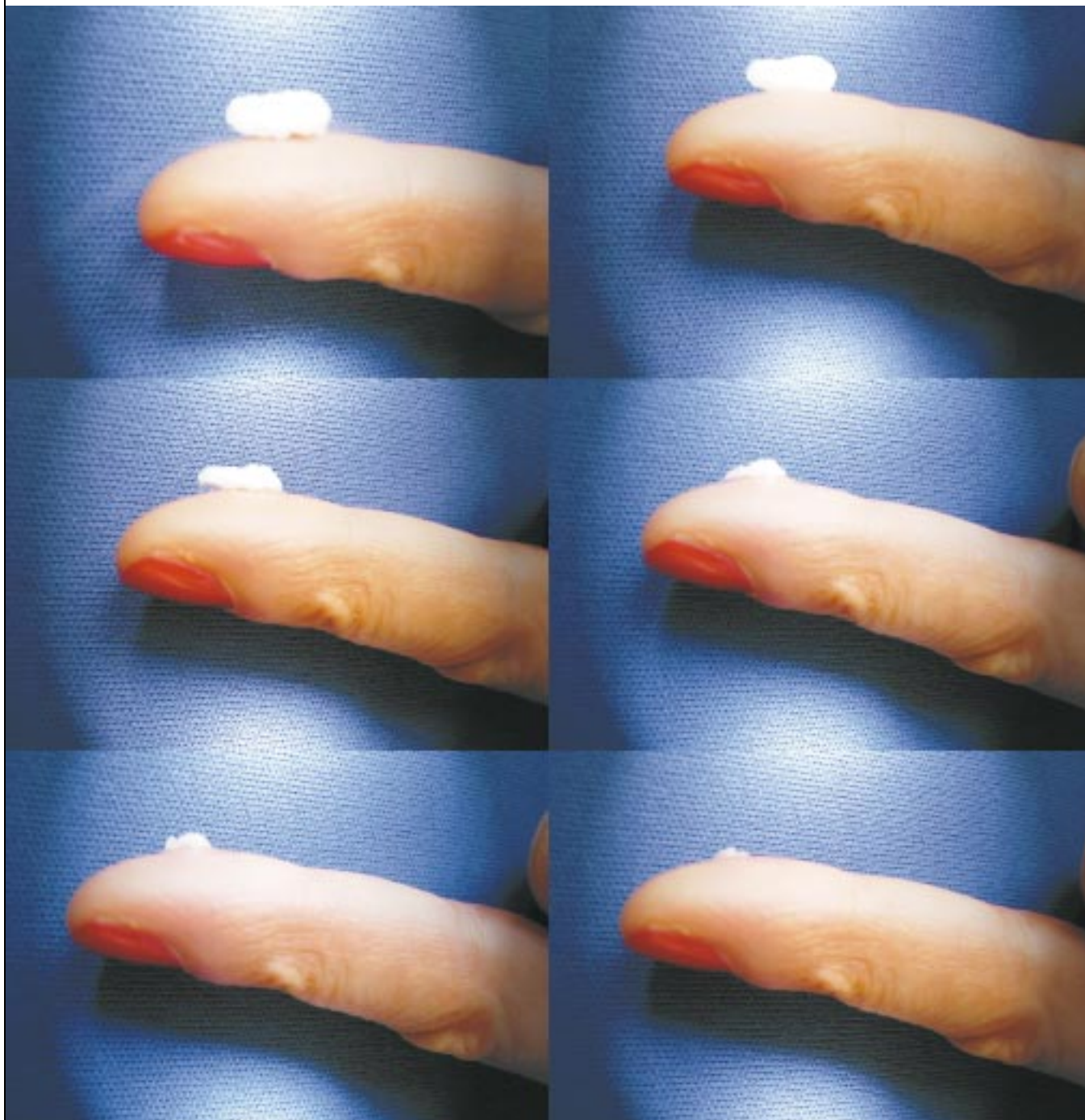


# Carbonic Acid ( $\text{H}_2\text{CO}_3$ ) on the Finger Tip



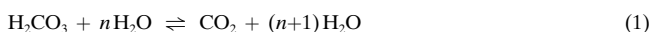
Decay of carbonic acid ( $\text{H}_2\text{CO}_3$ ) in an ice matrix on warming from the temperature of liquid nitrogen (77 K) on the finger tip of Ingrid Kohl over a period of about two minutes. More about this on the following pages.

On the Surprising Kinetic Stability of Carbonic Acid (H<sub>2</sub>CO<sub>3</sub>)\*

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The hydration of carbon dioxide is one of the most fundamental reactions in biological systems.<sup>[1–3]</sup> The reaction partner, namely carbonic acid (H<sub>2</sub>CO<sub>3</sub>), has received considerable attention both from an experimental<sup>[4–8]</sup> and theoretical viewpoint.<sup>[9–13]</sup> Synthesis of carbonic acid—one of the most fundamental compounds in inorganic and organic chemistry as well as in biochemistry—proved to be rather elusive. For a long time even the observation of intermediary formed carbonic acid appeared unlikely due to the apparently rapid decay. Despite the belief of the nonexistence of carbonic acid, chemists recently succeeded first in recognizing the stability of carbonic acid<sup>[4,5]</sup> and then in isolating and characterizing<sup>[6,7]</sup> pure carbonic acid. It was even possible to sublime and recondense the solid and therefore prove the stability of gas-phase carbonic acid.<sup>[8]</sup> Quantum-chemical investigations revealed the gas-phase dimer of carbonic acid to be energetically similar to its constituents, water and carbon dioxide,<sup>[13]</sup> whereas the monomer is thermodynamically unstable.<sup>[9,12,14]</sup>

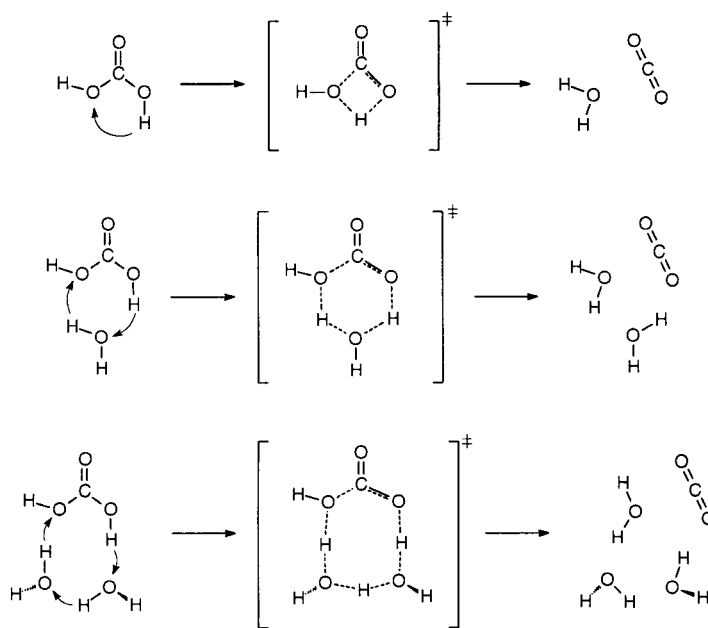
Here, we elucidate the influence of water molecules on the decomposition rate, that is the kinetic stability of carbonic acid in the presence of water [Eq. (1),  $n = 0–2$ ].



We address the issue of the kinetic stability of carbonic acid in terms of transition state theory (TST) based on Eyring's concepts.<sup>[15]</sup> The exact calculation of reaction rates requires thorough investigation of at least three completely different contributions: a) the energy differences between the reactants, the transition state, and the products, b) a multidimensional description of possible paths connecting reactants and products, and c) an accurate description of quantum effects, such as tunneling and zero point energies, arising from the dual particle-wave nature of the atoms. These three criteria are considered within the canonical variational transition state theory (TST) formalism used herein<sup>[15]</sup> with corrections for multidimensional tunneling effects developed by Truhlar and co-workers.<sup>[16–20]</sup> Recently, we confirmed the methodological details required to obtain chemically meaningful results.<sup>[21,22]</sup> For the benchmark double proton transfer reaction in carboxylic acid dimers we reached nearly quanti-

tative agreement to results of T<sub>1</sub> NMR spin-lattice relaxation spectroscopy, inelastic neutron scattering experiments, and fluorescence line narrowing in terms of reaction rate constants between 0 and 400 K, apparent activation energy curves, crossover temperatures, kinetic isotope effects, and vibrational and electronic ground-state tunneling-splittings.<sup>[23]</sup>

The stationary points of the reaction hypersurfaces investigated here using  $n = 0–2$  water molecules are depicted in Scheme 1. The geometries agree well with the results of previous calculations<sup>[9–12,14,24–29]</sup> as well as with structures



Scheme 1. Geometries of the stationary points of the decomposition of carbonic acid in the presence of zero ( $n = 0$ ), one ( $n = 1$ ), and two ( $n = 2$ ) water molecules as found at MP2/aug-cc-pVDZ level of theory.<sup>[43]</sup>

obtained from microwave spectroscopy.<sup>[30,31]</sup> The reaction barrier for the decomposition of isolated carbonic acid of 44 kcal mol<sup>-1</sup> is a first indication of its kinetic stability (Figure 1), which we established by accurate molecular quantum mechanics.<sup>[32]</sup> The catalytic effect, that is the lowering of the reaction barriers due to the participation of a

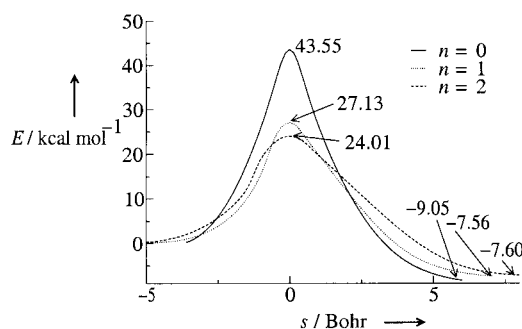


Figure 1. Energy along the classical reaction path obtained from a CCSD(T)/aug-cc-pVDZ//MP2/aug-cc-pVDZ///B3LYP/6–31 + G(d)<sup>[44–46]</sup> interpolation of the decomposition of carbonic acid in the presence of zero ( $n = 0$ ), one ( $n = 1$ ), and two ( $n = 2$ ) water molecules.

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[\*\*] The work was supported in part by grants of the Austrian Academy of Sciences (T.L.) and the Austrian Science Fund (P13930-PHY).

single water molecule,<sup>[14]</sup> amounts to  $16 \text{ kcal mol}^{-1}$ . The movement of the nuclei within the reaction is described by the reaction path, which is classically the path of lowest possible energy connecting reactants with products (minimum energy path, MEP). However, in the case of the decomposition of carbonic acid, the reaction can be divided in two sharply separable parts: a) approach of oxygen atoms without variation of the O–H bond length, and b) transition of hydrogen atoms, while oxygen atoms remain in their positions. Noticeably, this reaction path clearly deviates from the classical MEP, because part b is highly amenable to tunneling due to the low mass of the moving protons. The combination of these tunneling paths and the precise energy barriers (see Figure 1) directly leads to the reaction rate constants depicted in Figure 2. These plots show non-Arrhenius behavior,

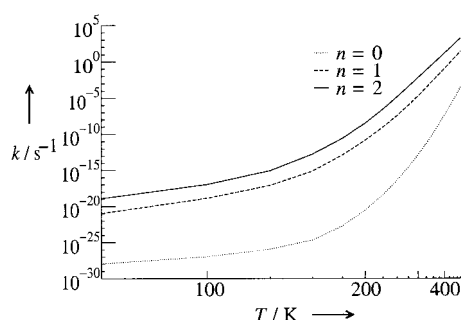


Figure 2. Arrhenius plot for the decomposition of carbonic acid in the framework of transition state theory including non-adiabatical multidimensional tunneling effects. The reaction path is calculated at B3LYP/6-31+G(d)<sup>[46]</sup> level of theory and interpolated to MP2/aug-cc-pVDZ<sup>[43]</sup> geometries, CCSD(T)/aug-cc-pVDZ//MP2/aug-cc-pVDZ energies and MP2/aug-cc-pVDZ ( $n=0$ ) or B3LYP/aug-cc-pVDZ ( $n=1,2$ ) frequencies at the stationary points.

emphasizing that quantum effects are indeed very important in these reactions. Especially at low temperatures, where tunneling plays the most important role, there is a big difference to rates determined from classical TST alone. For instance, through tunneling, the uncatalyzed reaction at 150 K is a factor of  $10^{20}$  faster than in the classical case. The low rates (Figure 2) for the decomposition of the carbonic acid monomer in the gas phase are in good agreement with the experiment, which demonstrates the kinetic stability at temperatures between 180 K and 220 K.<sup>[8]</sup> The decomposition rate of  $1.2 \times 10^{-13} \text{ s}^{-1}$  at 300 K, which corresponds to a half-life of 0.18 million years, indicates that carbonic acid is kinetically stable at room temperature. However, an autocatalytic process taking place after decay of the first molecule will lower this half-life in bulk  $\text{H}_2\text{CO}_3$  significantly. The released water molecules form  $\text{H}_2\text{CO}_3/\text{H}_2\text{O}$  complexes that decay much faster (Figure 2). Nevertheless, if synthesized free of water, carbonic acid is expected to be stable over a wide temperature range for the above-mentioned reasons.

On the other hand, carbonic acid in aqueous solution decomposes quickly.<sup>[33]</sup> This phenomenon is directly explained by Figure 2. The addition of a single water molecule to the carbonic acid molecule increases the rate of decomposition by a temperature-dependent factor of  $10^7$ – $10^9$ , that is the half-life is reduced to 10 h at 300 K. The addition of a second water

molecule further accelerates the reaction by a factor of  $10^2$ – $10^3$ , yielding a half-life of 119 s at 300 K. Together these two accelerations amount to the remarkable factor of 50 billion at 300 K. This is the reason why most chemists believe “carbonic acid” to be unstable. But instead of  $\text{H}_2\text{CO}_3$  (“carbonic acid”) they actually mean “carbon dioxide dissolved in water” (which leads to an equilibrium of 1 %  $\text{H}_2\text{CO}_3$  and 99 % loosely hydrated  $\text{CO}_2$  as well as to acidic behavior because of the  $\text{H}_2\text{CO}_3/\text{HCO}_3^-$  acid base pair).<sup>[34–38]</sup> The half-life of 30 days (two additional water molecules) at 225 K is consistent with the experimental fact that crystalline and amorphous  $\text{H}_2\text{CO}_3$  are kinetically stable in an ice matrix. The experimentally determined decomposition rate to carbon dioxide and water in neutral aqueous solution of  $18 \pm 7 \text{ s}^{-1}$  at room temperature<sup>[33, 39]</sup> is just 3000 times faster than the calculated one using  $n=2$ . This good agreement suggests that the decomposition mechanism involves at least two catalytically active water molecules besides the electrostatic effect of the bulk environment.

The remarkable kinetic stability of gaseous  $\text{H}_2\text{CO}_3$  in the absence of water has implications for its formation and detectability in outer space. Solid carbonic acid forms on proton irradiation not only of cryogenic  $\text{CO}_2/\text{H}_2\text{O}$  ice mixtures,<sup>[6]</sup> but also of pure solid  $\text{CO}_2$ .<sup>[40]</sup> The latter route appears promising for generating gaseous  $\text{H}_2\text{CO}_3$  because, once formed in the solid state in the absence of water, it can vaporize without decomposition. The ratio of the monomer/dimer mixture of gaseous carbonic acid depends on temperature.<sup>[8]</sup> In order to search for its existence in outer space in the gas phase, laboratory infrared spectra of the gaseous species are required for comparison with, for example, unidentified infrared bands.<sup>[41]</sup> Because of hydrogen bonding pronounced spectral changes are expected for many normal modes in going from the monomer to the dimer and the solid, in a similar manner to that observed for formic acid.<sup>[42]</sup> Therefore, infrared spectra of solid carbonic acid reported so far<sup>[6–8]</sup> seem unsuitable for the detection of gaseous carbonic acid in outer space.

Received: November 15, 1999 [Z14269]

- [1] D. N. Silverman, S. Lindskog, *Acc. Chem. Res.* **1988**, *21*, 30–36.
- [2] D. N. Silverman, *Methods Enzymol.* **1995**, *249*, 479–503.
- [3] A. S. Fauci, E. Braunwald, K. J. Isselbacher, J. D. Wilson, J. B. Martin, D. L. Kasper, S. L. Hauser, D. L. Longo, *Harrison's Principles of Internal Medicine*, 14th ed., McGraw Hill, London, **1998**.
- [4] J. K. Terlouw, C. B. Lebrilla, H. Schwarz, *Angew. Chem.* **1987**, *99*, 354–355; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 352–353.
- [5] H. Falcke, S. H. Eberle, *Water Res.* **1990**, *24*, 685–688.
- [6] M. H. Moore, R. K. Khanna, *Spectrochim. Acta Part A* **1991**, *47*, 255–262.
- [7] W. Hage, A. Hallbrucker, E. Mayer, *J. Am. Chem. Soc.* **1993**, *115*, 8427–8431.
- [8] W. Hage, K. R. Liedl, A. Hallbrucker, E. Mayer, *Science* **1998**, *279*, 1332–1335.
- [9] B. Jönsson, G. Karlström, H. Wennerström, B. Roos, *Chem. Phys. Lett.* **1976**, *41*, 317–320.
- [10] B. Jönsson, G. Karlström, H. Wennerström, S. Forßen, B. Roos, J. Almlöf, *J. Am. Chem. Soc.* **1977**, *99*, 4628–4632.
- [11] R. Janoschek, I. G. Csizmadia, *J. Mol. Struct.* **1993**, *300*, 637–645.
- [12] C. A. Wight, A. I. Boldyrev, *J. Phys. Chem.* **1995**, *99*, 12125–12130.
- [13] K. R. Liedl, S. Sekusak, E. Mayer, *J. Am. Chem. Soc.* **1997**, *119*, 3782–3784.

- [14] M. T. Nguyen, G. Raspoet, L. G. Vanquickenborne, P. T. Van Duijnen, *J. Phys. Chem. A* **1997**, *101*, 7379–7388.
- [15] H. Eyring, *J. Chem. Phys.* **1935**, *3*, 107–115.
- [16] “Generalized Transition State Theory”: D. G. Truhlar, A. D. Isaacson, B. C. Garrett, *Theory of Chemical Reaction Dynamics* (Ed.: M. Baer), CRC, Boca Raton, FL, **1985**, pp. 65–137.
- [17] “Dynamical Formulation of Transition State Theory: Variational Transition States and Semiclassical Tunneling”: S. C. Tucker, D. G. Truhlar in *New Theoretical Concepts for Understanding Organic Reactions* (Eds.: J. Bertrán, I. G. Csizmadia), Kluwer, Dordrecht, **1989**, pp.291–346 (*NATO ASI Ser. Ser. C* **1989**, 267).
- [18] D. G. Truhlar, M. S. Gordon, *Science* **1990**, *249*, 491–498.
- [19] Polyrate8.2, Y.-Y. Chuang, J. C. Corchado, P. L. Fast, J. Villá, E. L. Coitiño, W.-P. Hu, Y.-P. Liu, G. C. Lynch, K. A. Nguyen, C. F. Jackels, M. Z. Gu, I. Rossi, S. Clayton, V. S. Melissas, R. Steckler, B. C. Garrett, A. D. Isaacson, D. G. Truhlar, University of Minnesota, Minneapolis, **1999**.
- [20] Gaussrate8.2, J. C. Corchado, E. L. Coitiño, Y.-Y. Chuang, D. G. Truhlar, University of Minnesota, Minneapolis, **1999**.
- [21] T. Loerting, K. R. Liedl, B. M. Rode, *J. Am. Chem. Soc.* **1998**, *120*, 404–412.
- [22] T. Loerting, K. R. Liedl, B. M. Rode, *J. Chem. Phys.* **1998**, *109*, 2672–2679.
- [23] T. Loerting, K. R. Liedl, *J. Am. Chem. Soc.* **1998**, *120*, 12595–12600.
- [24] M. T. Nguyen, T.-K. Ha, *J. Am. Chem. Soc.* **1984**, *106*, 599–602.
- [25] J. R. Damewood, Jr., R. A. Kumpf, W. C. F. Mühlbauer, *J. Phys. Chem.* **1989**, *93*, 7640–7644.
- [26] K. M. Merz, Jr., *J. Am. Chem. Soc.* **1990**, *112*, 7973–7980.
- [27] J. Sadlej, P. Mazurek, *J. Mol. Struct.* **1995**, *337*, 129–138.
- [28] M. Hartmann, T. Clark, R. van Eldik, *J. Mol. Mod.* **1996**, *2*, 358–361.
- [29] C.-L. Lin, S.-Y. Chu, *J. Am. Chem. Soc.* **1999**, *121*, 4222–4228.
- [30] K. I. Peterson, W. Klempner, *J. Chem. Phys.* **1984**, *80*, 2439–2445.
- [31] K. I. Peterson, R. D. Suenram, F. J. Lovas, *J. Chem. Phys.* **1991**, *94*, 106–117.
- [32] Gaussian 98, Revision A.7, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. G. Johnson, W. Chen, M. W. Wong, J. L. Andres, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian, Inc., Pittsburgh, PA, **1998**.
- [33] E. Magid, B. O. Turbeck, *Biochim. Biophys. Acta* **1968**, *165*, 515–524.
- [34] F. A. Cotton, G. Wilkinson, *Advanced Inorganic Chemistry*, Wiley-Interscience, Chichester, **1962**.
- [35] R. T. Sanderson, *Inorganic Chemistry*, Reinhold, New York, **1967**.
- [36] R. E. Dickerson, I. Geis, *Chemie – Eine Lebendige und Anschauliche Einführung*, VCH, Weinheim, **1983**.
- [37] J. C. Bailar, Jr., T. Moeller, J. Kleinberg, C. O. Guss, M. E. Castellion, C. Metz, *Chemistry*, Academic Press, New York, **1984**.
- [38] P. W. Atkins, J. A. Beran, *General Chemistry*, W. H. Freeman, New York, 1992; P. W. Atkins, J. A. Beran, *Chemie – Einfach Alles*, VCH, Weinheim, **1996**.
- [39] Y. Pocker, D. W. Bjorkquist, *J. Am. Chem. Soc.* **1977**, *99*, 6537–6543.
- [40] J. R. Brucato, M. E. Palumbo, G. Strazzula, *Icarus* **1997**, *125*, 135–144.
- [41] E. Herbst, *Annu. Rev. Phys. Chem.* **1995**, *46*, 27–53.
- [42] R. C. Millikan, K. S. Pitzer, *J. Am. Chem. Soc.* **1958**, *80*, 3515–3521.
- [43] T. H. Dunning, Jr., *J. Chem. Phys.* **1989**, *90*, 1007–1023.
- [44] K. Raghavachari, G. W. Trucks, J. A. Pople, M. Head-Gordon, *Chem. Phys. Lett.* **1989**, *157*, 479–483.
- [45] C. Möller, M. S. Plesset, *Phys. Rev.* **1934**, *46*, 618–622.
- [46] A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648–5652.

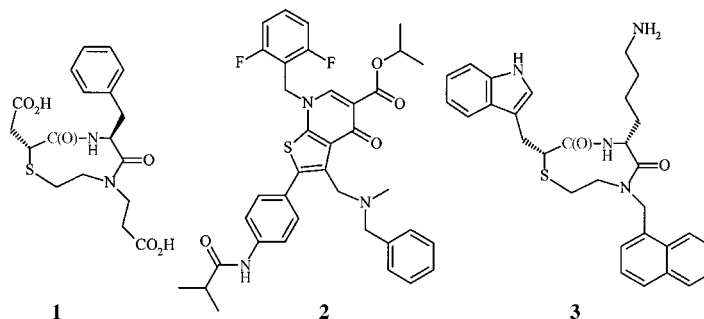
## Are $\beta$ -Turn Mimetics Mimics of $\beta$ -Turns?

Gerhard Müller,\* Gerhard Hessler, and Helene Y. Decornez

*Dedicated to Dr. Pol Bamelis on the occasion of his 60th birthday*

At the molecular level almost all important physiological and pathophysiological processes in the human organism are modulated by peptide–protein and protein–protein interactions. Consequently for pharmaceutical research these recognition phenomena represent attractive target systems for therapeutic intervention in a broad spectrum of disease states.<sup>[1]</sup> From the viewpoint of structural chemistry  $\beta$ -turns have been attributed a special importance as carriers of molecular recognition since within the context of pharmacophore arrangement they allow a sterically controlled presentation of two to four interaction-mediating amino acid side chains.<sup>[2]</sup> In medicinal chemistry the retention of the orientation of the amino acid side chains with simultaneous replacement of the peptide backbone by nonpeptide druglike structures, so-called “ $\beta$ -turn mimetics”, has progressed to become an established topic in the structural design of peptide mimetics.<sup>[3]</sup>

The relevance of the design element “ $\beta$ -turn” with variable decoration in the molecular periphery has recently been convincingly confirmed by combinatorial chemistry and classical medical chemistry. This work resulted in, for example, high-affinity and selective peptidomimetic  $\alpha_4\beta_1$ -integrin antagonists such as **1**,<sup>[4]</sup> LHRH antagonists such as **2**,<sup>[5]</sup> and somatostatin antagonists such as **3**.<sup>[6]</sup>



Here we take up the problem of the conformational compatibility of  $\beta$ -turn mimetics with the secondary structural elements that are to be imitated, and we introduce a simulation procedure with which is possible to evaluate not

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