayashi, Chihiro, 405  
Kimura, Masaru, 375  
King, Margaret A., 400  
Klumpp, Gerhard W., 438  
Knight, Kyle S., 354  
Kochi, J. K., 396  
Kong, Jian-She, 353  
Kong, Kwang-Cheng, 423  
Kroto, Harold W., 412  
Labbe, Pierre, 386  
Lacombe, S., 403  
Langenbahn, Meinhard, 447  
Lattuada, Luciano, 437  
Lau, W., 396  
Le Maréchal, Jean-François, 360  
Leeper, Finian J., 384  
Lewis, Jack, 365  
Li, Can, 410  
Licandro, Emanuela, 437  
Longobardo, Luigi, 391  
Lucht, Brett L., 400  
McArdle, P., 432  
Macdonald, Norman M., 402  
Machinaga, Nobuo, 405  
MacManus, David A., 376  
Maiorana, Stefano, 437  
Manjunatha, Sulur G., 372  
Mansuy, D., 440  
Maruya, K., 410  
Mascherpa, M., 364  
Mattar, Saba M., 358  
Moret, Massimo, 421  
Moriyama, Kazuhiko, 373  
Morosawa, Shiro, 375  
Moutet, Jean-Claude, 386  
Musco, A., 364  
Nabeshima, Tatsuya, 373  
Nakache, Didier, 442  
Naumann, Dieter, 447  
Neuhaus, David, 419  
Niwa, Masazo, 444  
Onishi, T., 410  
Ozaki, Shoichiro, 428  
Papagni, Antonio, 437  
Parsons, Simon, 358, 369  
Passmore, Jack, 358, 369  
Peacock, Robert D., 402  
Pearson, Anthony J., 392, 394  
Pérez-Carreño, Enrique, 353  
Petit, Michel A., 442  
Pfister-Guillouzo, G., 403  
Pisano, Carmelina, 421  
Pluth, Joseph J., 363  
Pollini, Gian P., 390  
Pontellini, R., 364  
Poss, Mitchell J., 400  
Povey, David C., 349  
Pu, Lyong Sun, 429  
Raithby, Paul R., 365  
Rajappa, Srinivasachari, 372  
Ramirez, Arthur P., 358  
Ramón, Diego J., 398  
Reverdy, Gilbert, 386  
Richmond, Thomas G., 400  
Robinson, Ward T., 362  
Robson, Richard, 445  
Saharan, Vijay P., 365  
Sakaki, Jun-ichi, 434  
Sakane, Kazuo, 425  
Sakata, Y., 410  
Sankararaman, S., 396  
Saple, Ashok R., 356  
Sato, Masayuki, 434  
Schnik, Wolfgang, 414  
Schriver, Melbourne J., 369  
Schulman, Jerome M., 411  
Sheerin, D., 432  
Shimoyama, Masahiko, 375  
Shinohara, Tomoichi, 428  
Simpson, Stephen J., 388  
Sironi, Angelo, 421  
Smith, Edward H., 431  
Smith, Joseph V., 363  
Spalluto, Giampiero, 390  
Srinivasan, Kumar, 392  
Stoeckli-Evans, Helen, 447  
Sugita, Yoshiaki, 434  
Süss-Fink, Georg, 447  
Tagliavini, Emilio, 391  
Takahashi, Junko, 408  
Taylor, James P., 380, 382  
Taylor, Roger, 412  
Titman, Jeremy J., 419  
Tomás, Miguel, 353  
Trent, John, 362  
Trombini, Claudio, 391  
Turner, Nicholas J., 380, 382  
Umani-Ronchi, Achille, 391  
Utermöhlen, Ralf, 416  
van Elkema Hommes, Nicolaas J. R., 438  
Vidal, Joëlle, 435  
Vögtle, Fritz, 414  
Wahab Allaf, A., 412  
Wallace, Ian H., 378  
Walton, David R. M., 412  
Watanabe, Yutaka, 428  
Went, Michael J., 349  
White, Peter S., 369  
Williams, D. Lyn H., 407  
Wong, Wing Tak, 365  
Yamamoto, Tetsu, 444  
Yano, Yumihiko, 373  
Yasuda, Nobuyoshi, 425  
Yus, Miguel, 398  
Zanirato, Vinicio, 390  
Zhuo, G., 364

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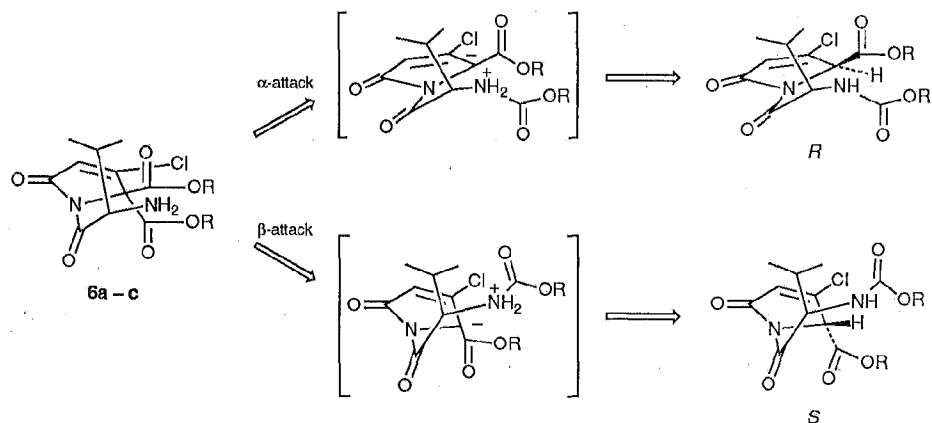


Fig. 2 Reaction pathway for novel oxycarbonyl rearrangement

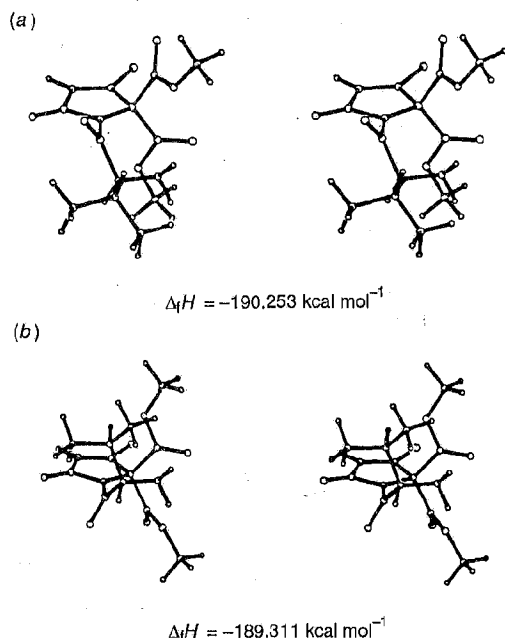


Fig. 3 (a) Stereoview of conformer A; (b) stereoview of conformer B (MNDO calculations)

highly stabilized carbanion, which would be immediately protonated from the resultant oxycarbonylammonium species, as shown in Fig. 2. Therefore, the stereochemistry at the newly formed chiral centre would be determined by the

orientation of nucleophilic attack of the free nitrogen. In order to determine this orientation, we attempted an MNDO conformational analysis. In the case of attack at the  $\alpha$ -carbonyl carbon, a chair-like conformer (*A*), containing the bulky isopropyl moiety ( $\text{Pr}^i$ ) in a pseudoequatorial orientation, is the most favoured conformation and leads to the *R*-ester. In the case of attack at the  $\beta$ -carbonyl carbon, a chair-like conformer (*B*) containing  $\text{Pr}^i$  in a pseudoaxial orientation is the preferred one and leads to the *S*-ester. Their MNDO-calculated optimized conformations and heats of formation are shown in Fig. 3 (a) and (b). As a result, *A* is the most favoured conformation, and the energy difference between *A* and *B* was calculated to be  $0.942 \text{ kcal mol}^{-1}$  ( $1 \text{ cal} = 4.184 \text{ J}$ ). This energy difference corresponds well with the stereoselectivity (*ca.* 80% at room temp.) in this reaction.

We thank Dr Akito Tanaka for conformational analyses by the MNDO method and Dr Toshiji Tada for the single crystal analyses.

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## Hydration in Organic Crystals: Prediction from Molecular Structure

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The proportion of non-ionic, metal free, organic compounds that crystallise as hydrates increases, within the class, with an increase in the number of hydrogen-bond acceptor groups with respect to the donor groups.

The inclusion of water within organic crystals is a matter of both fundamental and practical importance and is quite unlike the inclusion of other solvents of crystallisation. Because of its small size and excellent hydrogen bonding ability, water is almost never an innocuous bystander in an organic crystal

structure. With the recent impetus in crystal engineering,<sup>1</sup> there has been much interest in the prediction of crystal packing<sup>2-4</sup> and hydrogen bond patterns<sup>5</sup> using simple molecular descriptors. Such efforts have been greatly facilitated by the existence of machine-readable databases such as the

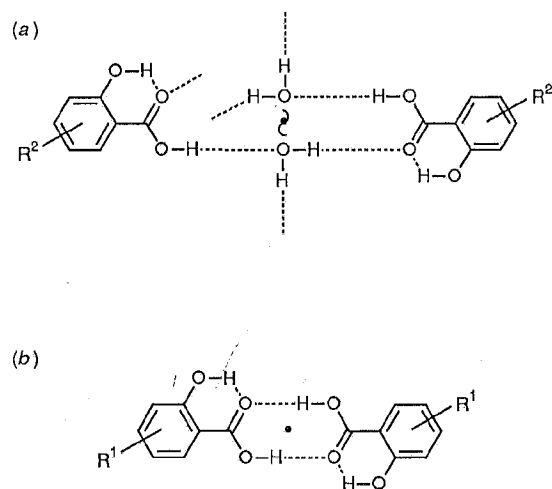


Fig. 1 Hydrogen bonding schemes for hydrated acid **1** (a) and anhydrous acids **2**, **3** and **4** (b). In acid **1**, the water molecules are also hydrogen bonded to nitro groups which are not shown here.

Cambridge Structural Database (CSD).<sup>6</sup> Accordingly, this communication deals with the prediction of the likelihood of an organic molecule to crystallise as a hydrate.

Water is incorporated into organic crystals far more frequently than other common solvents. Of the 69 691 entries in the 1988 (3.1) version of the CSD, 33 886 do not contain any metal atom and of these, 3696 are solvates. It is appropriate to consider only those entries without metal atoms since water enters the coordination sphere of transition metal ions so readily. Even when these 'pure' organics are surveyed, the number of entries having water of crystallisation is far in excess of the number having other solvents. The following statistics were obtained: water (2566); methanol (306); diethyl ether (175); benzene (173); ethanol (168); acetone (108); chloroform (102); others (98). These figures are striking because water is not a particularly good solvent for organic compounds and also because of the possibly comparable frequencies with which any of the above common solvents were used for crystallisation.

This study was prompted by the observation that 3,5-dinitrosalicylic acid **1** crystallises as a monohydrate while the related compounds salicylic acid **2**, 5-nitrosalicylic acid **3** and 3-amino-5-nitrosalicylic acid **4** form anhydrous crystals.<sup>7</sup> In all four structures, the phenolic hydroxy group is intramolecularly hydrogen bonded to the carbonyl oxygen of the carboxy group and does not seem to play any differentiating role. The crystal structure of **1** is unusual in that, unlike **2**, **3** and **4**, the molecules do not form centrosymmetric hydrogen bonded dimers but rather form hydrogen bonds along a catemer in which water molecules connect carbonyl and carboxy oxygen atoms (Fig. 1). These water molecules act in effect as hydrogen bond donors to the former ( $O \cdots O$  2.92 Å) and as hydrogen bond acceptors from the latter ( $O \cdots O$  2.52 Å). Normally the catemer motif is not accessible to aromatic carboxylic acids for steric reasons.<sup>8</sup> In the structure of **1**, however, water molecules act as spacers so that the aromatic rings move sufficiently apart to avoid repulsive contacts with the catemer itself. Now, the interesting question is why this unusual structure is adopted at all. A possible rationale is obtained by considering that the number of hydrogen bond donors (two) and acceptors (seven) in acid **1** is quite unbalanced. It has been stated that all good proton donors and acceptors are used in hydrogen bonding.<sup>5</sup> If this is the case, three-centre interactions<sup>9</sup> would appear inevitable in order that the maximum number of acceptors be included in the hydrogen bonding scheme. However, an alternative possibility to redress the donor: acceptor imbalance is by the

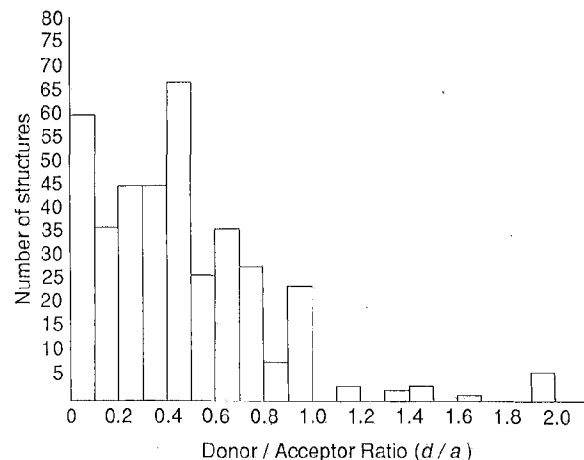


Fig. 2 Histogram of donor/acceptor ratios ( $d/a$ ) for 411 hydrated crystal structures. Compounds are metal-free and not salts.

inclusion of one or more water molecules. In the present case, the 2:7 donor:acceptor ratio becomes a 4:8 ratio in the monohydrate. This possibility is an attractive one since stronger hydrogen bonds would be formed; this is so because not as many of them need be of the three-centre type.

The next step in the analysis was to extend the argument with the CSD. From the 2566 hydrates mentioned above, salts and cyclodextrins were excluded. It is not surprising that charged species should crystallise as hydrates, while it may be easy for water molecules to enter the large cavities of the cyclodextrins. Since, at this stage, the structures had to be examined manually (and individually) in order that the number of hydrogen bond donors and acceptors in the molecular structure be counted, a smaller group of 411 structures was selected. To avoid any bias the structures were chosen according to journal.<sup>†</sup>

The following groups were defined as proton donors ( $d$ ): 1° (primary) amine (2 donors); 2° amine (1); 1° amide (2); 2° amide (1); imine (1); alcohol, phenol, carboxylic acid, sulphonic acid (1). The following were defined as proton acceptors ( $a$ ): N in amine, amide, imine (1); O in hydroxy and carboxy (1);  $sp^3$  O in ethers and esters (1);  $sp^2$  O in carbonyl compounds (1); O in nitro (2); N in nitrile and isonitrile (1); F in a C-F bond was not included as a proton acceptor.

Barring a single structure,<sup>10</sup> all the selected hydrates contain groups capable of participating in hydrogen bonding. Fig. 2 is a histogram of the number of structures as a function of the donor: acceptor ratio ( $d/a$ ). There are hardly any structures where  $d/a$  is greater than unity but this is not surprising; from the definitions of donor and acceptor used here, only a few types of compounds such as 1° amines and some of their derivatives would be expected to have  $d > a$ . The vast majority of hydrogen bonded compounds (hydrated or otherwise) would probably have  $d/a$  ratios in the range 0.5–1.0. What is significant, however, is that 65% of the hydrated structures have  $d/a < 0.5$  with 16% of them having  $d/a < 0.1$ . In many of these hydrates therefore, the number of hydrogen bond donor groups is far less than the number of acceptors. There are a number of reasons why such a correlation should be indistinct: the existence of three-centre bonds; the possibility of water hydrogen bonding to itself rather than to the organic compound and water performing a space-filling role within the lattice of an awkwardly-shaped molecule. Indeed all these situations were encountered among the 400-odd structures

<sup>†</sup> Structures were selected if they appeared in any of the following journals: *J. Chem. Soc.* (all sections); *Acta Chem. Scand.*; *Acta Crystallogr.* (prior to bifurcation); *Angew. Chem.*; *Bull. Chem. Soc. Jpn.*; *J. Chem. Phys.*; *J. Am. Chem. Soc.*; *J. Org. Chem.*; *Tetrahedron*; *Tetrahedron Lett.*

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Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

## API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

## LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

## FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

## E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.