lose-1-phosphate (Fuc-1-P) aldolase (EC 4.1.2.17),[7] and 2-deoxyribose-5-phosphate aldolase (DERA, EC 4.1.2.4).[8] The first three aldolases use dihydroxyacetone phosphate (DHAP) as donor and a number of aldehydes as acceptors to form two new stereogenic centers with 3*S*,4*R*, 3*R*,4*S*, and 3*R*,4*R* configurations, respectively; DERA expresses relaxed substrate specificity with both donor and acceptor components to form one (when acetaldehyde or acetone is used as donor) or two (when propionaldehyde is used as donor) new stereogenic centers with 3*S* or 2*R*,3*S* configurations.[8] The stereospecificity remains the same in all aldolase reactions with natural and unnatural substrates. Thus, with the use of DHAP[9] and racemic 3-azido-2-hydroxypropanal (3 equiv)[4c] as substrates, compounds **1a** and **5a** were obtained selectively from Rham-1-P aldolase and Fuc-1-P aldolase reactions, respectively (Scheme I). Both Rham-1-P and Fuc-1-P aldolases accept the *S* aldehyde as substrate, whereas FDP aldolase is selective for the *R* enantiomer.[4a,b] Pd-mediated reductive amination of **1a** and **5a** gave **3a** and 1:1 **7a** + **7b**, respectively, each in ~90% yield. Reductive amination of the phosphate-free **1a** and **5a**, however, gave **2a** and **6a**,[3i,w] respectively, also in ~90% yield. Compound **4b** was obtained from the product of Rham-1-P aldolase reaction with (*R*)-3-azido-2-hydroxypropanal.[4c] The reductive aminations are all diastereoselective and consistent with our previous finding[4c] that hydrogens attack the imine intermediate regioselectively to avoid the torsional strain developed during the reduction with the exception of **1b** and **5a**. This study reveals that hydrogens always approach from the side opposite to the axial substituent, and this steric effect seems to override the torsional strain effect. The same situation was observed in the reductive amination of the DERA products **10b** and **10c**.[10] The $A_{1,2}$ strain seems not to affect the stereochemical course of the reduction. Reduction of the five-membered-ring imines **8a–8c**[11] prepared via FDP aldolase reactions also gave trans products **9a** and **9b** preferentially in >90% yield. A lower diastereoselectivity (~6:1) was observed for **1a**, **5a**, and **8c** compared to the phosphate-free counterparts, which exhibit >90% diastereoselectivity. The stereochemistry and conformation of each compound were determined with NMR together with NOE, proton–proton decoupling, and coupling. Compounds **2a**, **3a**, **7a**, **9b,c**, and **11a–c** prepared in this study are new. Compound **9b**, 2(*R*),5(*S*)-bis-(hydroxymethyl)-3(*R*),4(*R*)-dihydroxypyrrolidine, was found to be a competitive inhibitor of brewer's yeast α-glucosidase (K_i = 2.8 μM), almond β-glucosidase (K_i = 19 μM), green coffee bean α-galactosidase (K_i = 50 μM), and jack bean α-mannosidase (K_i = 3.1 mM), but no inhibition (up to 1 mM) of *Escherichia coli* β-galactosidase was observed.[12] Compound **3a** (*rhamnojirimycin*) is structurally related to rhamnose and may be a selective antimicrobial agent or herbicide as rhamnose is often found in mi-

croorganisms or plants, but not in humans or animals. Though the enzymes used in this study are not recovered after reactions, they are quite stable and could be immobilized and recovered for reuse.

Formation of Organozinc Cations and Anions from Diorganozinc Compounds

Ronaldo M. Fabicon, Anthony D. Pajerski, and Herman G. Richey, Jr.*

*Department of Chemistry
The Pennsylvania State University
University Park, Pennsylvania 16802*

Some coordinating agents cause organomagnesium compounds to disproportionate to magnesiate anions and coordinated organomagnesium cations.[1–4] With a favorable cryptand (2,1,1-cryptand)[1,2] or crown ether (1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane = 14N4)[3] and benzene as the solvent, conversion of dialkyl- and diarylmagnesium compounds to the ions shown in eq 1 (C = a cryptand or crown ether) can be essentially quantitative. Discrete NMR absorptions are seen for $RMgC^+$

$$2R_2Mg + C \rightleftharpoons RMgC^+ + R_3Mg^- \qquad (1)$$
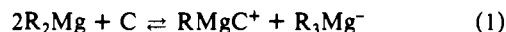
and R_3Mg^-; some systems are homogeneous, but others have a second, dense phase, which contains most of the ions.

A similar disproportionation of R_2Zn (eq 2) would form interesting ions. To our knowledge, no RZn^+ ion has been char-

$$2R_2Zn + C \rightleftharpoons RZnC^+ + R_3Zn^- \qquad (2)$$
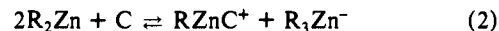
acterized in solution.[5] Solutions having the composition R_3ZnM (M = alkali metal) have been prepared.[6] These solutions, however, may contain species in which M is partially bonded to the α-carbons of the R groups[7] rather than free organozincate ions, such as R_3Zn^-.[8]

Addition of cryptands to benzene solutions of diorganozinc compounds provides no evidence for disproportionation to ions.[9]

(7) *E. coli* K40 was used as a source for Rham-1-P aldolase and *E. coli* K58 was used as a source for Fuc-1-P aldolase. The cells were treated with lysozyme (to release the enzyme) and used directly without further purification. For procedure, see: Drueckhammer, D. G.; Durrwachter, J. R.; Pederson, R. L.; Crans, D. C.; Daniels, L.; Wong, C.-H. *J. Org. Chem.* **1989**, *54*, 70. Fuc-1-P aldolase from *E. coli* was cloned and overexpressed (Ozaki, A.; Toone, E. J.; von der Osten, C. H.; Sinskey, A. J.; Whitesides, G. M. *J. Am. Chem. Soc.* **1990**, *112*, 4970.
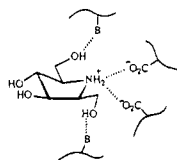
(8) Prepared according to Barbas et al.: Barbas, C. F., III; Wang, Y.-F.; Wong, C.-H. *J. Am. Chem. Soc.* **1990**, *112*, 2013.

(9) Pederson, R. L.; Esker, J.; Wong, C.-H. *Tetrahedron* **1991**, *47*, 2643.

(10) Compounds **10a–c** were selectively obtained from DERA-catalyzed reactions with racemic 3-azido-2-hydroxypropanal. Three equivalents of the aldehyde were used.

(11) Compound **8b** is an imine intermediate obtained in the FDP aldolase reaction with racemic 2-azido-3-hydroxypropanal followed by the reductive amination. The *S* aldehyde was preferentially converted to the aldol product, in a thermodynamically controlled process.

(12) The high potency may be due to the half-chair-like envelope conformation binding to the active site.
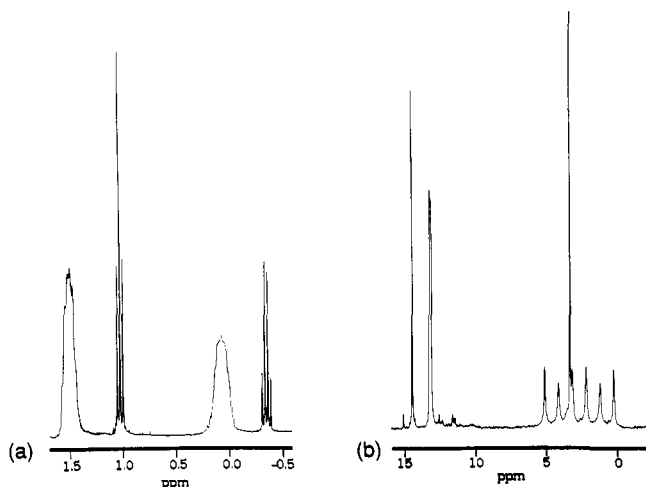

(1) Squiller, E. P.; Whittle, R. R.; Richey, H. G., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 432.

(2) Kushlan, D. M. *J. Am. Chem. Soc.* **1987**, *109*, 2510. Kushlan, D. M., The Pennsylvania State University, unpublished observations.

(3) Pajerski, A. D., The Pennsylvania State University, unpublished observations.

(4) Pajerski, A. D.; Parvez, M.; Richey, H. G., Jr. *J. Am. Chem. Soc.* **1988**, *110*, 2660.

(5) However, a solid of composition $MeZnBH_4$ that contains $MeZn^+$ ions somewhat "coupled" to BH_4^- ions has been studied (Nibler, J. W.; Cook, T. H. *J. Chem. Phys.* **1973**, *58*, 1596).

(6) For a review, see: Nützel, K. *Methoden Org. Chem. (Houben-Weyl)*, 4th Ed. **1973**, *13*, (Part 2a), 553.

(7) Powder diffraction studies of solid lithium tetramethylzincate (Weiss, E.; Wolfrum, R. *Chem. Ber.* **1968**, *101*, 35) and potassium tetraethynylzincate (Weiss, E.; Plass, H. *J. Organomet. Chem.* **1968**, *14*, 21) show significant bonding of the alkali metals to the α-carbons of the alkyl groups.

(8) Zincate ions prepared from R_2Zn and salts have been studied. KH: Kubas, G. J.; Shriver, D. F. *J. Am. Chem. Soc.* **1970**, *92*, 1949. Kubas, G. J.; Shriver, D. F. *Inorg. Chem.* **1970**, *9*, 1951. Shriver, D. F.; Kubas, G. J.; Marshall, J. A. *J. Am. Chem. Soc.* **1971**, *93*, 5076. Ashby, E. C.; Beach, R. G. *Inorg. Chem.* **1971**, *10*, 2486. Ashby, E. C.; Watkins, J. J. *Inorg. Chem.* **1973**, *12*, 2493. KOR': Fabicon, R. M.; Parvez, M.; Richey, H. G., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 1412. Salts of composition $Pr_4N^+RZnX_2^-$ have been prepared by electrolysis of RX in a $Pr_4N^+X^-$ solution (Habeeb, J. J.; Osman, A.; Tuck, D. G. *J. Organomet. Chem.* **1980**, *185*, 117).

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Figure 1. Partial NMR spectra of the lower phase of the mixture formed from equimolar amounts of Et_2Zn, Et_3Al, and 2,1,1-cryptand in benzene-d_6. (a) ^1H NMR spectrum (300 MHz), chemical shifts relative to benzene-d_5 (δ 7.15). (b) ^{13}C NMR spectrum (75 MHz), chemical shifts relative to benzene-d_6 (δ 128.00).

Phase separation is never noted, and only single sets of sharp absorptions are seen for R and for the cryptand. Even bonds that might be expected between one or two heteroatoms[10] of the cryptand and the Zn atom must form and break rapidly on the NMR time scale and not lead to significant alterations (>0.1 ppm) in the chemical shifts of the ^1H NMR absorptions of either component. The behavior upon addition of crown ethers to R_2Zn is similar, except that in some instances an additional set of NMR absorptions is seen for a component having the composition $R_2Zn(crown)$.[9,11,12] Such components are thought to have "threaded" structures in which the O atoms of the crown ether surround the Zn atom in an equatorial fashion and the organic groups occupy apical positions.[13]

Although treatment of R_2Zn with a cryptand or crown ether does not produce $RZn(C)^+$ and R_3Zn^-, each can be prepared by a modification of this approach. Combination in benzene of equimolar amounts of Et_2Zn, Et_3Al, and 2,1,1-cryptand or 14N4 leads to separation of a small, dense, liquid phase that contains most of the solute. Several features of NMR spectra (Figure 1) of this phase indicate that it contains $EtZnC^+Et_4Al^-$ (eq 3, R = Et). (1) The ^1H NMR spectra show two sets of Et absorptions

$$R_2Zn + R_3Al + C \rightleftharpoons RZnC^+ + R_4Al^- \qquad (3)$$

in a ratio of 1:4. (2) The smaller of the two absorptions due to CH_2 of Et is at significantly lower frequency than that of Et_2Zn (δ 0.13), just as the CH_2 absorption of $EtMgC^+$ is at lower frequency than that of Et_2Mg.[1-3] (3) As also observed for $EtMgC^+$, some absorptions of the cryptand or crown ether are at lower frequency than those of the free species. (4) The effects of coupling to ^{27}Al are striking. There are two ^{13}C NMR absorptions for CH_2 of Et. The smaller is a singlet, but the larger is a multiplet of six equally spaced lines, the consequence of coupling ($J = 72.8$ Hz) of ^{13}C with the $^5/_2$ spin of ^{27}Al. The excellent resolution of this multiplet indicates that the Al is in a symmetrical environment, as in Et_4Al^- *if this anion has little specific interaction with the cation.*[14] Interaction of the anion should be minimal with $EtZnC^+$,

which is large and must have a diffuse charge. The larger set of Et absorptions in the ^1H NMR spectrum also shows the effects of coupling with ^{27}Al; the sole absorption in the ^{27}Al NMR spectrum is a multiplet, but becomes a singlet on irradiation of the ^1H's. (5) If excess Et_2Zn or Et_3Al is used, the ^1H NMR spectrum of the lower phase is unchanged except for exhibiting weak, additional absorptions that can be attributed to the compound used in excess; the upper phase, however, now has strong absorptions identical in position with those of the reagent in excess.

R_3Zn^- can be formed from R_2Zn in a similar fashion by using R_2Mg as the other organometallic component (eq 4).[15] Addition

$$R_2Mg + R_2Zn + C \rightleftharpoons RMgC^+ + R_3Zn^- \qquad (4)$$

of 1 equiv of Et_2Mg to a benzene solution containing 1 equiv each of Et_2Zn and 14N4, for example, results in formation of a second, denser liquid phase. The ^1H NMR spectrum of this phase shows two sets of Et absorptions in a 1:3 ratio. Although this ratio does not indicate which metal is in the cation and which is in the anion, the chemical shifts make this evident. The smaller set has the absorptions at δ −0.93 (CH_2) and δ 1.18 (CH_3), and the larger set at δ 0.30 (CH_2) and δ 1.71 (CH_3). The CH_2 absorption of the smaller set is in essentially the same position observed[3] for that of $EtMg(14N4)^+$ in the presence of other anions, such as Et_3Mg^-, but at significantly lower frequency than found for that of $EtZn(14N4)^+$ in the presence of Et_4Al^-. The CH_2 absorption of the larger set is at significantly higher frequency than noted[3] for Et_3Mg^- in the presence of $EtMg(14N4)^+$. A second phase also forms in a similar experiment with 15-crown-5, and ions presumably are its principal components. Only a single set of Et ^1H NMR absorptions is seen, however. With this crown ether, which is less effective than 14N4 at coordinating with $EtMg^+$, equilibration of the Et groups of the cation and anion via formation of "free" Et_2Mg may be rapid on the NMR time scale.

Both organozinc cations and anions (eq 5) are formed when 14N4 is added to a benzene solution containing equal amounts of Et_2Zn and Ph_2Zn. The ^1H NMR spectrum of the resulting

$$Et_2Zn + Ph_2Zn + C \rightleftharpoons EtZnC^+ + Ph_2ZnEt^- \qquad (5)$$

solution (no phase separation is noted) exhibits the absorptions characteristic of $EtZn(14N4)^+$; all other absorptions are consistent[16] with $EtPh_2Zn^-$. The cation also is $EtZn(14N4)^+$ but the anion is essentially Ph_3Zn^- if the stoichiometry is near 1-(Et_2Zn):3(Ph_2Zn):2(14N4).

Equilibria such as those in eqs 3–5 provide information about the relative abilities of organometallic compounds to accept or (in concert with a crown ether or cryptand) to donate an "R^-" group. The equilibria in eqs 1 and 2 require that an organometallic compound serve as both the "R^-" donor and acceptor. The sum of the donor and acceptor abilities of either Et_2Zn or Ph_2Zn is insufficient for disproportionation to be significant. Providing a more effective "Et^-" donor (Et_2Mg plus cryptand or crown ether) or acceptor (Et_3Al or Ph_2Zn), however, permits Et_2Zn to enter into such equilibria. Determining the positions of equilibria such as those in eqs 3–5 could establish scales of donor and acceptor abilities.

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(12) Fabicon, R. M., The Pennsylvania State University, unpublished observations.

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(14) For references to spectra of R_4Al^- ions, see: Delpuech, J. J. In *NMR of Newly Accessible Nuclei*; Laszlo, P., Ed.; Academic: New York, 1983; Chapter 6.

(15) Although zincate ions are written here as Et_3Zn^- or Ph_3Zn^-, the solutions may contain dimers of these species.[6]

(16) A characteristic of the conversion of Ar_2Mg to Ar_3Mg^- is a shift to higher frequency of the ^1H NMR absorption of the ortho H's. The absorption for the ortho H's of Ph_2Zn is at δ 7.78 and for the Ph groups in the Et_2Ph-Ph_2Zn-14N4 solution at δ 8.33.