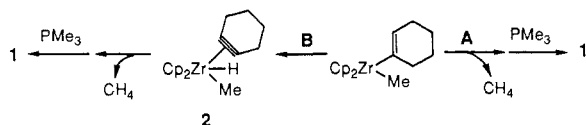**Scheme III**

2

Complex **1** is an air- and moisture-sensitive solid which reacts with a wide variety of unsaturated organic groups as shown in Scheme II. Thus **1** reacts cleanly with nitriles,[6] alkynes,[7] aldehydes, and ketones. Although **1** fails to react with most substituted olefins, it reacts quite cleanly with 1,3-pentadiene (in a completely regiospecific manner) and with ethylene.[8]

It should be noted that if 1-cyclohexenylmethylzirconocene is prepared at low temperature and is treated with nitriles or alkynes at −20 °C, followed by warming to room temperature, metallacyclic products identical with those formed from **1** are observed. However, a similar reaction with isobutyraldehyde led to a complex mixture of products.

Shown in Scheme III are what we feel are the two most likely mechanistic pathways to form **1** from its 1-cyclohexenyl-methylzirconocene precursor. In path A, **1** is formed by a C–H activation mechanism with simultaneous production of methane.[9] Such a mechanistic path is completely analogous to that proposed by Erker for the production of a zirconocene–benzyne complex from diphenylzirconocene.[9] An alternate mechanism, shown by path B, would involve a β-hydride elimination to form intermediate **2** followed by reductive elimination of methane. Since **2** would have the zirconium in a d^0 configuration, no back-bonding would be possible to stabilize the cyclohexyne moiety. We feel that **2** would be prohibitively high in energy and we, thus, favor path A.

In summary, we have prepared and structurally characterized the trimethylphosphine adduct of a zirconocene–cyclohexyne complex. We have shown that it structurally more closely resembles a metallacyclopropene rather than a metal–alkyne complex.[10] In addition we have reported on some of the rich reaction chemistry manifested by **1**.

We are currently working on the conversion of the metallacyclic products derived from **1** into synthetically useful organic products and the use of **1** to prepare bimetallic complexes and as an olefin polymerization catalyst. We are also currently attempting to use methodology similiar to that used to prepare **1** to prepare other transition-metal complexes of strained and unstrained systems and we will report on this work in due course.

(5) Numbers in parentheses refer to isolated yields of purified compounds except for the isobutyraldehyde- and ethylene-derived metallacycles where they refer to yields estimated by ¹H NMR.

(6) Buchwald, S. L.; Sayers, A.; Watson, B. T.; Dewan, J. C., submitted for publication in *J. Am. Chem. Soc.*

(7) There are a number of examples of group 4 metallocenes inducing reductive coupling of two alkynes; Cf.: Nugent, W. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1984**, *106*, 6422 and references therein. Cohen, S. A.; Bercaw, J. E. *Organometallics* **1985**, *4*, 1006.

(8) For examples of group 4 metallocene induced reductive coupling of an olefin with an alkyne, Cf.: Negishi, E.; Holmes, S. J.; Tour, J. M.; Miller, J. A. *J. Am. Chem. Soc.* **1985**, *107*, 2568. Erker, G.; Kropp, K. *J. Am. Chem. Soc.* **1979**, *101*, 3659.

(9) Erker, G. *J. Organomet. Chem.*, **1977**, *134*, 189. C–H activation by d^0 metals is well precedented; for a recent review, Cf.: Rothwell, I. P. *Polyhedron* **1985**, *4*, 177.

(10) Collman, J. P.; Hegedus, L. S. *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1980.

Rotational Preference in "Cage" Dissociation–Recombinations: Thermal Automerization of Optically Active Methyl *threo*-2,3-Diphenylbutane-2-carboxylate

W. von E. Doering* and Ludmila Birladeanu

Department of Chemistry, Harvard University Cambridge, Massachusetts 02138-2902

First conceived by Franck and Rabinowitch,[1] the "cage" or geminate effect on the recombination of radical pairs is well established, although "the precise definition of the dimensions or other characteristics of this solvent property remains a problem today".[2] In terms of organic chemical phenomenology, the geminate effect relates to those products of radical recombination whose residual amount is irreducible under the influence of efficient traps for *free* radicals.

In this paper, we report the first example of the operation of the "cage" effect on the stereochemical outcome of a thermal epimerization occurring by necessarily single or odd-numbered rotational processes. The original stimulus came from a desire to compare the single rotational preferences which might obtain in a ring of infinite size with those uncovered in the liquid phase, "diradical" automerizations of optically active methyl *threo*-1,2-diphenylcyclopropane-1-carboxylate ($R_A = 18$)[3] and methyl *threo*-1,2-diphenylcyclopentane-1-carboxylate ($R_A = 3.4$)[4] to their erythro epimers.[5]

The desired permutation is arranged simply by replacing the rings with two methyl groups! The resulting *acyclic* system of threo configuration is resolved and allowed to automerize thermally to its erythro epimer, in which the preference of one radical component to rotate over the other can be deduced unequivocally (Figure 1). First shedding of light on rotation in a "cage" came from the definitive, independent works of Kopecky and Gillan[7] and Greene et al.[8] on the generation of α-phenylethyl radicals from optically active azo precursors in the presence of scavengers. Both groups observed some retention of activity. The probability of rotation ($x = 0.50$ corresponds to random) occurring prior to geminate recombination in the work of Greene et al. ($x = 0.44_7$), using 2-methyl-2-nitrosopropane (1.15 M) as scavenger in benzene (Figure 2), compares well with that ($x = 0.43_6$) found by Kopecky and Gillan, using butanethiol (1.2 M) also in benzene.

Complications stemming from the generation of two radicals in a ménage à trois (N_2 and CO_2 in several examples[2]) were avoided in a bond-breaking, bond-making, pas de deux sequence developed by Singer et al.[9] In their ingenious, pioneering example,

(1) Franck, J.; Rabinowitch, E. *Trans. Faraday Soc.* **1934**, *30*, 120–131.

(2) Koenig, T.; Fischer, H. In *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, 1973; Vol. 1, Chapter 4.

(3) Doering, W. v. E.; Robertson, L. A.; Ewing, E. E. *J. Org. Chem.* **1983**, *48*, 4280–4286.

(4) Doering, W. v. E.; Birladeanu, L. *J. Am. Chem. Soc.* **1983**, *105*, 7461–7462.

(5) These processes are effected by internal rotation of the benzylic component or the carbomethoxyphenyl component and are defined quantitatively by the thermodynamic ratio, R_A, of the single rotational propensities.[6]

(6) Doering, W. v. E.; Sachdev, K. *J. Am. Chem. Soc.* **1974**, *96*, 1168–1187.

(7) Kopecky, K. R.; Gillan, T. *Can. J. Chem.* **1969**, *47*, 2371–2386.

(8) Greene, F. D.; Berwick, M. A.; Stowell, T. C. *J. Am. Chem. Soc.* **1970**, *92*, 867–874.

Communications to the Editor

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Table I. Automerization of Optically Active **3t** to **3e** at 300 °C for 30 Min

educt	$[\alpha]_D{}^c$	trap^a	rec^b	3e/3t	3e^c	ee^d	3t^c
(−)-3t^e	−214.4°	none	58	0.31	+7.5	3.9	−14.2
(−)-3t^e	−21.4°	CNPy; 26	60	0.39	+6.5	3.4	−13.5
(−)-3t^e	+23.1°	DHAn; 11	52	0.08	−45.0	21.5	+21.9
(−)-3t^e	−23.7°	DHAn; 10	33	0.05	+50.1	26.1	−20.4
(+)-3t	+23.5°	DHAn; neat	33	0.06	−56.0	29.2	+21.5

^{a} Concentration as molar ratio of trap to **3t**; β-cyanopyridine (CNpy) and 9,10-dihydroanthracene (DHAn). ^{b} Total recovery of **3e** + **3t** as percent of educt. ^{c} Specific rotation, $[\alpha]_D$, measured by a Perkin-Elmer 141 polarimeter in $CHCl_3$ at 25 °C. ^{d} Enantiomeric excess as percent of optical purity,[14] corrected for optical purity of starting **3t**. ^{e} 2% (g/mL) **3t** in o-dichlorobenzene.
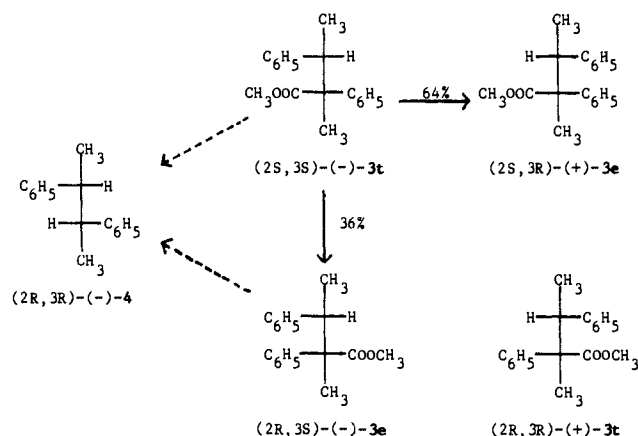
Figure 1, Thermal automerization at 300 °C of optically active *threo*-2-carbomethoxy-2,3-diphenylbutane (**3t**) is shown. Configurational relations are established by decarboxylation of potassium carboxylates corresponding to esters **3t** and **3e** to (2R,3R)-(−)-2,3-diphenylbutane (and the uninformative meso diastereomer).
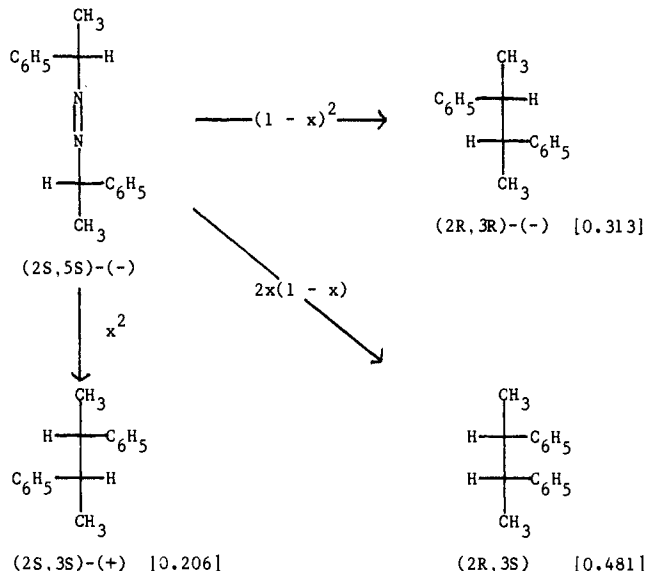

Figure 2, Thermal decomposition of optically active azobis(α-phenylethane) reveals a value for rotational probability, x = 0.44₇ (based on Greene's data, given in brackets, 2-nitro-2-methylpropane as scavenger).[8]

rearrangement of an optically active ketimine revealed a lower rotational aptitude, x = 0.23₄, corresponding to $\Delta\Delta G^{\ddagger}$(318 K) = 750 cal/mol for the disfavored rotation of the α-phenylethyl radical in the absence of a third occupant of the "cage".

The first actors in the present work, *threo*- and *erythro*-2-cyano-2,3-diphenylbutane (**1t** and **1e**, respectively), are prepared by the reaction of 1-(chloroethyl)benzene and 1-(cyanoethyl)-benzene with 50% aqueous sodium hydroxide under phase-transfer catalysis (benzyltrimethylammonium chloride).[10,11] Pure **1e** crystallizes from small amounts of methanol at −15 °C: mp 107–108 °C. From the residual mixture of **1e** (10%) and **1t** (59%), a small sample of pure **1t** (liquid) is isolated by flash chromatography and preparative GLC.

As in the cyclopentane series,[4] conversion of the nitriles **1** to carboxylic acids **2** is effected circuitously by reduction[12] to the aldehyde followed by oxidation:[13] **2t**, mp 185.8–186.5 °C; **2e**, mp 150–151 °C.

Resolution by quinine concentrates the (−) enantiomers, whereas (+)-α-phenylethylamine yields the (+) enantiomers (both from ethyl acetate–ethanol). Reaction with diazomethane affords methyl esters **3e** and **3t**.[14]

Relative configurations of (−)-**2t** and (−)-**2e** follow from thermal decarboxylation of their potassium salts, each giving (2R,3R)-(−)-2,3-diphenylbutane (**4**)[15,16] (and approximately 2 parts of the meso isomer, separated by GLC).[17] Thus, **2t** of $[\alpha]_D$ −27.9° and

2e of $[\alpha]_D$ −213.6° give **4** of $[\alpha]_D$ −99.0° (0.5% meso) and $[\alpha]_D$ −98.0° (1.6% meso), respectively.[19]

Thermal rearrangements are effected in sealed, evacuated Pyrex tubes in o-dichlorobenzene at 300 °C for 30 min. Products are isolated by evaporative distillation of solvent and flash chromatography and finally purified by GLC (3-m 5% OV225 on Anachrom 60/80 at 180 °C). Results are recorded in Table I.

With an ineffective trap (β-cyanopyridine) or no trap, optical activity in the epimerized product, **3e**, is low (4%) and racemization in recovered **3t** is substantial (34%). By contrast, addition of 9,10-dihydroanthracene as radical trap[20] lowers the yield of recovered material markedly (59% to 33%) because dissociated radicals are precluded from reassociating (a process that would lead in approximately equal amount to racemic threo and erythro compounds[21]). At the same time, racemization in recovered **3t** drops to 5–10%, the fraction of **3e** in recovered material drops from 0.35 to 0.05, and, most strikingly, optical activity in **3e** rises from 3.6% to 28% of optical purity.

From specific rotations and the established configurational relations, this result translates into a surprisingly large rotational preference of α-phenylethyl radical over the α-carbomethoxy-α-phenylethyl radical of 1.8, which corresponds to $\Delta\Delta G^{\ddagger}$(574 K) = 655 cal/mol. This is a minimum value owing to complications

(9) Lee, K.-W.; Horowitz, N.; Ware, J.; Singer, L. A. *J. Am. Chem. Soc.* **1977**, *99*, 2622–2627.

(10) Makosza, M.; Jonezyk, A. *Org. Synth.* **1976**, *55*, 91–95.

(11) Satisfactory IR, NMR, and MS were obtained for all compounds.

(12) Miller, A. E. G.; Biss, J. W.; Schwartzman, L. H. *J. Org. Chem.* **1959**, *24*, 627–630.

(13) Sale, T.; Sargent, M. W. *J. Chem. Soc., Chem. Commun.* **1978**, 253–254.

(14) Specific rotations, $[\alpha]_D$ at 25 °C in chloroform, of optically pure acids and esters of same configuration at C-2: **2t**, −30.3 ± 2°; **2e**, −233.0 ± 5°; **3t**, −25.6°; **3e**, −209.0°.

(15) Ott, H. *Ber. Dtsch. Chem. Ges.* **1928**, *61*, 2124–2142.

(16) Jackman, L. M.; Sternhell, J. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon: New York, 1969, p 163.

(17) Although correct assignment of threo–erythro configuration is not essential to this work, we have made tentative assignments by analogy with the work of Beckhaus, Hellmann, and Rüchardt.[18]

(18) Beckhaus, H.-D.; Hellmann, G.; Rüchardt, Ch. *Chem. Ber.* **1978**, *111*, 3764–3779.

(19) Verkade, P. E.; de Vries, K. S.; Wepster, B. M. *Rec. Trav. Chim. Pays-Bas* **1964**, *83*, 1149–1159.

(20) Franz, J. A.; Barrows, R. D.; Camioni, D. M. *Abstracts of Papers*, 183rd National Meeting of the American Chemical Society, Washington, DC, American Chemical Society: Washington, DC, 1983; FUEL 32.

(21) Eichin, K.-H.; Beckhaus, H.-D.; Hellmann, S.; Fritz, H.; Peters, E.-M.; Peters, K.; von Schnering, H.-G.; Rüchardt, Ch. *Chem. Ber.* **1983**, *116*, 1787–1821.

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 ménage à 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**.

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

Walda Jones and Richard Wolfenden*

*Department of Biochemistry, University of North Carolina Chapel Hill, North Carolina 27514*

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.
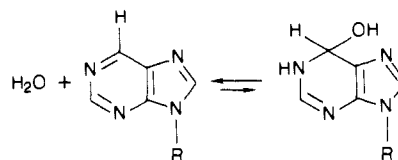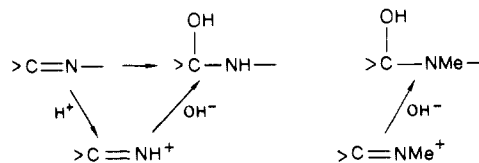
Scheme I

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$_2$SO 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]

(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$_2$O): 45.2 (CH$_3$N-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). ^{1}H NMR (ppm, D$_2$O): 3.9 (m, 2 H, ribose); 4.2–4.9 (m, 3 H, ribose); 4.5 (s, 3 H, CH$_3$N-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.