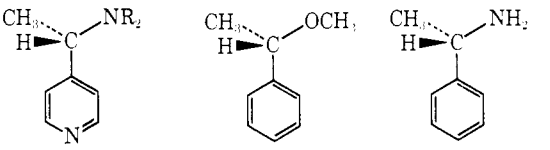
A 4-Pyridyl Group Attached to a Carbon Acid Introduces an Isoinversion Component into the Base-Catalyzed Racemization of the System[1]

Sir:

Previous studies demonstrated that functional groups capable of distributing the negative charge of carbanion intermediates onto electronegative atoms usually provided to the optically active conjugate carbon acids an isoinversion mechanism for base-catalyzed racemization.[2] Carbanion-conjugating substituents such as nitro,[2a,c,e] cyano,[2a,d] *N*,*N*-dimethylcarboxamido,[2a-c,e] sulfonyl (as part of a ring system),[2f] and pentachlorophenylcarboxy ester[2g] all exhibited this property in appropriate systems and media. A conducted tour mechanism provided a hypothesis for most of the isoinversion results.[2,3] In contrast, alkyl,[2e,4a,c] alkenyl,[4c,d] aryl,[4a-d] methoxyl,[4a,b] and haloaryl[2e] groups attached to carbanions generated from optically active carbon acids provided no isoinversion reaction pathway for racemization catalyzed by ordinary alkoxides or tertiary amine bases. With such substituents, base-catalyzed isotopic exchange of optically active carbon acids occurred with net retention of configuration in nonpolar media such as *tert*-butyl alcohol.

Because of the presence of the 4-pyridyl moiety in the imines that are involved in the biologically important transamination reaction,[5a] we have determined what effect this substituent has on the stereochemical fate of carbanions generated from optically active *N*,*N*-dimethyl-α-(4-pyridyl)ethylamine (**1**). The pyridyl nitrogen of **1** acidifies the carbon acid considerably[5b] through its ability to carry the negative charge of the derived carbanion. This structural feature might make a conducted tour mechanism for isoinversion available to the system. Comparison of the behavior in base-catalyzed hydrogen–deuterium exchange reactions of **1** and of **3**[4a] allows the effect of the pyridyl nitrogen to be assessed. The effects of a methoxy and of an *N*,*N*-dimethylamino group on a carbanion's stereochemical fate have been found to be identical.[6]

Racemic α-(4-pyridyl)ethylamine (**2**) was prepared as follows. Treatment of 4-cyanopyridine (Aldrich) with methyllithium in ether at −20° (3 hr) gave (52%) methyl 4-pyridyl ketone,[7] characterized as its picrate, mp 128–130°, lit.[8] mp 130–131°. The corresponding



(−)-(*S*)-1, R = CH_3
(−)-(*S*)-2, R = H

(−)-(*S*)-3

(−)-(*S*)-4

oxime was prepared (70%), mp 152–154°, lit.[9] mp 142°. This substance was reduced in ethanol with Raney nickel and hydrogen to give (70%) **2**, bp 104–106° (7 mm). Three–five recrystallizations of the salt of **2** and *d*-tartaric acid from aqueous methanol provided (30%) (−)-**2**[7] of maximum rotation (pure to glc), $[\alpha]^{25}_{589}$ −23.1°, $[\alpha]^{25}_{576}$ −26.6°, $[\alpha]^{25}_{546}$ −31.5° (*c* 1.53, ethanol). Exhaustive further recrystallizations of the tartrate salt and of other salts of optically active acids and **2** did not change the rotation of (−)-**2**, and the material is presumed to be essentially optically pure. The absolute configuration of (−)-**2** was shown to be *S* by CD spectral comparisons with optically pure (−)-α-phenylethylamine[10a] ((−)-**4**) of established *S* configuration.[10b] A 6×10^{-3} *M* solution of (−)-**4** in absolute ethanol gave a B-band[11] maximum at 257 nm (ϵ 167) in its uv spectrum and a low-intensity negative Cotton effect centered at 240 nm in its CD spectrum. A 1.2×10^{-3} *M* solution of (−)-**2** has a B-band[11] maximum at 255 nm (ϵ 2060) in its uv spectrum and a higher intensity negative Cotton effect centered at 237 nm in its CD spectrum. Eschweiler–Clark[12] methylation of optically pure (−)-**2** carried out for 48 hr at 25° and 2 hr at 40–50° gave partially racemic (−)-**1** (82%), pure to glc, whose hydrochloride salt was fractionally crystallized to provide racemic **1** and (−)-**1** (40%) of higher optical purity, $[\alpha]^{25}_{546}$ −42.8° (*c* 1.44, absolute ethanol). Reductive methylation of optically pure (−)-**2** with formaldehyde, hydrogen, and palladium[13] gave (98%) of (−)-**1**, which after preparative glc gave (−)-**1**[7] of $[\alpha]^{25}_{546}$ −60.6° (*c* 0.80, $CHCl_3$), $[\alpha]^{25}_{546}$ −44.6° (neat, 1 dm). Possibly configurational homogeneity was partially lost during this reductive methylation.

The above sample of (−)-**1** was used in measurements of the pseudo-first-order rate constants for racemization (k_α) and isotopic exchange (k_e). In *tert*-butyl alcohol-*O*-*d* (98% D by pmr),[4a] 0.038 *M* in (−)-**1** and 0.140 *M* in potassium *tert*-butoxide at 50.7 ± 0.1°, the racemization was followed polarimetrically with seven (ampoule technique) kinetic points through 74% reaction. Rotations were taken at 25° on the reaction solution, and use of hexadecane as an internal standard for glc analysis demonstrated that after 4.5 half-lives, 96 ± 3% of the original **1** was present. The isotopic exchange was followed by isolation (glc) of **1** from each ampoule and determination of deuterium content by a standardized mass spectral technique based on the molecular ion. Second-order rate constants[14] were

(1) This work was supported by U. S. Public Health Service Research Grant No. GM 12640-09 from the Department of Health, Education and Welfare.

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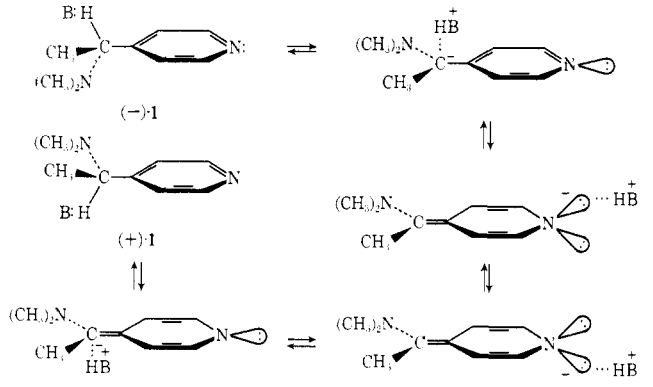
(14) Least-squares fit ± two standard deviations, correlation coefficients 0.9997–0.9611. M^{-1} sec^{-1}.

$k_e = 6.03 \pm 0.13 \times 10^{-6}$ and $k_\alpha = 8.05 \pm 0.18 \times 10^{-6}$. A second run was made similarly in 67% (by volume) hexamethylphosphoramide–33% *tert*-butyl alcohol-*O*-*d* (98% D by pmr),[4a] 0.100 *M* in (−)-**1** and 0.56 *M* in 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) at 175.0 ± 0.1°. The reactions were followed with seven points through 82% racemization with controls similar to the first run. Rate constants[14] were $k_e = 1.38 \pm 0.10 \times 10^{-6}$ and $k_\alpha = 3.30 \pm 0.25 \times 10^{-6}$. A third run identical with the second except that the reaction mixture was 0.005 *M* in DBN–DI gave the same rate constants within probable error of those obtained in the second run. Control runs established that (−)-**1** was optically stable to the temperatures of runs 1–3 in the absence of the added base and to glc purification conditions.

In *tert*-butyl alcohol–potassium *tert*-butoxide, $k_e/k_\alpha = 0.75$, whereas in HMPA–*tert*-butyl alcohol–DBN, $k_e/k_\alpha = 0.42$. The contrast in behavior of (−)-**1**, which contains a 4-pyridyl group, with that of (−)-**3**, which contains a phenyl group,[4a] is striking. The system without an electronegative atom on which to distribute the negative charge of its derived carbanion gave isotopic exchange with high retention of configuration in *tert*-butyl alcohol–potassium *tert*-butoxide ($k_e/k_\alpha \simeq 7$).[4a] In the same medium, 4-biphenylmethoxyphenylmethane gave isotopic exchange with even higher retention of configuration ($k_e/k_\alpha \simeq 33$).[4b] Clearly the nitrogen of the pyridyl group is responsible for this difference between systems **1** and **3**.

The results indicate the presence of an isoinversion mechanistic component in the racemization reactions of (−)-**1**. Thus the proton abstracted from the carbon acid is transported by the base from one face of the carbanion to the other, where it is released to form inverted carbon acid. This process must compete with drowning of the proton in the deuterium pool of the surrounding medium. The ion pair is structured somewhat by a series of hydrogen-bonded intermediates. This hypothesis is strengthened by the direct observation by Hogen-Esch[15] of hydrogen-bonded carbanions that are much stabilized by charge delocalization. The conducted tour mechanism envisioned for isoinversion is formulated.



The enzymatic 1,3-proton shifts in aza allylic systems that involve imines formed from pyridoxal or pyridoxamine and amino acids or α-keto acids occur stereospecifically.[16] Our results suggest that although the 4-pyridyl moiety of these imines offers an isoinversion mechanistic option for loss of stereospecificity, the enzyme system confines the proton being transferred to the aza allylic part of the anion's total π system.

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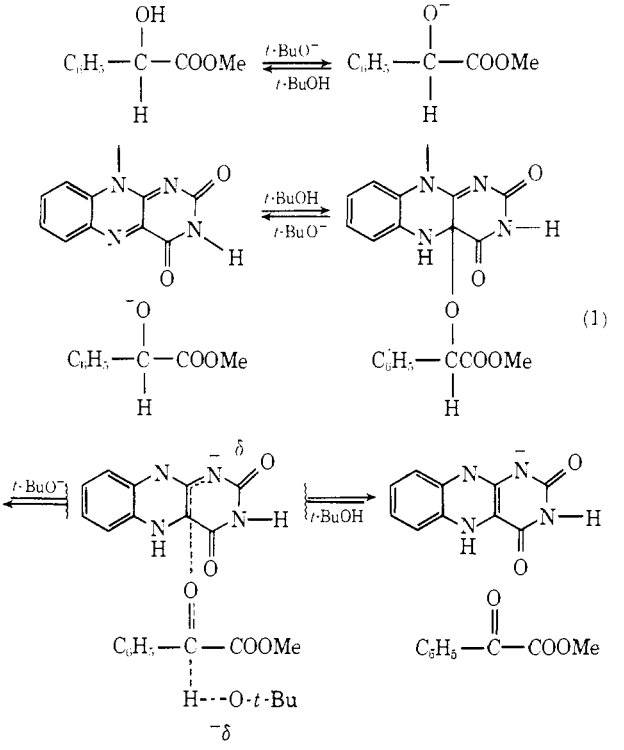
The Question of Covalent Intermediate Formation in the Flavine-Catalyzed Carbonyl to Carbinol Oxidation–Reduction Reaction

Sir:

The mechanisms by which flavoenzymes catalyze oxidation–reduction reactions are of much concern. We address ourselves herein to the interconversion of aldehydes (ketones) and alcohols coupled to the oxidation–reduction of flavine. In a study of the oxidation of 10-phenylisoalloxazine Brown and Hamilton[1] proposed 4a addition of alkoxide followed by base-catalyzed elimination of ketone (eq 1). In the forward



(1)

direction this mechanism has much appeal but in actuality model reactions involving oxidation of alcohol by flavine require extreme conditions. The reverse reaction requires nucleophilic attack of an enamine anion on the *carbonyl oxygen* with proton donation to the *carbonyl carbon*. No precedent for this highly unfavorable type reaction exists so that if the mechanism of eq 1 were correct the reduction of carbonyl compounds by reduced flavine should be a most difficult process. In fact, nonenzymatic flavine-catalyzed reduction of aldehydes and ketones may, depending on the carbonyl function, be quite facile in dilute aqueous

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