The differences in free energies of hydration were obtained from Monte Carlo simulations by using the same procedures described in detail previously for the interconversion of methanol and ethane in water.[5] Statistical perturbation theory[18] allowed computation of $\Delta\Delta G^{hyd}$ as one solute was progressively mutated into another. Three steps were used for the interconversion of the neutral molecules and four for the anions with double-wide sampling.[5] The simulations were run at 298 °C and 1 atm for the solute plus 216 water molecules in a cube with periodic boundary conditions. Metropolis and preferential sampling were employed along with an 8.5-Å cutoff for the intermolecular interactions, feathered between 8.0 and 8.5 Å,[9] and based on roughly the center-of-mass separations. Each step in a mutation had an equilibration phase of ca. 10^6 configurations followed by averaging over an additional 1.5×10^6 or 2×10^6 configurations. Convergence of the $\Delta\Delta G^{hyd}$'s was rapid and was verified by running several of the perturbations forwards and backwards.

The critical input to the simulations is the intermolecular potential functions. The well-proven TIP4P model was used for water,[19] and parameters for CH_3SH,[20] CH_3CH_3,[21] and CH_3CN[22] were available from prior extensive studies of the corresponding pure liquids. Coulomb and Lennard-Jones interactions are included acting between sites located mostly on the nuclei. The parameters for the anions were derived by fitting to geometrical and energetic results from ab initio 6-31+G(d) calculations on low-energy forms of anion-water complexes, as in previous studies.[9,23] This basis set has been shown to perform extremely well in reproducing experimental anion-water interaction energies.[12] The resultant atomic charges and Lennard-Jones parameters for the anions are summarized in Table I. The latter are quite standard and transferable, so most of the fitting involved the charges. All atoms are explicit for the anions and an additional interaction site was found to be needed in a lone-pair location for $C_2H_5^-$. It should be noted that these three anions were chosen in part because they all have optimal interactions with a water molecule weaker than 20 kcal/mol: CH_3S^- (12), CH_2CN^- (13), and $CH_3CH_2^-$ (18). This helps limit potential errors in the perturbation calculations.

The key results are summarized in Table II. For acetonitrile, the computed $\Delta\Delta G^{hyd}$'s for both the anion and acid agree well with the experimental data. The error in the ab initio gas-phase acidity is also not large, so the resultant prediction for the pK_a (28.6) is close to the experimental value (25 ± 1)[24] and supports the viability of the computational procedure. If the ab initio $\Delta\Delta G_{gas}$ is replaced by the experimental finding (11.7), the predicted pK_a is 23.7.

For ethane, the experimental $\Delta\Delta G^{hyd}$ for the acids is well reproduced, and the ethyl anion is predicted to be better hydrated by 6.4 kcal/mol than methanethiolate. Combination with the ab initio $\Delta\Delta G_{gas}$ yields an a priori predicted pK_a of 50.6 which would be reduced to 47.3 with use of the experimental $\Delta\Delta G_{gas}$.[16] These are direct estimates in water, uncomplicated by aggregation and ion-pairing effects or use of nonaqueous solvents.[2] The largest uncertainty in the calculations is in the choice of potential function parameters and lack of explicit polarization in the functions themselves. However, the parameters were obtained in a uniform manner from the 6-31+G(d) calculations, and the perturbation method is conducive to some cancellation of errors for the polarization problem, consistent with the excellent results for acetonitrile. The favorable hydration of $CH_3CH_2^-$ may be somewhat overestimated owing to the stronger anion-water interactions than for CH_3S^-. The effect should not amount to more than a few pK_a units, so our best estimate for the pK_a of ethane in water is still about 50. The a priori computation of this elusive quantity illustrates the power and versatility of modern theoretical methodologies.[26]

Supplementary Material Available: Geometrical and energetic details for the anions and anion-water complexes obtained from the ab initio calculations and potential functions (5 pages). Ordering information is given on any current masthead page.

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Haller–Bauer Cleavage of Open-Chain and Cyclic α-Phenyl Ketones Proceeds with Retention of Configuration

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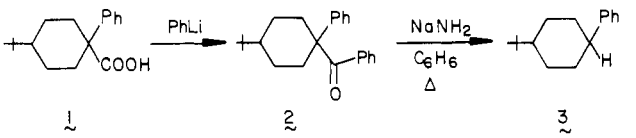
Originally, the Haller–Bauer reaction was designed to provide a means for amide synthesis via cleavage of nonenolizable ketones by $NaNH_2$.[1] In more recent times, the process has seen its greatest use as a tool for effecting the replacement of a carboxyl group by hydrogen as in the conversion of **1** to **3**.[2] C–C bond



1 2 3

cleavage is particularly effective when the incipient carbanion is stabilized, e.g., in benzylic[3] and cyclopropyl situations.[4] Walborsky has made particularly elegant use of Haller–Bauer decarboxylation in demonstrating that anionic centers on three-membered rings are configurationally stable.[4a-d] However, the inability of cyclopropyl anions to undergo inversion of configuration is intrinsic to these systems[5] and sheds no light in general terms on the stereochemical course of this useful reaction. We have now examined the Haller–Bauer cleavage of several open-chain and cyclic α-phenyl ketones and herein provide evidence showing conclusively that the *bond scission does not lead to racemic benzyl carbanions*

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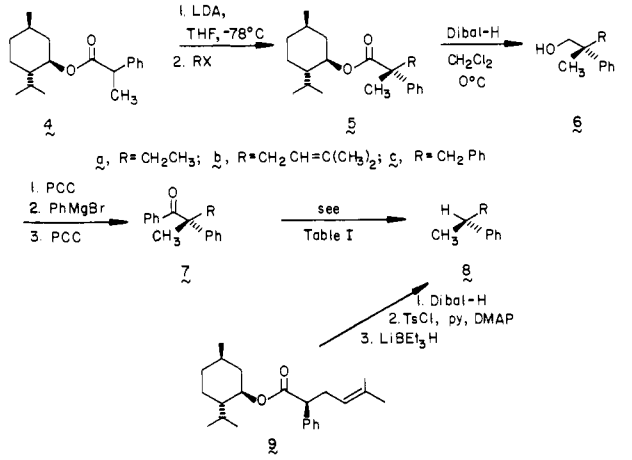
Table I. Haller–Bauer Cleavages of Optically Active **7b**, **7c**, and **14**

substrate	base	solvent	yield,[a] %	ee, %	optcl course[e]
		Open-Chain Series			
7b[b]	$NaNH_2$	C_6H_6	43	17	73, 27
	$LiNH_2$	C_6H_6	40–49	21	78, 22
	KO-*t*-Bu	*t*-BuOH	54–63	32	92, 8
7c[c]	$NaNH_2$	C_6H_6	35–36	22	72, 28
	KO-*t*-Bu	*t*-BuOH	57–66	41	91, 9
	KO-*t*-Bu	C_6H_6	51–56	30	80, 20
		Cyclic Series			
14[d]	$NaNH_2$	C_6H_6	26–32	16	72, 28
	KNH_2	C_6H_6	68	20	79, 21
	$LiNH_2$	C_6H_6	35–53	21	80, 20
	KO-*t*-Bu	*t*-BuOH	30–33	29	90, 10

[a] Duplicate experiments at a minimum. [b] Material of 38% ee. [c] Material of 50% ee. [d] Material of 36% ee. [e] % retention, % inversion.

but occurs reliably with retention of configuration. Consequently, with knowledge of the absolute configuration of the reaction substrate, this three-dimensional information can confidently be transferred to the product under normal circumstances.

The *l*-menthyl ester **4**[6] was transformed into its enolate and alkylated in turn with ethyl iodide, prenyl bromide, and α-bromotoluene. Capillary GC analysis revealed one diastereomer to



4, **5**, **6**

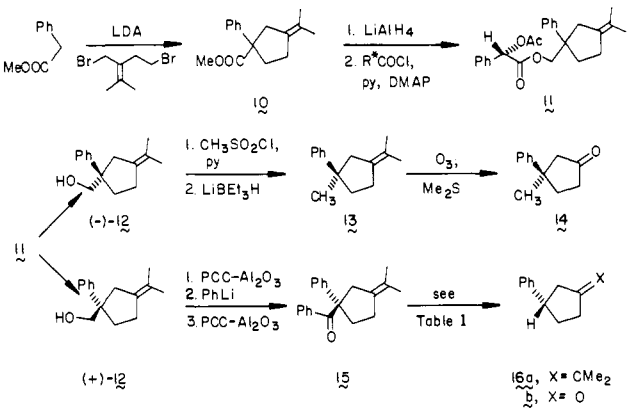
a, R = CH_2CH_3; **b**, R = $CH_2CH{=}C(CH_3)_2$; **c**, R = CH_2Ph

7, **8**, **9**

predominate in each case (63:37, 59:41, and 57:43, respectively). The diastereomeric excesses in the latter two examples could be increased to levels of 38% and 50% by MPLC methods.[7] The absolute configuration of the dominant stereoisomer in the ethyl series was ascertained by Dibal-H reduction of the mixture to **6a**, the pure *S* enantiomer of which has been reported, $[\alpha]^{25}_D$ +6.80° (neat).[3a] The rotation of the alcohol so produced, $[\alpha]^{25}_D$ −1.77° (neat), showed it to be enriched in material possessing the *R* configuration. Since **5a–c** are formed from a common intermediate,[8] the new quaternary centers in all three compounds are assumed to be configurationaly related. The subsequent elaboration of **7b** and **7c** was accomplished conventionally.

The results of the series of cleavage reactions carried out on **7b** (38% ee) and **7c** (50% ee) are summarized in Table I. The enantiomeric excess of **8b** was determined by comparison of the $[\alpha]_D$ value with that obtained for material derived from menthyl ester **9** of 27% de (capillary GC analysis). The absolute configuration of **8b** was elucidated by sequential ozonolysis and sodium borohydride reduction to give (*S*)-(+)-3-phenylbutanol.[9] Comparison of the $[\alpha]_D$ values recorded for **8c** with those reported[10] for 1,2-diphenylpropane revealed the absolute configuration and enantiomeric excess directly.

An independent line of investigation was pursued in the cyclopentane series. Ideally, the site of Haller–Bauer cleavage should not be subjected to any element of serious steric compression. Principally for this reason, a remote isopropylidene substituent as in **10** was deployed to introduce chirality. Following reduction



10, **11**, (−)-**12**, **13**, **14**, (+)-**12**, **15**, **16a**, X = CMe_2; **b**, X = O

of racemic **10**, the alcohol was converted to its *O*-acetylmandelate ester **11**, and the diastereomers were partially separated by chromatography.[11] After saponification, the proper absolute configurational assignments to (−)-**12** (30% ee) and (+)-**12** (36% ee) were formalized by reduction of (−)-**12** to (−)-**13** and ozonolysis to give **14**, $[\alpha]^{26}_D$ +4.8° (*c* 1.02, $CHCl_3$). That this ketone is the *R* enantiomer rests on its rotatory relationship to the known (*R*)-(+)-*p*-tolyl homologue.[12] Once (+)-**12** had been transformed into (+)-**15** as before, the various cleavage reactions compiled in Table I were performed. Direct evidence bearing on the *S* configuration and enantiomeric purity of (+)-**16a** was gained by conversion to *S*-(−)-**16b**.[13]

For those cleavage reactions involving amide ion in refluxing benzene solution, the stereospecificity ranges from 72–80% retention, with counterion effects in the order $Na^+ < K^+ \sim Li^+$.[14] The level of stereochemical control can be enhanced appreciably by making recourse of potassium *tert*-butoxide in *tert*-butyl alcohol solution,[15] where levels of retention on the order of 80–84% are routinely attained. Since the nucleophiles and solvents differ from each other in so many respects, some alteration in mechanism is unavoidable. Nonetheless, these changes do not affect the obviously strong preference for replacing benzoyl by hydrogen from the front side of the stereogenic center.[16]

(6) Although higher stereoselectivity might be attainable with other controller groups (for example, Corey, E. J.; Peterson, R. T. *Tetrahedron Lett.* **1985**, 5025), menthol was selected because of its ready availability and low cost, and because the level of stereoselectivity is adequately high for the present purposes.

(7) For **5a**, $[\alpha]^{23}_D$ −59.2° (*c* 6.4, $CHCl_3$); **5b**, $[\alpha]^{24}_D$ −64.2° (*c* 3.3 $CHCl_3$); **5c**, $[\alpha]^{24}_D$ −87.9° (*c* 4.2, $CHCl_3$). The values reported for **5b** and **5c** are for the enriched mixtures after chromatography.

(8) The actual *E*:*Z* distribution of enolates within 4^- is not known. The common predominance of *R* stereochemistry in **5a–c** is not only inferred primarily on mechanistic grounds but also derives from the uniformly levorotatory nature of the alcohols and the more rapid elution of the major diastereomers during MPLC and GC.

(9) The reported $[\alpha]^{25}_D$ value for the *R* alcohol is −39.0° (neat): Cram, D. J. *J. Am. Chem. Soc.* **1952**, *74*, 2137.

(10) The reported $[\alpha]^{25}_D$ values of this hydrocarbon are (*S*) = +76.7° (*c* 2.3, $CHCl_3$) and (*R*) = −76.3° (*c* 2.0, $CHCl_3$): Barnes, R. A.; Juliano, B. R. *J. Am. Chem. Soc.* **1959**, *81*, 6462.

(11) The use of *O*-acetylmandelate esters for resolution was first reported by Whitesell [Whitesell, J. K.; Reynolds, D. *J. Org. Chem.* **1983**, *48*, 3548].

(12) $[\alpha]^{25}_D$ +9.8° ($CHCl_3$), 90% ee. Posner G., private communication. Consult Posner et al. (Posner, G. H.; Kogan, T. P.; Hulce, M. *Tetrahedron Lett.* **1984**, 383).

(13) For the optically pure ketone, $[\alpha]^{25}_D$ −84.9° (*c* 0.72, $CHCl_3$). Posner, G., private communication. Compare: Taber et al. (Taber, D. F.; Raman, K.; Gaul, M. D. *J. Org. Chem.* **1987**, *52*, 28, footnote 14) and Posner et al. (Posner, G. H.; Hulce, M. *Tetrahedron Lett.* **1984**, 379).

(14) This ordering is presently viewed as being applicable only to benzylic systems. The manner in which counterion effects operate in heteroatomic systems is currently under active investigation.

(15) The level of stereochemical control reaches a maximum in *tert*-butyl alcohol. Consult also footnote 16. In addition, *n*-butylamine has given evidence of being widely variable in its ability to support chirality in an intermediate carbanion.

(16) In ethylene glycol with the potassium salt as base, **7c** cleaves to give **8c** with 61% inversion. This reversal in stereoselectivity as a function of solvent composition has been noted previously in a different context (Cram, D. J.; Kopecky, K. R.; Hauck, F.; Langemann, A. *J. Am. Chem. Soc.* **1959**, *81*, 5754).

What lies behind the tendency of the Haller-Bauer process to preserve configuration at the reaction center? Expectedly, the appreciable stereoselectivity parallels that noted when secondary and tertiary alcohols of related structure are subjected to base-promoted cleavage.[17] Closely related phenomena are certainly at play. Specific details will be presented in the full paper. Suffice it to say that the capacity for generating benzylic carbanions in chiral condition can now be conveniently accomplished.[18]

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FTIR Difference Studies on Apoproteins. Protonation States of Aspartic and Glutamic Acid Residues during the Photocycle of Bacteriorhodopsin

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Bacteriorhodopsin (bR) contained in the purple membrane of *Halobacterium halobium* is a light-driven proton pump coupled to ATP synthesis.[1] The chromophore of the functionally active light-adapted form (LA) is *all-trans*-retinal bound to the apoprotein Lys-216 via a protonated Schiff base (SBH^+), while that of the inactive dark-adapted form (DA) is a 6:4 mixture of 13-*cis*- and *all-trans*-retinal. Light isomerizes the chromophore to 13-cis and triggers the proton-translocation photocycle: $LA \rightarrow K_{625} \rightarrow L_{550} \rightarrow M_{412} \rightarrow O_{640} \rightarrow LA$. Clarification of protonation states of amino acid residues in this cycle is essential for understanding the proton-pumping mechanism. Fourier transform infrared (FTIR) difference spectroscopy is especially suited for this since it can detect changes occurring in single amino acid residues as well as the chromophore during the photocycle.[2-4]

Table I. Summary of Changes in Asp Groups in Various Bacteriorhodopsins[a]

	DA	LA	K	L	M
Asp-1	COO^- 1392	COO^-	COO^- 1395	COO^-	COOH 1761
Asp-2	COO^-	COO^-	COO^-	COO^-	COOH 1747
Asp-3	COOH 1734	COOH 1741	COOH 1734	COO^- 1399	COOH 1737
Asp-4	COOH	COOH 1734	COOH	COOH 1739	COO^- 1393

[a] Asp residues are numbered 1-4 simply for the ease of following the changes (also see text); thus FTIR difference bands tabulated in the same line may not necessarily represent the same Asp group. The Asp-3 1741 cm^{-1} value for LA is the average of 1738 (Figure 1a), 1742 (1b), 1741 (1c), and 1742 (1d). The Asp-4 1734 cm^{-1} value for LA is the average of 1736 (Figure 1c) and 1732 cm^{-1} (1d). The time-resolved FTIR results[3a,d] for L and M intermediates have been taken into account.

The studies have been performed on LA, DA, K, L, and M species of native bR and pigments enriched with [4-^{13}C]Asp and [5-^{13}C]Glu; bR regenerated from [9,13-CD_3]retinal[5] has also been used. The studies show that four Asp's undergo protonation/deprotonation or environmental changes and that Glu is not involved. Some earlier results[3d,4e,6] have been clarified or modified.

Syntheses of ^{13}C-labeled amino acids, incorporation into bR by growing the bacteria in a synthetic medium[7] containing the labeled amino acids, and isolation of purified bR[8] were carried out as described.[4e,6] Spectra were measured with Nicolet 7199 or Mattson SIRIUS 100 spectrometers. Since the Asp ω-carboxyl can be converted to Glu α-COOH (TCA cycle), prolonged incubation leads to a decrease in labeled Asp. Although conditions for achieving maximal incorporation of labeled Asp are not known, the [4-^{13}C]Asp content of the sample used in the present studies was ca. 85% (Figure 1d), this high incorporation being the crucial factor in the current FTIR analysis. Integrity of the sample was checked by electrophoresis[9] since bR grown in the synthetic medium[7] occasionally gave preparations with cleaved chains.

FTIR difference spectra between LA and other species are shown in Figure 1 (parts a-d) for regions 1780-1620 cm^{-1} and ca. 1390 cm^{-1}; negative and positive peaks belong, respectively, to LA and the other species. The following two characteristic bands were used: (a) The COOH bands at 1770-1720 cm^{-1} (solid curves), which shift to lower frequencies by $\sim$10 and $\sim$40 cm^{-1}, respectively, upon conversion to $COOD$[2-4] and ^{13}COOH.[3d,4e] (b) The ν_s COO^- bands at 1390 cm^{-1} (insets);[10] since δ CH_3 bands overlap in this region, [9,13-CD_3]retinal-bR spectra were also taken to corroborate results.

Conclusions derived from Figures 1a-1d (see also Table I) are as follows.

† Deceased August 14th, 1985. This paper is dedicated to the memory of L.E.

‡ Leave of absence from the Faculty of Pharmaceutical Sciences, University of Tokyo.

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(9) The system used was buffered at pH 8.8 (3.0 M Tris-HCl) and contained 0.1% SDS in 12.5% polymerized gel.

(10) The 1610-1550 cm^{-1} ν_{as} COO^- bands could not be seen due to overlap with amide II and water bands.

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