Observations Concerning the Existence and Reactivity of Free α-Amino Aldehydes as Chemical Intermediates: Evidence for Epimerization-Free Adduct Formation with Various Nucleophiles

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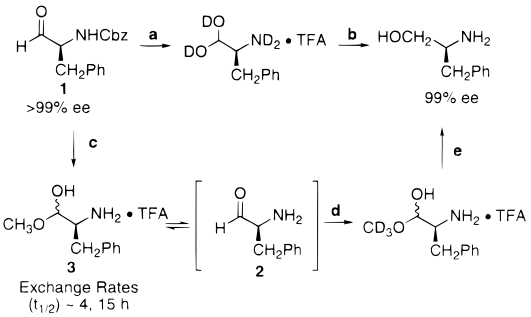
The idea that chiral α-amino aldehydes are viable chemical intermediates that can be generated and sustained in solution without protective groups has not been widely considered, if at all. In the course of the development of synthetic routes to a series of antitumor alkaloids[1] we were led to investigate fundamental properties of chiral α-amino aldehydes. Our research has shown that α-amino aldehydes can be prepared without protective groups, under conditions defined herein, and that they undergo a series of largely epimerization-free transformations, a finding of potentially great practical consequence.

The literature concerning free α-amino aldehydes dates at least to 1908 with Fischer's description of the preparation of glycine aldehyde in solution, by the semi-reduction of glycine ethyl ester with sodium amalgam. His success in the procedure was ascertained by derivatization experiments; the enhanced stability of the proposed intermediate amino aldehyde at acidic pH and the possibility that it might exist as the hydrate were noted.[2] The literature on the topic following this work is not large, and we are unaware of any discussions of unprotected chiral α-amino aldehydes as viable intermediates in solution nor of their use in asymmetric transformations.[3] The notion that α-amino aldehydes are subject to spontaneous dimerization followed by air oxidation to form pyrazines also dates to the beginning of the last century and has been incorporated in at least one organic chemistry textbook.[4] Results from our own experiments led us to question whether unprotected α-amino aldehydes might not be viable species in solution and, moreover, whether such intermediates might be held and trapped without epimerization of the stereogenic "α" center. The following exploratory studies address these questions.

N-Carbobenzyloxy phenylalaninal (**1**, >99% ee), prepared in 98% yield by oxidation of the corresponding alcohol with the Dess−Martin periodinane in dichloromethane at 23 °C,[5] was subjected to hydrogenolysis in a 1:1 mixture of D_2O and dioxane-d_8 containing 1.05 equiv of trifluoroacetic acid (final pH ∼3). The "free" α-amino aldehyde (**2**) was formed in nearly quantitative yield, as determined by ^{1}H NMR analysis (Figure 1). From the ^{1}H NMR spectrum it was evident that **2** existed entirely as the aldehyde hydrate. In this state compound **2** displays remarkable stability. Even after standing in solution for 90 d at 23 °C in the air, **2** showed no evidence of decomposition, nor any evidence of deuterium incorporation into the α-position (^{1}H NMR analysis). From the latter finding it was concluded that enolization did not occur at a detectable rate under these conditions. This conclusion was confirmed when the addition of sodium borohydride to the aqueous solution of aldehyde hydrate was found to produce phenylalaninol in quantitative yield and >99% ee. After 90 d, reduction produced phenylalaninol of 99.2% ee. These experiments demonstrate what, in retrospect, may seem obvious: α-amino aldehydes are autoprotective at acidic pH; the α-amino group is protonated[6] and, by virtue of the strongly electron-withdrawing ammonium ion, the aldehyde exists completely as its tetrahedral solvent adduct. The solvent adduct is not formed irreversibly, however. This was shown in the case of the methanol adducts **3**, formed in quantitative yield by hydrogenolysis of **1** in methanol (H_2, Pd/C, 1.05 equiv CF_3CO_2H, 23 °C). The diastereomeric mixture of methyl hemiacetals (ratio 1.1:1) underwent dynamic exchange of the methoxyl groups with the solvent upon dissolution in methanol-d_3. Analysis by ^{1}H NMR established that both the major and minor diastereomeric hemiacetals exchanged with the solvent, with half-lives of 15 and 4 h, respectively. Although slow, the exchange reaction is still much faster than enolization of the aldehyde, for after 5 d at 23 °C reduction of the mixture of hemiacetals **3** with sodium borohydride afforded phenylalaninol of 99.1% ee (96% yield). These experiments show that the rates of nucleophilic addition of water, methanol, and borohydride to the transient α-amino or α-ammonio aldehyde intermediate are much faster than enolization under the conditions specified. When the pH of the aqueous or methanolic solutions of the α-amino aldehyde intermediate was raised to above ∼5, self-condensation of the α-amino aldehyde did occur, as evidenced by clouding of the reaction solution and the formation of 2,5-dibenzylpyrazine, among other products. However, even under more basic conditions it is possible to generate and trap free α-amino aldehydes more rapidly than they epimerize, a finding suggested by the borohydride addition experiments above and further supported by experiments described below.



a. H_2, Pd/C, TFA (1.0 eq),1:1 D_2O-dioxane-d_8, 23 °C. **b**. 90 d, 23 °C, air; $NaBH_4$, 99%. **c**. H_2, Pd/C, TFA (1.0 eq), CH_3OH, 23 °C. **d**. CD_3OH, 23 °C. **e**. 5 d, 23 °C; $NaBH_4$, 85%.

Figure 1.

Addition of 1 equiv of potassium cyanide to the diastereomeric mixture of methyl hemiacetals **3**, derived from **2** as described above, led to complete and clean conversion (99% yield, ^{1}H NMR analysis) to a 1.2:1 mixture of diastereomeric cyanohydrins **4** (final pH 8).[7] The product α-amino cyanohydrins (**4**) did not survive chromatography on silica gel. Their optical purity was assessed by reduction with sodium borohydride to form phenylalaninol of 99% ee. In addition to establishing the optical purity of the cyanohydrins **4**, the latter experiment demonstrated that expulsion of cyanide and reduction of the intermediate α-amino aldehyde proceeded without competing epimerization under the

(1) Myers, A. G.; Kung, D. W. *J. Am. Chem. Soc.* **1999**, *121*, 10828−10829.

(2) Fischer, E. *Chem. Ber.* **1908**, *41*, 1019−1023.

(3) Adams successfully prepared optically active histidinal by Fischer's method: Adams, E. *J. Biol. Chem.* **1955**, *217*, 317−324. See also: Bullerwell, R. A. F.; Lawson, A. *J. Chem. Soc.* **1951**, 3030−3032. 2-Deoxy-2-amino sugars are formally derivatives of α-amino aldehydes but are not included as part of this discussion.

(4) Nenitzescu, C. D. *Chimie Organica*; Editura Didactica: Bucharest, Romania, 1968; p 716.

(5) Myers, A. G.; Zhong, B.; Movassaghi, M.; Kung, D. W.; Lanman, B. A.; Kwon, S. *Tetrahedron Lett.* **2000**, *41*, 1359−1362.

(6) The pK_a of the protonated amino group is estimated to be 8, using 2-deoxy-2-amino D-glucose as a reference: Blasko, A.; Bunton, C. A.; Bunel, S.; Ibarra, C.; Moraga, E. *Carbohydr. Res.* **1997**, *298*, 163−172.

(7) This method of preparing α-amino cyanohydrin intermediates, such as **4**, involving sequential hydrogenolysis, filtration to remove catalyst, and addition of potassium cyanide, requires no purification and is generally superior to the two-step procedure we previously employed[9] using *N*-Fmoc-protective groups.

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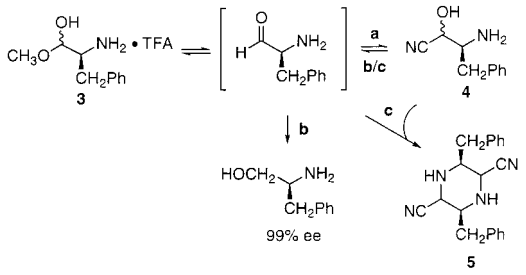


a. KCN, CH_2Cl_2, CH_3OH, 0 °C, >90%. **b**. $NaBH_4$, CH_3OH, 0 °C, 96%. **c**. CH_3OH, 23 °C, 57%.

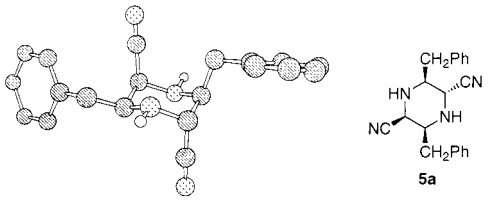
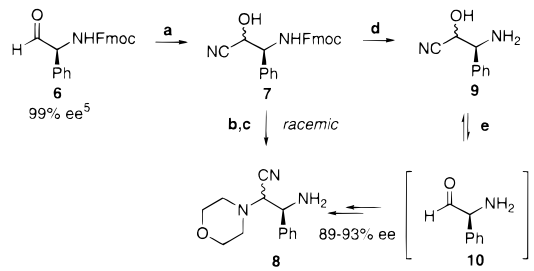


Figure 2.

basic conditions of the borohydride addition. It is perhaps surprising that compounds **4** could be formed at all, given their potential for self-condensation by the Strecker reaction. Somewhat fortuitously, it was learned that methanolic solutions of cyanohydrins **4** (0.2 M) dimerized spontaneously upon standing. The products of this dimerization reaction are diastereomeric 2,5-dicyanopiperazines (**5**), resulting from consecutive inter- and intramolecular Strecker condensation reactions, respectively. The yield of cyclic dimers is typically ~55%, following their isolation by chromatography on Sephadex LH-20, and the proportion of the three diastereomeric products is 8:1:1. The cyclic dimers also cannot be chromatographed on silica gel without material loss. Nevertheless, flash column chromatography on silica gel (12% EtOAc−hexanes eluent) did provide a pure sample of the major diastereomeric dimer **5a** (28% yield), a cystalline solid whose three-dimensional structure was determined by X-ray analysis (structure shown, Figure 2). Both nitrile groups are axial and antiperiplanar to a nitrogen lone pair, a common feature among amino nitrile structures recorded in the Cambridge Crystallographic Data Base. The "α" centers are homochiral, suggesting that epimerization did not occur during the dimerization process. This was confirmed by chiral HPLC analysis (Chiralcel OD column, 2-propanol−hexanes graded eluent) using authentic standards of dimers derived from antipodal and racemic phenylalanine. In this manner, the major diastereomer (**5a**) was shown to be of 96% ee. The minor diastereomeric products are tentatively assigned on the basis of ^{1}H NMR analysis as the two alternative dimeric structures that are possible without epimerization of the α-center; in each, one cyano group is epimeric with respect to structure **5a**. To our knowledge, *N*-unsubstituted cyclic dimers such as **5** have not been described before and represent intriguing compounds for further study in terms of their reactivity, biological activity, and potential occurrence in nature.

The idea that free α-amino aldehydes can serve as viable, and perhaps even advantageous, intermediates in asymmetric synthesis has already impacted our research in a practical way. In an effort to broaden the scope of our published methodology to prepare "*C*-protected" α-amino aldehydes we found that treatment of *N*-Fmoc phenylglycinal (**6**, 99% ee),[5] a substrate exceedingly prone to base-catalyzed epimerization, under the reported conditions [cyanohydrin formation (**7**) with HCN in methanol-dichloromethane, amino nitrile formation with morpholine in trifluoroethanol,[8] and Fmoc cleavage with DBU in dichloromethane][9] produced the diastereomeric morpholino nitriles **8** in 97% combined yield, but with complete racemization. The racemizing



a. HCN, CH_2Cl_2, MeOH, 0 °C. **b**. morpholine, CF_3CH_2OH, 23 °C. **c**. DBU, CH_2Cl_2. **d**. morpholine, DMF, 0 °C. **e**. morpholine, CF_3CH_2OH, 23 °C, 79%.

Figure 3.

event was traced to the second step of the sequence and almost certainly involved epimerization of the intermediate *N*-Fmoc phenylglycinal (**6**) (Figure 3).[10] When modification of reaction conditions failed to provide any improvement in optical activity, the possibility of accessing **8** via the free α-amino aldehyde (in effect, inverting the ordering of the last two steps of the sequence) was considered. Remarkably, this proved highly successful. Thus, treatment of the cyanohydrins derived from *N*-Fmoc phenylglycinal (**7**) with morpholine in *N*,*N*-dimethylformamide efficiently cleaved the Fmoc group[8] to furnish the corresponding α-amino cyanohydrins **9**. Further subjection of this mixture to morpholine in trifluoroethanol as solvent then furnished the diastereomeric morpholino nitriles **8** in 79% combined yield and 89−93% ee. There is little question that this process involved the intermediacy of free phenylglycinal (**10**). That this intermediate is trapped by morpholine addition, further progressing to morpholinium ion formation and trapping by cyanide, faster than any racemizing event, is noteworthy. Further studies have shown this protocol to be optimal for producing optically active morpholino nitrile adducts such as **8** with a wide range of chiral α-amino aldehydes as substrates.

In summary, we have shown that the propensity for α-amino aldehydes to undergo nucleophilic addition to the aldehyde carbonyl group generally outpaces any racemization event. Nucleophiles examined thus far include water, methanol, borohydride, cyanide, morpholine, and the α-amino group of another α-amino aldehyde (or its equivalent). We have shown that chiral α-amino aldehydes form stable solvent adducts in mildly acidic, polar media such as water or methanol and that adduct formation occurs reversibly and without epimerization. In addition, we have prepared cyclic dimers of primary α-amino cyanohydrins, compounds which have not been previously prepared to our knowledge and which certainly warrant further study. Most importantly, we have demonstrated that α-amino aldehydes are viable intermediates for consideration in proposed transformations (biosynthetic, laboratory) involving the transfer of molecular asymmetry.

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Supporting Information Available: Reproductions of ^{1}H NMR spectra of compounds **2**, **3**, **4**, **5a**, **8**, and crystal structure data for compound **5a** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) There is a marked solvent effect in the reaction of **7** with morpholine. In the protic solvent trifluoroethanol, Strecker reaction occcurs without Fmoc cleavage. In the dipolar aprotic solvent DMF, cleavage of the Fmoc group occurs without competing Strecker condensation.

(9) Myers, A. G.; Kung, D. W.; Zhong, B.; Movassaghi, M.; Kwon, S. *J. Am. Chem. Soc.* **1999**, *121*, 8401−8402.

(10) The facility with which *N*-protected α-amino aldehydes epimerize is well documented. For reviews of *N*-protected α-amino aldehydes as synthetic intermediates, see: (a) Jurczak, J.; Golebiowski, A. *Chem. Rev.* **1989**, *89*, 149−164. (b) Fisher, L. E.; Muchowski, J. M. *Org. Prep. Proced. Int.* **1990**, *22*, 399−484. (c) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531−1546. (d) Sardina, F. J.; Rapoport, H. *Chem. Rev.* **1996**, *96*, 1825−1872. (e) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121−1162. Strategies to minimize the epimerization of *N*-protected α-amino aldehydes include Rapoport's 9-(9-phenylfluorenyl) substitution of the α-amino group, (f) Lubell, W. D.; Rapoport, H. *J. Am. Chem. Soc.* **1987**, *109*, 236−239, and Reetz' *N*,*N*-dibenzyl derivatization: (g) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141−1143.