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Reactions of Amino Alcohols in Superacid: The Direct Observation of Dicationic Intermediates and Their Application in Synthesis

Douglas A. Klumpp,* Sharon L. Aguirre, Gregorio V. Sanchez, Jr., and Sarah J. de Leon

Department of Chemistry, California State Polytechnic University, 3801 West Temple Avenue, Pomona, California 91768

daklumpp@csupomona.edu

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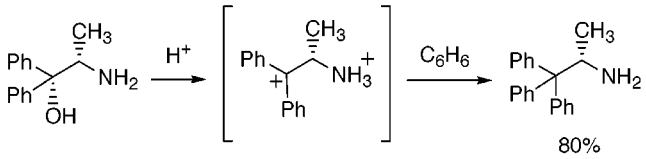
ABSTRACT



The chemistry of amino alcohols has been studied in superacidic media, and these compounds have been found to ionize cleanly to the dication intermediates. Several dicationic species have been directly observed by low-temperature ^{13}C NMR, including those from epinephrine (adrenaline) and synephrine. Amino alcohols react (70–99% yields) with C_6H_6 in triflic acid (CF_3SO_3H) by electrophilic aromatic substitution.

During the mid-1970s, Olah and co-workers found that nitronium salts and other electrophilic systems exhibit heightened reactivities in superacids.[1] These observations led to the proposal of superelectrophilic activation.[2] In the case of the nitronium electrophile, superelectrophilic activation involves protonation (or coordination to a Lewis acid) of the nitronium ion to produce the dicationic species, or superelectrophile. In our studies, we have found several examples in which nitrogen base sites are ionized in superacid and dramatically enhance the reactivities of adjacent electrophilic groups.[3] For example, piperidones condense with arenes in superacidic CF_3SO_3H (triflic acid, TfOH), while under the same conditions cyclohexanone does not react.[3c] It was proposed that reactive, dicationic electrophiles are generated from the piperidones, but the cyclohexanone forms less reactive monocationic species. In this Letter, we wish to report our studies of the chemistry of amino alcohols in superacid, including the direct observation of dicationic intermediates by low-temperature ^{13}C NMR and the reactions of the amino alcohols by electrophilic aromatic substitution chemistry.

A variety of amino alcohols were reacted with benzene and the Bronsted superacid CF_3SO_3H (Table 1). Due in part to their activities related to the central nervous system, the β-phenethylamines are compounds of general interest.[4] Several β-phenethylamines (**1**−**6**) and related compounds were found to give the respective condensation products (**12**−**17**) in good yields. Amino acids can be readily converted to amino alcohols (**9**−**10**),[5] which then react to give the optically active, trityl-substituted amines (**20**−**21**).

(1) (a) Olah, G. A.; Germain, A.; Lin, H. C.; Forsyth, D. *J. Am. Chem. Soc.* **1975**, *97*, 3928. (b) Olah, G. A.; Germain, A.; Lin, H. C.; Forsyth, D. *J. Am. Chem. Soc.* **1975**, *97*, 2928.

(2) (a) Olah, G. A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 767. (b) *Stable Carbocation Chemistry*; Prakash, G. K. S., Schleyer, P. v. R., Eds.; Wiley: New York, 1997.

(3) (a) Klumpp, D. A.; Lau, S. L. *J. Org. Chem.* **1999**, *64*, 7309. (b) Klumpp, D. A.; Jones, A.; Lau, S.; DeLeon, S.; Garza, M. *Synthesis* **2000**, *8*, 1117. (c) Klumpp, D. A.; Garza, M.; Jones, A.; Mendoza, S. *J. Org. Chem.* **1999**, *64*, 6702.

(4) (a) Giringauz, A. *Medicinal Chemistry*; Wiley-VHC: New York, 1997. (b) *Pharmaceuticals*; McGuire, J. L., Ed.; Wiley-VHC: New York, 2000.

(5) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551.

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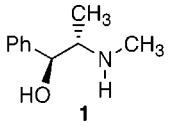
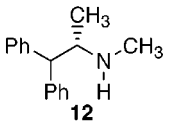
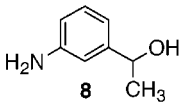
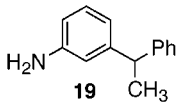
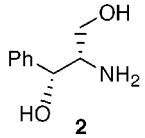
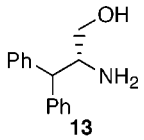
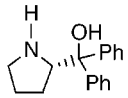
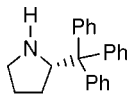
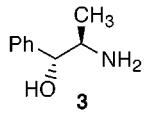
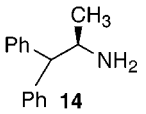
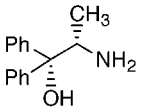
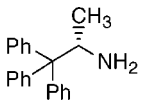
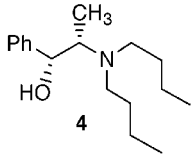
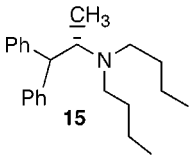
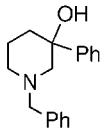
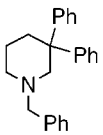
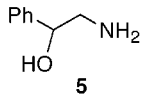
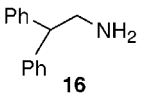
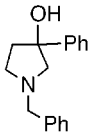
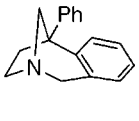
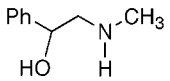
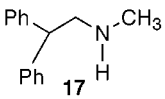
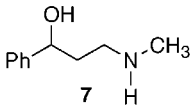
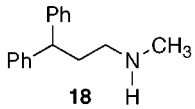
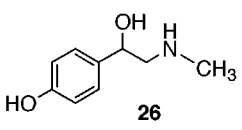
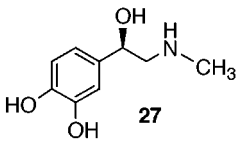
Table 1. Products from the Reactions of Amino Alcohols (**1**−**10**, **22**, and **24**) with C_6H_6 in CF_3SO_3H

starting material	product	% yield[a]	starting material	product	% yield[a]
 **1**	 **12**	99%	 **8**	 **19**	99%
 **2**	 **13**	72%	 **9**	 **20**	70%
 **3**	 **14**	83%	 **10**	 **21**	80%
 **4**	 **15**	88%	 **22**	 **23**	99%
 **5**	 **16**	83%	 **24**	 **25**	67%
 **6**	 **17**	86%			
 **7**	 **18**	83%			

[a] Yields are reported as the isolated crude products (see Supporting Information).

While the piperidinol derivative **22** gives the expected diphenylpiperidine, the analogous pyrrolidinol **24** undergoes an intramolecular cyclization to give **25** as the only major product. If 1-benzyl-3-piperidone or 1-benzyl-3-pyrrolidone is reacted with TfOH and C_6H_6, then products **23** and **25** are formed, respectively. The pyrrolidinol and piperidinol systems exhibit different chemistry presumably due to ring conformation effects. When synephrine (**26**) or epinephrine (**27**) is reacted under similar conditions, complex product mixtures are formed. Despite the fact there is an earlier report

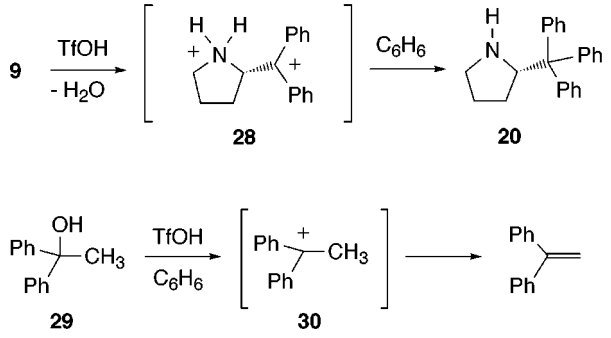

26


27

of **1** being converted to **12** in benzene and $AlCl_3$,[6] we found that amino alcohols **1**, **6**, and **7** do not give the expected products (**12**, **17**, and **18**, respectively) at 25 °C when H_2SO_4 is substituted for TfOH.[7] Complex product mixtures resulted from these reactions.

We propose that the amino alcohols **1**−**11**, **22**, and **24** react in superacid to form dicationic electrophiles. For example, compound **9** is protonated at the nitrogen and hydroxy group, which upon loss of water gives the dicationic intermediate (Scheme 1). Despite the resonance stabilization of the carbocation, intermediate **28** is sufficiently electrophilic to react with C_6H_6. In contrast, 1,1-diphenylethanol (**29**) ionizes in TfOH to give a monocationic intermediate (**30**) which is completely unreactive toward C_6H_6 (aqueous workup of the reaction gives the olefin). The ammonium group in **28** must enhance the reactivity of the adjacent

Scheme 1



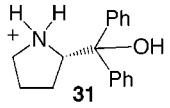
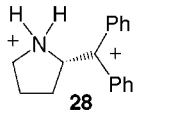
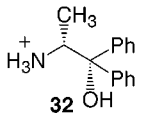
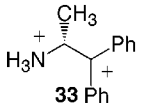
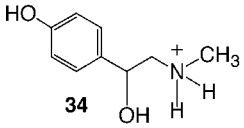
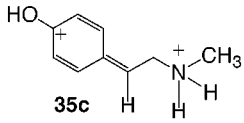
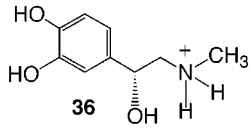
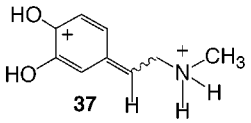
carbocationic center. This increased reactivity may be due to electrostatic effects or inductive effects. In the case of H_2SO_4, it is not sufficiently acidic to cleanly ionize the amino alcohols to the dications and complex product mixtures result.

To characterize the intermediates generated from the amino alcohols, compounds **9**, **10**, **26**, and **27** were dissolved in either CF_3CO_2H or FSO_3H-SbF_5 and studied by ^{13}C NMR. Compound **9** ionizes in CF_3CO_2H to the ammonium cation **31** (Table 2), which shows eight signals for the diastereotopic phenyl groups. When compound **9** is dissolved in FSO_3H-SbF_5 (1:1) and SO_2ClF at −60 °C, the dication structure (**28**) is observed in the ^{13}C spectrum. The benzylic signal in **31** (77.4 ppm) disappears, and the new carbocationic resonance appears at 210 ppm, which is comparable to those of other diphenylmethyl cations.[8] Moreover, ionization to the dication leads to the collapse of the eight aryl signals to four signals. Compound **10** shows spectral data similar to those of **9**: the monocationic derivative (**32**) shows eight diastereotopic ^{13}C signals for the phenyl groups, while the dicationic derivative (**33**) shows the expected four ^{13}C signals. Interestingly, the ^{13}C resonance at 141.6 ppm shows significant broadening at −50 to −80 °C. This suggests some type of restricted rotation of the phenyl groups.

When synephrine **26** is ionized in FSO_3H-SbF_5, the ^{13}C spectrum shows signals for all nine carbons. This suggests the formation of a dicationic structure having the positive charge delocalized into the aryl ring and the *p*-hydroxy group (**35c**). The monocationic derivative (**34**) shows the expected number of ^{13}C signals (seven) for that involving a *p*-hydroxyphenyl ring. Epinephrine (**27**) is ionized in CF_3CO_2H, and the ^{13}C NMR is consistent with the monocationic structure **36**. The methine carbon appears at 74.9 ppm, and there are six aryl carbon signals. Upon ionization in FSO_3H-SbF_5, the methine signal disappears and 13 downfield signals appear from 118.2 to 180.4 ppm. These results suggest that epinephrine also ionizes to a dicationic intermediate (**37**). In the case of **27**, the 3,4-substitution pattern on the aryl ring leads to the formation of a mixture of two stereoisomers of the dication **37**.

Several different resonance forms can represent dications **35** and **37**. For the synephrine dication, there is the benzylic cation **35a**, the ring-delocalized structures **35b** (and the related 1,5-dication) and **35c**, and the quinone methide structure **35d** (Figure 1). The NMR results indicate little or no rotation of the aryl group and rule against a major contribution from **35a**; this structure is probably disfavored due to electrostatic effects involving the two charge centers. Theoretical studies have shown that benzylic cations tend to delocalize to a greater extent when substituted by adjacent electron-withdrawing groups or cationic charge centers.[9] We propose that the synephrine dication is a structure which is best represented by **35b**−**d**. Ab initio calculations were carried out on the synephrine dication, and the carbon−

Table 2. ^{13}C NMR Data for Cationic Species Arising from Protonation of Amino Alcohols

	^{13}C NMR signals, ppm (acid solvent, temp°C)
 **31**	141.1, 140.9, 128.6, 128.2, 128.1, 127.9, 124.3, 124.1, 77.8, 68.1, 46.9, 24.9, 23.1 (CF_3CO_2H, -10°C)
 **28**	210.1, 149.5, 140.8, 136.6, 132.1, 65.6, 50.6, 36.6, 25.3 (FSO_3H-SbF_5 SO_2ClF, -80°C)
 **32**	140.1, 139.3, 129.1, 128.8, 128.5, 128.4, 125.1, 125.0, 79.3, 55.8, 12.7 (CF_3CO_2H, 25°C)
 **33**	211.5, 150.1, 141.6, 136.8, 132.4, 55.1, 21.2 (FSO_3H-SbF_5 SO_2ClF, -50°C)
 **34**	155.4, 127.8, 125.3, 116.2, 75.4, 53.2, 34.0 (CF_3CO_2H, 25°C)
 **35c**	187.5, 166.3, 155.4, 144.8, 135.1, 124.7, 123.2, 49.0, 34.9 (FSO_3H-SbF_5 SO_2ClF, -60°C)
 **36**	144.3, 143.1, 125.2, 119.7, 116.4, 113.6, 74.9, 52.9, 33.8 (CF_3CO_2H, 25°C)
 **37**	179.7, 163.5, 154.7, 146.1, 143.4, 140.9, 136.1, 132.2, 123.5, 122.0, 117.6, 48.9, 34.8 (FSO_3H-SbF_5 SO_2ClF, -80°C)

(6) (a) Klosa, J. *J. Prakt. Chem.* **1966**, *34*(5−6), 335. (b) Klosa, J. *Naturwissenschaften* **1966**, *53*(17), 433. (c) Excess $AlCl_3$ itself can produce superacid-like conditions, and the $HCl-AlCl_3$ system is also a well-known superacid system, see: Olah, G. A.; Prakash, G. K. S.; Sommer, J. In *Superacids*; Wiley: New York, 1985; pp 51−52.

(7) Although no other superacids were used in our synthetic studies, less expensive superacid systems such as $HF-BF_3$ would be expected to give comparable results. However, TfOH does not possess the most serious hazards of the HF-based acid systems. A procedure has been reported for the quantitative recycling of TfOH: Booth, B. L.; El-Fekky, T. A. *J. Chem. Soc., Perkin Trans. I* **1979**, 2441.

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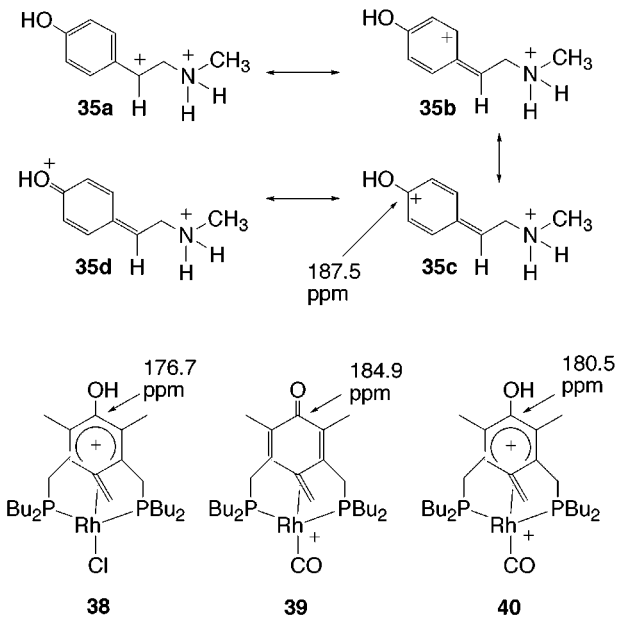

Figure 1. Synephrine dication (**35a**−**d**) and related organometallic systems (**38**−**40**).

oxygen bond distance was estimated to be 1.324 Å.[10] Phenolic carbon−oxygen single bonds are generally around 1.35 Å.[11] Moreover, there are striking similarities between the synephrine dication **35c** and the metal complexes **38**−**40** reported recently by Milstein and co-workers (Figure 1).[12] NMR and crystallographic studies indicated a slightly shortened single bond (1.338 Å) between the carbon and oxygen in structure **38**. On the basis of structural data, the dicationic complex **40** was also proposed to have predominantly arenium ion character. Structural forms **35c** and **35d** suggest the interesting possibility that epinephrine, synephrine, or related amino alcohols may be able to form quinone methide products from dehydration reactions. However, our attempts to trap quinone methide intermediates were unsuccessful.

In summary, we have found that amino alcohols react in superacid to generate dicationic intermediates. The resulting dicationic intermediates are highly electrophilic and can react with benzene to give products from electrophilic substitution in good yields. With triflic acid, trityl-substituted amines, β-phenethylamines, and heterocyclic systems can be prepared. Using low-temperature NMR, dicationic intermediates can be directly observed from the reaction of amino alcohols and FSO_3H-SbF_5.

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Supporting Information Available: Experimental procedures, spectroscopic data of new compounds obtained, ^{13}C NMR specta for dicationic species **28**, **33**, **35c**, and **37**, and computational results. This material is available free of charge via the Internet at http://pubs.acs.org.

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