from further reaction of initially formed erythro and from double-rotational racemization of threo. These complications could be eliminated (but have not been) by extrapolating several results at short times of reaction to zero time.

The image of "cage" fixing such a firm embrace on its occupants comes to us, and perhaps to others, as unexpected. We will try to observe the effect of mēnage ā trois by generating the same two radicals from optically active congeneric azo compounds.

This value of the "cage" rotational factor, $R_A = 1.8$, is not much lower than that found for the cyclopentane analogue, $R_A = 3.4$.[4] We suggest that some, if not all, of the rotational preference in the cyclic compound may be attributable to the environmental effect of the "cage" and not entirely to constraint by the three-carbon chain binding the two radicals together. Among other experiments planned are repetition of this rearrangement in a wider range of lower concentrations of 9,10-dihydroanthracene and refinement of the "cage" racemization of **3t**.

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How Rare Are the Covalent Hydrates of Purine Ribonucleoside and Nicotinamide? A Method for Estimating Positions of Highly Unfavorable Equilibria

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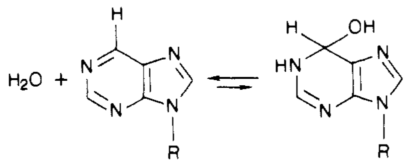
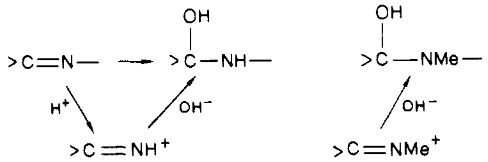
Water adds to C=N double bonds during their hydrolysis, yielding unstable carbinolamine intermediates. Among the few carbinolamines stable enough to be observed directly are the covalent hydrates of pteridine and quinazoline. Other heterocycles, such as purine and pyridine, have not been observed to form covalent hydrates to a detectable extent even in their protonated forms,[1] so that hydration is presumably very unfavorable. Despite the rarity of these hydrated species, they are of considerable potential interest. Purine ribonucleoside, for example, is a powerful inhibitor of adenosine deaminase.[2] A rare hydrated form of purine ribonucleoside, if that were present in small quantities (Scheme I), could serve as the actual inhibitor because of its resemblance to a rare hydrated form of the substrate that the enzyme stabilizes as part of the catalytic process.[3] It seems probable that covalent hydrates also serve as intermediates in reactions catalyzed by cytidine deaminase, IMP dehydrogenase, and xanthine oxidase, but no information is available concerning their abundances relative to those of the starting materials. Approximate values of their free energies of formation would be useful in diagramming the potential course of these reactions, and knowledge of their physical properties might be useful in identifying methods by which they could be detected in trace quantities. We wish to describe a method, based on the use of N-methylated heterocycles, that can be used to assess the positions of hydration equilibria that are not susceptible to direct observation.

Scheme I



Scheme II



The principle of this method is illustrated in Scheme II. The equilibrium constant for addition of water to a C=N bond should be equivalent to the product of the equilibrium constants for successive addition of a proton and a hydroxide ion, multiplied by the ion product of water (eq 1). The equilibrium constant

$$K_{\text{hydration}} = \frac{[>C(OH)NH-]}{[>C=N-]} = K_{H^+}K_{OH^-} \times 10^{-14}$$

$$\text{where } K_{H^+} = \frac{[>C=NH^+]}{[H^+][>C=N-]} \tag{1}$$

$$\text{and } K_{OH^-} = \frac{[>C(OH)NH-]}{[OH^-][>C=NH^+]}$$

for protonation is readily calculated from the pK_a value of the conjugate acid, but the equilibrium constant for hydroxide addition to the protonated species cannot be determined directly in cases where hydration occurs only to a very small extent.[4] The equilibrium constant for hydroxide addition to the protonated species should, however, be similar to the equilibrium constant for pseudobase formation from the quaternary ammonium compound produced by methylation of the nitrogen atom in question (Scheme II). The near-equivalence of $=NCH_3$ to $=NH$ in such systems was established by earlier studies in which the 3-methylquinazolinium ion, for example, was found to be virtually identical with the conjugate acid of quinazoline in its affinity for the hydroxide ion.[5]

The iodide salt of 1-methylpurinium ribonucleoside was obtained by treating purine ribonucleoside with 1 equiv of iodomethane in Me_2SO for 7 days at room temperature. The major product, purified by elution from cellulose with increasing ethanol in chloroform, showed carbon and proton resonances with integrated intensities consistent with methylation of a single ring nitrogen.[6] As expected for alkylation of N-1, we observed strong dipole–dipole interaction of the methyl group with protons at C-6 and C-2 but not with the proton at C-8.[7] Spectrophotometric titration of the iodide salt of 1-methylpurinium ribonucleoside[8] showed a single pK_a of 9.0, forming an unstable conjugate base with an ultraviolet absorption spectrum similar to those of 1,6-saturated derivatives of purine ribonucleoside generated by electrochemical reduction[9]

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[1] Albert, A. *Adv. Heterocycl. Chem.* **1976**, *20*, 117.

[2] Wolfenden, R.; Kaufman, J.; Macon, J. B. *Biochemistry* **1969**, *8*, 2412.

[3] Wolfenden, R. *Annu. Rev. Biophys. Bioeng.* **1976**, *5*, 271.

[4] Albert, Perrin and their associates have shown that this number can be determined by rapid reaction techniques, if hydration occurs to such an extent in the cation or the neutral species that it can be measured directly (for a review, see ref 1).

[5] Albert, A.; Armarego, W. L. F.; Spinner, E. *J. Chem. Soc.* **1961**, 5267.

[6] ^{13}C NMR (ppm, D_2O): 45.2 (CH_3N-1); 60.9, 70.0, 74.3, 85.5, 89.2 (ribose); 133.1 (C-5); 143.9 (C-8); 149.0 (C-6); 151.2 (C-2), 152.9 (C-4). ^1H NMR (ppm, D_2O): 3.9 (m, 2 H, ribose); 4.2–4.9 (m, 3 H, ribose); 4.5 (s, 3 H, CH_3N-1), 6.35 (d, 1 H, ribose); 9.15 (s, 1 H, H-8); 9.4 (s, 1 H, H-2), 9.62 (s, 1 H, H-6).

[7] Identified by comparison with: Chenon, M. T.; Pugmire, R. J.; Grant, D. M.; Panzica, R. P.; Townsend, L. B. *J. Am. Chem. Soc.* **1975**, *97*, 4627.

[8] UV maxima: 270 nm (log ϵ = 3.8) in 0.1 N HCl; 284 nm (log ϵ = 3.9) in 0.1 N KOH.

[9] Smith, D. L.; Elving, P. J. *J. Am. Chem. Soc.* **1962**, *84*, 1412.

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and photochemical alkylation.[10] The conjugate acid of purine ribonucleoside, with a $\mathrm{p}K_a$ value of 2.05,[11] is also protonated at N-1.[12] Equation 1 yields an equilibrium constant of 1.1×10^{-7} for hydration of purine ribonucleoside to form 1,6-dihydro-6-hydroxypurine ribonucleoside. In general, substitution at carbon strongly disfavors water addition to $C{=}N$ groups (see ref 1), so that the equilibrium constant for 1,6-hydration of adenosine is presumably some orders of magnitude lower still. Recent work indicates that the equilibrium constant for activation, in the uncatalyzed hydrolytic deamination of adenosine which may proceed by water addition at the 1,6-position, is approximately 10^{-13}.[13] Accordingly, the instability of the water adduct of adenosine may approach that of the transition state for its deamination.

A similar approach can be taken to other heterocyclic systems. For example, 1-methylnicotinamide appears to add hydroxide ion reversibly to form a pseudobase with an absorption maximum at 325 nm, in a reaction with an equilibrium constant in the neighborhood of 0.25 M^{-1} or less.[14-16] The $\mathrm{p}K_a$ value of the conjugate acid of nicotinamide is 2.1,[17] so that the equilibrium constant for covalent addition of water to nicotinamide can be estimated as 3×10^{-13} or less.[18] In principle, this method can also be used to determine equilibria of addition of nucleophiles other than water. The chief requirements are that methylation can be carried out at the position at which proton addition would occur and that anion addition to the resulting quaternary amine yields a product of sufficient stability to allow determination of the equilibrium constant for its formation.

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(10) Evans, B.; Wolfenden, R. *J. Am. Chem. Soc.* **1970**, *92*, 4751.

(11) Brown, G. B.; Weliky, V. S. *J. Biol. Chem.* **1953**, *204*, 1019.

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(13) Frick, L.; Mac Neela, J. P., personal communication.

(14) Kaplan, N. O.; Colowick, S. P.; Barnes, C. C. *J. Biol. Chem.* **1951**, *191*, 461.

(15) Martin, R. B.; Hull, J. G. *J. Biol. Chem.* **1964**, *239*, 1237. These authors note that this ionization probably corresponds in part to amide ionization, so that the equilibrium constant for hydroxide addition (including all possible sites) is presumably less than 0.25 M^{-1}.

(16) Guilbert, C. C.; Johnson, S. L. *Biochemistry* **1977**, *16*, 335.

(17) Rowen, J. W.; Kornberg, A. *J. Biol. Chem.* **1951**, *193*, 497.

(18) This is a composite equilibrium constant that includes adducts formed at all possible sites of water addition (1-2, 1-4, and 1-6). Guilbert and Johnson[16] suggest that hydroxide addition occurs mainly at C-2. If that is the case, equilibrium constants for addition at other sites must be less favorable.

Book Reviews*

Nuclear Magnetic Resonance: A Specialist Periodical Report. Volume 14. Edited by G. A. Webb (University of Surrey). The Royal Society of Chemistry: London. 1985. 1 + 383 pp. $127.00. (Available from the ACS, Washington.) ISBN 0-85186-372-8.

This annual volume surveys the NMR literature for the period from June 1983 to May 1984. In the process, it documents the impressive scope and vitality of current NMR research. The volume contains 4633 references, including a list of 441 books and review papers pertaining to NMR that were published during the review period.

The book contains twelve chapters: Theoretical and Physical Aspects of Nuclear Shielding (Cynthia J. Jameson), Applications of Nuclear Shielding (G. E. Hawkes), Theoretical Aspects of Spin–Spin Couplings (A. Laaksonen), Applications of Spin–Spin Couplings (D. F. Ewing), Nuclear Spin Relaxation in Liquids and Gases (H. Wiengartner), Solid State NMR (P. S. Belton, S. F. Tanner, and K. M. Wright), Multiple Resonance (H. C. E. Farlane and W. McFarlane), Natural Macromolecules (D. B. Davies), Synthetic Macromolecules (A. V. Cunliffe), NMR of Living Systems (P. G. Morris), NMR of Paramagnetic Species (K. G. Orrell), and NMR of Liquid Crystals and Micellar Solutions (O. Soderman).

This volume is highly recommended for anyone who is trying to keep up with the NMR literature, and the series as a whole is an excellent place to begin a literature search for NMR data.

Douglas C. McCain, *University of Southern Mississippi*

Handbook of Stochastic Methods for Physics, Chemistry and The Natural Sciences. 2nd Edition. By C. W. Gardiner (University of Waikato, New Zealand). Springer-Verlag: New York. 1985. xix + 442 pp. $34.50. ISBN 3-540-15607-0.

An understanding of stochastic processes and the mathematical methods for their quantitation can provide substantial insight into many physical phenomena. This is a book of considerable value in that it provides the physical scientist with relatively easy access to that understanding. The author's intent is to provide, in relatively simple and appealing terms, an accurate and fairly comprehensive treatment of subject matter discussed in many other similarly titled books at either a superficial or impractically detailed level. The author has succeeded in this regard; the book is, indeed, comprehensive, accurate, yet mercifully non-rigorous. Practical examples and demonstrations rather than formal proofs provide the target audience with an intuitive understanding of some rather difficult material. Nevertheless, those with a more advanced tinuity of the discussion as well as the somewhat unusual approach the author has taken.

The book's ten chapters may be grouped into three "parts". Part I (1. Introduction; 2. Probability Concepts and Definitions; 3. Markov Processes) provides a clear introduction to the primary material which follows. The reader is assumed to have a good working knowledge of advanced calculus and partial differential equations. Part II (4. Ito Calculus and Stochastic Differential Equations; 5. The Fokker–Planck Equation; 6. Approximation Methods for Diffusion Processes) forms the "primary core" of the book. Rather than basing his discussion upon the Fokker–Planck equation, the author has chosen to discuss stochastic processes in terms of the associated stochastic differential equations. His unique presentation of the essential elements of Ito calculus facilitates this approach which, in turn, facilitates the demonstration of approximation methods (small noise perturbational expansion and adiabatic elimination) which should appeal to the pragmatically minded. Part III (7. Master Equations and Jump Processes; 8. Spatially Distributed Systems; 9. Bistability, Metastability, and Escape Problems; 10. Quantum Mechanical Markov Processes) provides illuminating demonstrations and applications of the foregoing material.

This second edition includes some reference to recent progress in the field but differs from the first edition primarily in providing a more correct definition of the Stratonovich stochastic integral and a somewhat better discussion of predetermined boundary conditions of the Fokker–Planck equation. Unlike the first edition, the second is available only in soft-cover, presumably to offset the cost of the superlative typesetting.

This book would be an excellent resource for any serious student of stochastic processes.

Robert S. Pearlman, *The University of Texas at Austin*

Books on Mathematics and Physics

The Elements of Graphing Data. By William S. Cleveland (AT&T Bell Laboratories). Wadsworth Advanced Books and Software: Monterey, CA. 1985. xii + 323 pp. Cloth: $27.95. ISBN 0-534-03729-1. Paper: $18.95. ISBN 0-534-03730-5.

A goal of this book is "to raise the effectiveness of graphical data analysis and presentation in scientific and engineering journals." Both traditional and new methods are described, with many intriguing illustrations, and it does indeed look as though attention to the book's content would improve the communication of scientific data.

Statistical Analysis of Measurement Errors. By John L. Jaech (Exxon Nuclear Company). John Wiley & Sons: New York. 1985. xxvi + 293 pp. $29.95. ISBN 0471-82731-2.

The author uses maximum likelihood for experimental situations in

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*Unsigned book reviews are by the Book Review Editor.