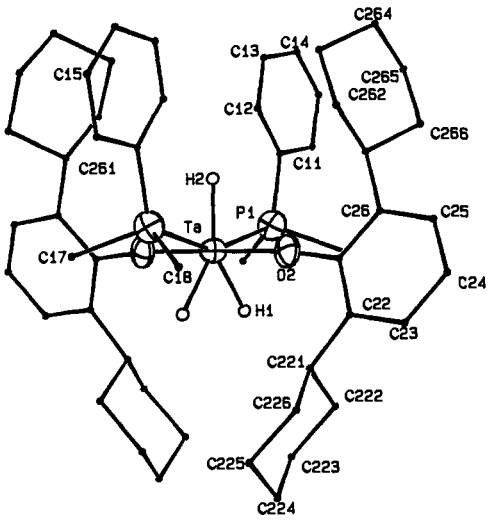

Figure 2. ORTEP view of **3a** emphasizing the central coordination sphere. Selected bond distances (Å) and angles (deg): Ta–O(2), 1.901 (6); Ta–P(1), 2.615 (3); Ta–H(1), 1.77 (9); Ta–H(2), 1.6 (2); O(2)–Ta–O(2), 179.2 (5); P(1)–Ta–P(1), 155.0 (1); P(1)–Ta–O(2), 89.0 (2), 91.2 (2); H(1)–Ta–H(1), 75 (5); H(1)–Ta–H(2), 143 (3); Ta–O(2)–C(21), 172.1 (8).

combined with the structural and infrared data unequivocally rule out the presence of an η^2-H_2 group in **1**.[5-7] The ^{1}H NMR spectra of the trihydride compounds (**2** and **3**) clearly resolve different multiplets in the ratio of 2:1 for the chemically nonequivalent hydride groups.[14] Although the unique hydride appears as a triplet of triplets, the remaining two hydrides are a complex pattern. The NMR spectroscopic data for all of the compounds show that exchange of the two chemically equivalent, cis hydride ligands is slow on the NMR time scale.[15,16]

Solutions of the trihydride compound (**3a**) in cyclohexane will carry out the catalytic hydrogenation of naphthalene to tetralin. Preliminary studies of this reactivity show a lack of pressure dependence above 300 psi of H_2, while at lower pressures the conversion rate decreases.[17] Furthermore the reaction is inhibited by addition of an extra equivalent of PMe_2Ph to the reaction mixture. Further mechanistic studies of this and of other reactivity of these new hydride compounds are underway.

Acknowledgment. B.C.A. would like to thank the SERC for the award of a NATO Postdoctoral Fellowship.

Supplementary Material Available: Microanalytical and full spectroscopic data for the new compounds, full details of the crystallographic studies, and tables of fractional coordinates, anisotropic thermal parameters, and full bond distances and angles (41 pages); tables of observed and calculated structure factors for **1b** and **3b** (26 pages). Order information is given on any current masthead page.

(14) Selected ^{1}H NMR data (200 M Hz; C_6D_6): (**1a**) δ 15.89 (m, 2 H, Ta-H); ^2J(P–H) = 65.8 Hz, ^2J(P'–H) = 7.0 Hz, ^2J(H–H) = –7.4 Hz, ^2J(P–P) = 163.6 Hz. (**1b**) δ 16.55 (m, 2 H, Ta-H); ^2J(P–H) = 64.4 Hz, ^2J(P'–H) = 7.2 Hz, ^2J(H–H) = –7.9 Hz, ^2J(P–P) = 159.0 Hz. (**1c**) δ 17.77 (m, 2 H, Ta-H); ^2J(P–H) = 65.0 Hz, ^2J(P'–H) = 7.0 Hz, ^2J(H–H) = –6.2 Hz, ^2J(P–P) = 156.7 Hz. (**2**) δ 13.54 (m, 2 H); δ 12.80 (tt, 1 H), ^2J(P–H) = 36.4 Hz, ^2J(H–H) = 5.5 Hz. (**3a**) δ 13.60 (m, 2 H, Ta-H), δ 12.98 (tt, 1 H, Ta-H); ^2J(P–H) = 34.0 Hz, ^2J(H–H) = 5.6 Hz. (**3b**) δ 13.52 (m, 2 H, Ta-H), δ 13.34 (m, 1 H, Ta-H).

(15) Luo, X.-L.; Schulte, G. K.; Demou, P.; Crabtree, R. H. *Inorg. Chem.* **1990**, *29*, 4268.

(16) Leeaphon, M.; Fanwick, P. E.; Walton, R. A. *J. Am. Chem. Soc.* In press.

(17) A typical experiment utilized 0.10 mmol of $(OAr)_2Ta(H)_3(PMe_2Ph)_2$ (**3a**) and 2.0 mmol of naphthalene in 3.0 mL of cyclohexane and was run unstirred in a Parr series 4561 minireactor. After 24 h at 90 °C/1200 psi of H_2, analysis of the reaction mixture by ^{1}H NMR spectroscopy showed 61% conversion to tetralin with <95% of the original trihydride compound still present.

General Method for Determining Kinetic Isotope Effects That Utilizes Isotopically Engendered Chirality

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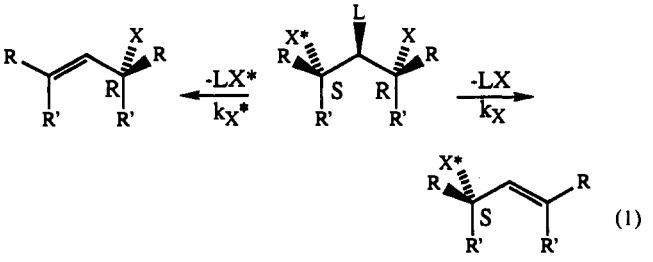
Kinetic isotope effects (KIE) are particularly useful in deducing transition-state characteristics in a variety of chemical transformations. Such measurements have typically involved inter- and intramolecular competitive rate studies of isotopically labeled substrates or mass spectral analysis of reaction products to determine the isotope distribution. We now introduce a method based on the relative rates of the formation of "nominal enantiomers" from a single chiral precursor that contains two isotopes of the same element. The method can be applied to reactions in which a molecule with a plane of symmetry gives, under normal conditions, a racemic mixture. If the plane of symmetry is removed by stereospecific isotopic substitution, then the ratio of an enantiomer to its isotopically labeled optical antipode in the product arises directly from the kinetic isotope effect. In any system the rates of reaction of enantiotopic atoms (X) are identical. However, this degeneracy of rates can be removed by an isotopic substitution (X*), and preferential reaction involving X or X* will, in principle, lead to an excess of one stereoisomer. The measurement of the optical purity of the starting material and the product can then be used to determine the ratio of rate constants k_X/k_{X*} (eq 1). Strictly speaking, the reaction does not produce two enantiomers. Although the primary chiral units will be of opposite absolute configuration, one of the stereoisomers will be isotopically labeled. The chirality at C_3, as a result of isotopic substitution (X*), should have a negligible effect upon the optical rotation of the final product.



To formulate an equation in which the k_H/k_D is determined from optical purity, the definition of enantiomeric excess (ee) can be used to derive an expression for the KIE utilizing initial (ee_i) and final (ee_f) optical purities.

$$ee = \frac{\text{atoms of } R - \text{atoms of } S}{\text{atoms of } R + \text{atoms of } S} = \frac{k_H - k_D}{k_H + k_D} \text{ and } \frac{k_H}{k_D} = \frac{ee_i - ee_f}{ee_i + ee_f} = ([\alpha]^{25}_i - [\alpha]^{25}_f)/([\alpha]^{25}_i + [\alpha]^{25}_f)$$

The validity of this method has been demonstrated by applying it to the enantiomeric selectivity in the formation of the chiral alkene (*E*)-cyclooctene (**1**). The highly strained (*E*)-cyclooctene (**1**) is formed by a suprafacial (syn) mode of elimination from **2** (eq 2) irrespective of the base–solvent system employed.[1a,b,e] With strong bases such as RLi,[1b] $CH_3SOCH_2^-Na^+$ in DMSO,[1e] or KNH_2,[1a] the elimination proceeds through an α',β (ylide) mechanism while an E2 pathway has been established for the

(1) (a) Bach, R. D.; Andrzejewski, D. *J. Am. Chem. Soc.* **1971**, *93*, 7118. (b) Bach, R. D.; Bair, K. W.; Andrzejewski, D. *J. Am. Chem. Soc.* **1972**, *94*, 8608. (c) Bach, R. D.; Bair, K. W.; Andrzejewski, D. *J. Chem. Soc., Chem. Commun.* **1974**, 819. (d) Bach, R. D.; Andrzejewski, D.; Bair, K. W. *J. Chem. Soc., Chem. Commun.* **1974**, 820. (e) Bach, R. D.; Knight, J. W. *Tetrahedron Lett.* **1979**, 3815.

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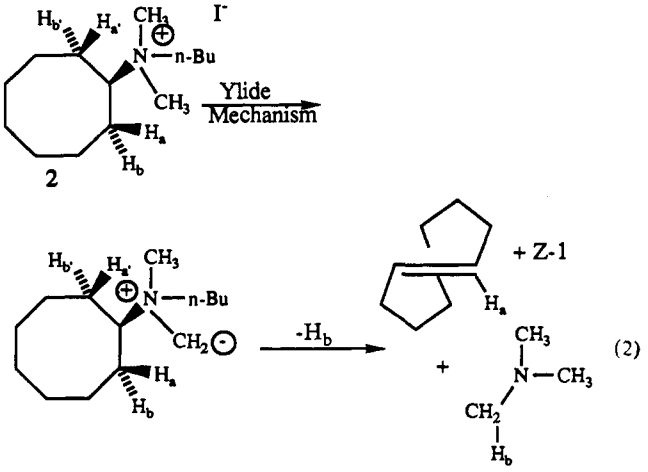
Table I. Elimination of (1*S*,2*S*)-**2** with Various Bases

base/solvent	*T*, °C	*Z*:*E*[a]	k_H/k_D[b]	$[\alpha]_f$[c]	k_H/k_D[d]	TC[e]
NaH/DMSO	25	56:54	1.40[f]	57.45	1.39 ± 0.02	
KNH_2/NH_3	−33	31:69	2.30	144.85	2.41 ± 0.03	1.50
t-BuOK/DMSO	25	18:82	3.25	185.74	3.27 ± 0.08	

[a] Determined by gas liquid phase chromatography. [b] Determined by mass spectral techniques. [c] $[\alpha]_i$ −349.6°. [d] Determined by optical rotation method. [e] Temperature corrected to 25 °C. [f] See ref 1.

weaker oxygen bases such as $KOC(CH_3)_3$ in DMSO or benzene solvent.[1e,2]



The synthesis of optically active **2** was achieved as previously reported for the racemic compound by a series of chemical interconversions of known stereochemistry.[1] The monosubstituted cyclooctylammonium iodide **2** has four diastereotopic β-hydrogens. Base abstraction of one of the equivalent syn protons (H_a or $H_{a'}$) by a suprafacial mode of elimination or antarafacial elimination of H_b (or $H_{b'}$) affords the (*Z*)-alkene. Since antarafacial elimination to form (*E*)-cyclooctene has been excluded[1a,b,c] for strain and steric reasons, the only pathway for (*E*)-alkene formation is a suprafacial 1,2-elimination of an anti β-hydrogen (H_b or $H_{b'}$). Examination of molecular models reveals the existence of two rapidly equilibrating conformers of **2**, where the leaving group and the *pro-S* and *pro-R* hydrogens enjoy the synperiplanar relationship required in the transition state for suprafacial elimination (Figure 1).

Introduction of molecular chirality at either of the two adjacent prochiral centers in **2** by stereospecific anti isotopic substitution of either the *pro-S* or *pro-R* hydrogen with deuterium will introduce two chiral centers in the molecule. Elimination of the *pro-S* or *pro-R* hydrogen (H_b or $H_{b'}$) at identical rates would obviously afford a racemic mixture of enantiomers of the inherently dissymmetric (*E*)-cyclooctene. If $k_H/k_D > 1$ then one enantiomer of (*E*)-cyclooctene will be formed at a faster rate than the other and allow the direct measurement of k_H/k_D for alkene formation by either the ylide or the E2 pathway. A suprafacial α′,β deuterium abstraction from (1*S*,2*S*)-**2** will afford the starting alkene (−)-(*R*)-**1**, while hydrogen abstraction will yield (+)-(*S*)-**1** *of the opposite absolute configuration* of the double bond. The optical yield (% ee) of such an elimination process would thereby provide a direct measurement of a primary kinetic isotope effect.

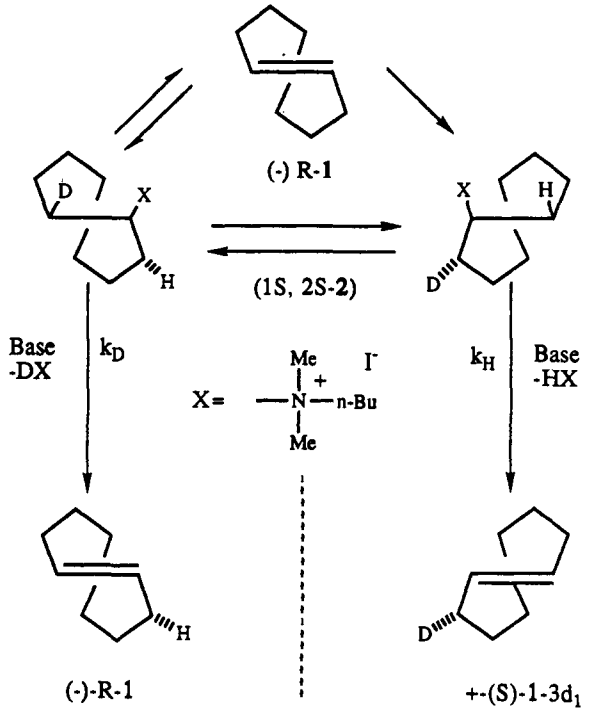


Figure 1.

Suprafacial (α′β) elimination of (1*S*,2*S*)-**2**, derived from (*R*)-**1** ($[\alpha]^{25}_D$ −349.6°), with dimsyl anion in DMSO[1e] afforded a (*Z*)- to (*E*)-alkene ratio of 46.54. The (*E*)-cyclooctene, after purification by preparative gas liquid phase chromatography had $[\alpha]^{25}_D$ 57.5°. The kinetic isotope effect may be calculated from $[\alpha]^{25}_i$, the initial rotation of the starting alkene, and $[\alpha]^{25}_f$, the final rotation of the alkene after the elimination sequence. A syn k_H/k_D of 1.39 is in good agreement with a KIE of 1.4 previously determined by classical mass spectral analysis[1e] (Table I). An intramolecular ylide mechanism has also been established for elimination with KNH_2 in liquid ammonia.[1a] At the lower temperature (−33 °C) the recovered (*E*)-cyclooctene exhibited a rotation of $[\alpha]^{25}_D$ 144.9° and a syn k_H/k_D of 2.41. Elimination of (1*S*,2*S*)-**2** by the weaker oxygen base (*t*-BuOK/DMSO) proceeds by an exclusive syn E2 mechanism. The recovered (*E*)-**1** had an average rotation of $[\alpha]^{25}_D$ 185.7 and a syn k_H/k_D of 3.27, in excellent agreement with prior data.

This method for determining isotope effects is independent of the optical purity of the starting alkene and in principle may be used for any chiral alkene that is produced by a single reaction pathway from a chiral precursor.[10] These basic concepts can be

(2) With bicyclic substrates, competing E2 and ylide pathways were noted.[1c] The ylide intermediates are formed reversibly in NH_3[1d] and DMSO.[1e]

(3) Coke, J. L.; Mourning, M. C. *J. Am. Chem. Soc.* **1968**, *90*, 5561.

(4) *trans*-Cyclooctane-1,2-diol was resolved via its *trans*-monophthalate half-ester with strychnine as the resolving agent.[5] The corresponding (1*S*,2*S*)-10-phenyl-9,11-dioxobicyclo[6.3.0]undecane (**3**)[6] was prepared quantitatively by *p*-toluenesulfonic acid catalyzed acetal formation with benzaldehyde. The reaction of (1*S*,2*S*)-**3** with *n*-BuLi produced (−)-(*R*)-(*E*)-cyclooctene (**1**) (60%), which upon purification by preparative gas liquid phase chromatography (NMPN) had $[\alpha]^{25}_D$ −349.6° (*c* 1.35, CH_2Cl_2). This is clearly the method of choice for the large-scale preparation of optically active (*E*)-cyclooctene.[7] Suprafacial deuterioboration of the accessible face (*re*–*re*) of the carbon–carbon double bond of (*R*)-**1**, $[\alpha]^{25}_D$ −349.6°, generates two asymmetric centers of the same optical purity (81%) as the starting alkene. Substitution with NH_2Cl, which occurs with retention at C_1,[9] gave (1*S*,2*S*)-cyclooctylamine-2-d_1.

(5) Corey, E. J.; Shulman, J. I. *Tetrahedron Lett.* **1968**, 3655.

(6) Hines, J. N.; Peagram, M. J.; Thomas, E. J.; Whitham, G. H. *J. Chem. Soc. Perkin Trans. 1* **1973**, 2332.

(7) Resolution of (*E*)-cyclooctene is readily achieved by a platinum complex containing a chiral amine ligand.[8] However, large-scale resolution by this method is very expensive.

(8) Cope, A. C.; Moore, W. R.; Bach, R. D.; Winkler, H. J. S. *J. Am. Chem. Soc.* **1970**, *92*, 1243.

(9) Brown, H. C.; Wolfgang, R. H.; Breuer, E.; Murphy, W. S. *J. Am. Chem. Soc.* **1964**, *86*, 3565.

(10) This method is conceptually similar to the polarimeter differential method involving the reaction of a racemate made up of one labeled enantiomer. See: Bergson, G.; Matsson, O.; Sjoberg, S. *Chem. Scr.* **1977**, *11*, 25.

extended to the measurement of secondary KIE and those reactions involving heavy isotopes such as ^{13}C and ^{18}O (e.g., bis anionic oxy-Cope rearrangement).

Acknowledgment. Partial support of this work by the National Institutes of Health (CA 47348-03) and the Ford Motor Company is gratefully acknowledged.

The Anomalous Hydrophilic Character of Proline

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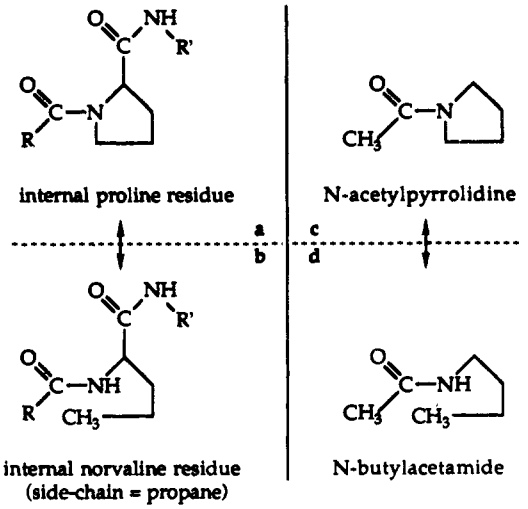
Amino acid residues vary greatly in their affinities for watery surroundings, as indicated by free energies of solvation of their side chains, determined by measuring their equilibria of transfer from neutral aqueous solution to the vapor phase[1] or to a nonpolar solvent such as cyclohexane.[2] These differences have proven useful in identifying portions of transmembrane proteins that are likely to be located within the lipid bilayer,[3] in analyzing the biological properties of peptide analogues and mutant proteins, and in attempting to understand the relationship between the three-dimensional structures of proteins and their amino acid sequences.[4]

Because amino acids and their derivatives do not enter truly nonpolar environments in quantities that can be detected, measurements of water-to-vapor and water-to-cyclohexane distribution coefficients have been confined to compounds of the type R-H, where R represents the side chain of an amino acid. Thus far, these scales of hydrophilic character have remained incomplete because the "side chain" of proline cannot be represented in this way (Scheme I).

The physical properties of proline might be considered to be comparable with those of valine or norvaline, nonpolar amino acids with which it shares a side chain containing three carbon atoms (Scheme I). However, amides of secondary amines are typically 10–20-fold less hydrophilic than amides of primary amides,[5] so that an internal proline residue would be expected to be correspondingly less hydrophilic (or more hydrophobic) than a valine or norvaline residue at a similar position. It seemed desirable to put this possibility to an experiment test.[6]

Scheme I shows a means of circumventing the difficulty of describing the side chain of proline by a side chain R. *N*-Acetylpyrrolidine (c) and *N*-butylacetamide (d) are structurally related to each other as an internal proline residue (a) is related to an internal norvaline residue with a normal propyl group as a side chain (b). If the water-to-vapor or water-to-cyclohexane distribution coefficients of *N*-acetylpyrrolidine and *N*-butylacetamide were known, then it should be possible to apply their ratio to the value for *n*-propane, to arrive at an approximate value for the effective distribution coefficient of the side chain of an internal proline residue,[7] placing it on a common side with the side chains of the other amino acids.

Scheme I[a]



[a] An internal proline residue (a) is related in structure to an internal norvaline residue (b) as *N*-acetylpyrrolidine (c) is related to *N*-butylacetamide (d).

Table I. Equilibria of Transfer from Vapor to Water ($K_{v\to w}$) and from Cyclohexane to Water ($K_{chx\to w}$)

	N-acetylpyrrolidine	*N*-butylacetamide
$K_{v\to w}$ (25 °C)	1.54 (±0.3) × 10^7	6.7 (±1.2) × 10^6
$\Delta G_{v\to w}$ (25 °C)	−9.77 ± 0.15 kcal/mol	−9.28 ± 0.12 kcal/mol
$K_{chx\to w}$ (8 °C)	459 ± 26	217 ± 15
$K_{chx\to w}$ (17 °C)	240 ± 4	130 ± 1.6
$K_{chx\to w}$ (25 °C)	172 ± 8	79 ± 0.3
$K_{chx\to w}$ (37 °C)	94.3 ± 2.4	40 ± 0.4
$\Delta G_{chx\to w}$ (25 °C)	−3.04 ± 0.03 kcal/mol	−2.58 ± 0.002
$\Delta H_{chx\to w}$ (25 °C)	−9.26 ± 0.3 kcal/mol	−10.2 ± 0.2 kcal/mol
$\Delta S_{chx\to w}$ (25 °C)	−20.9 ± 1.0 cal/(deg/mol)	−25.6 ± 0.6 cal/(deg/mol)
$T\Delta S_{chx\to w}$ (25 °C)	−6.22 ± 0.3 kcal/mol	−7.62 ± 0.3 kcal/mol

N-Acetylpyrrolidine and *N*-butylacetamide were prepared by treatment of the parent amines with acetic anhydride-*1*-^{14}C, followed by redistillation to remove the last traces of radioactive acetate. Water-to-vapor distribution coefficients were determined at 25 °C by dynamic vapor pressure measurements;[1] and water-to-cyclohexane distribution coefficients were determined by distribution measurements using radioactivity as a means of analysis[2] and also by proton NMR analysis.[2] These experiments were performed at 8, 17, 25, and 37 °C to determine enthalpies of transfer. The results are shown in Table I.

Solvation by water of *N*-butylacetamide was accompanied by a more negative enthalpy change than solvation *N*-acetylpyrrolidine, in accord with expectations based on their differing H-bonding capabilities. However, solvation of *N*-acetylpyrrolidine was accompanied by a very much less negative entropy change, more than fully compensating for this difference. As a result, *N*-acetylpyrrolidine was roughly twice as hydrophilic as *N*-butylacetamide. Proline often appears in solvent-exposed positions in proteins, in part because its structure excludes it from occupying internal positions in α-helices and β-structures but allows it to occur at reverse turns that tend to be found near protein surfaces.[8]

(1) Wolfenden, R.; Andersson, L.; Cullis, P. M.; Southgate, C. C. B. *Biochemistry* **1981**, *20*, 849.
(2) Radzicka, A.; Wolfenden, R. *Biochemistry* **1989**, *27*, 1664–1670.
(3) Kyte, J.; Doolittle, R. F. *J. Mol. Biol.* **1982**, *157*, 105.
(4) For a comprehensive review, see: Edsall, J. T.; McKenzie, H. A. *Adv. Biophys.* **1983**, *16*, 53.
(5) *N,N*-Dimethylacetamide exceeds *N*-methylacetamide by a factor of 13 in its water-to-vapor distribution coefficient (Wolfenden, R. *Biochemistry* **1978**, *17*, 201–204, and by a factor of 20 in its water-to-cyclohexane distribution coefficient (Gibbs, P.; Wolfenden, R., unpublished).
(6) Octanol–water distribution measurements on acylamino acid amides have suggested that proline residues may be more polar than valine (Yunger, L. M.; Cramer, R. D., III. *Mol. Pharmacol.* **1981**, *20*, 602). However, wet octanol has been found to interact specifically with certain heterocyclic solutes (ref 2) so that the meaning of this observation is uncertain.
(7) In most cases, free energies of solvation appear to be additive: Butler, J. A. V. *Trans. Faraday Soc.* **1937**, *33*, 229–237. Hine, J.; Mookerjee, P. K. *J. Org. Chem.* **1975**, *40*, 292–230. Cabani, S.; Gianni, P.; Mollica, V.; Lipori, L. *J. Solution Chem.* **1981**, *10*, 563–595.
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