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Charge Migration in Dicationic Electrophiles and Its Application to the Synthesis of Aza-polycyclic Aromatic Compounds

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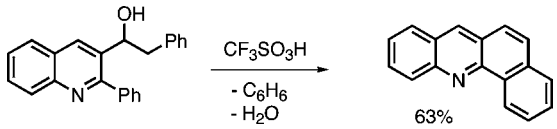
ABSTRACT



Superacid-promoted reactions of dicationic electrophiles have been studied, and the positive charge centers are found to migrate apart in a predictable manner. Using isotopic labeling the charge migration is found in one system to occur through successive deprotonation–reprotonation steps. The charge migration chemistry is the basis for new general synthetic route to aza-polycyclic aromatic compounds.

Aza-polycyclic aromatic compounds and the substituted derivatives have been of interest for their cytotoxic and other biological activities.[1] These types of compounds are also well-known as products from the incomplete combustion of organic materials, and several are known to be potent mutagens and carcinogens.[2] Aza-polycyclic aromatic compounds are also thought to be a major component of interstellar organic matter, some of which have been identified on the basis of their spectral data.[3] Moreover, aza-polycyclic aromatic compounds have been shown in recent applications to have useful optical properties. Consequently, there has been general interest in the development of new synthetic methodologies for these types of compounds. The recent development of superelectrophilic chemistry by Olah and co-workers has stimulated a substantial amount work related to electrophiles having two or more positive charges.[4] Often the stabilities of these dications are related to the distance between charge centers. Several examples are known in which dicationic species rearrange to generate more stable structures having an increased distance between the charge centers, especially if the rearrangement also leads to electronic stabilization of the charge center(s).[5] In the following Letter, we report the rearrangements of secondary and tertiary carbocationic centers to benzylic carbocations in dicationic systems. This rearrangement is the basis for a new general route to aza-polycyclic aromatic compounds.

A series of alcohols (**1**−**6**) were prepared and reacted with C_6H_6 in the presence of the Brønsted superacid CF_3SO_3H (Table 1). In all cases, the products (**7**−**11**, **13**) are generated from a rearrangement and subsequent phenylation. It is proposed that the alcohols initially ionize in superacid to generate 1,4-dications (entries 1−3) or 1,3-dications (entries 4 and 6) and charge migration then occurs to give 1,5-dications or 1,4-dications, respectively. On the basis of results from an isotopically labeled substrate (**3**, entry 3), charge migration is thought to occur by deprotonation (dedeutera-

(1) (a) Ioanoviciu, A.; Antony, S.; Pommier, Y.; Staker, B. L.; Stewart, L.; Cushman, M. *J. Med. Chem.* **2005**, *48*, 4803. (b) Armenise, D.; Trapani, G.; Arrivo, V.; Laraspata, E.; Morlacchi, F. *J. Heterocycl. Chem.* **2000**, *37* (6), 1611. (c) Kaloko, J.; Hayford, A. *Org. Lett.* **2005**, *7*, 4305.

(2) (a) Borosky, G. L.; Laali, K. K. *Org. Biorg. Chem.* **2005**, *3*, 1180. (b) Schmeltz, I.; Hoffmann, D. *Chem. Rev.* **1997**, *77*, 2295.

(3) Mattioda, A. M.; Hudgins, D. M.; Bauschlicher, C. W.; Rosi, M.; Allamandaola, L. J. *J. Phys. Chem. A* **2003**, *107*, 1486.

(4) Olah, G. A.; Klumpp, D. A. *Acc. Chem. Res.* **2004**, *37*, 211.

(5) (a) Zhang, Y.; Aguirre, S. A.; Klumpp, D. A. *Tetrahedron Lett.* **2002**, *43*, 6837. (b) Klumpp, D. A.; Fredrick, S.; Lau, S.; Prakash, G. K. S.; Jin, K. K.; Bau, R.; Olah, G. A. *J. Org. Chem.* **1999**, *64*, 5152. (c) Taescher, C.; Sorenson, T. *Tetrahedron Lett.* **2001**, *42*, 5339.

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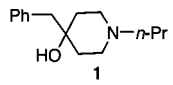
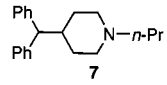
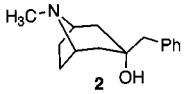
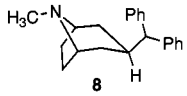
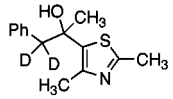
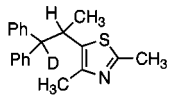
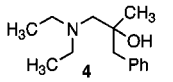
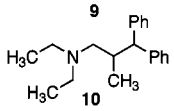
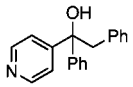
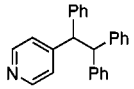
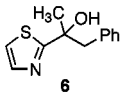
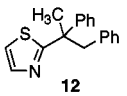
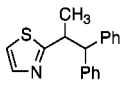
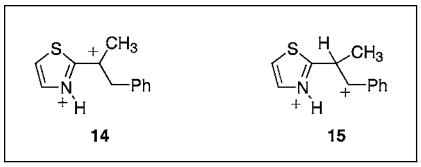
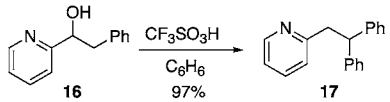
Table 1. Products and Yields from the Reactions of Alcohol Substrates (**1**−**7**) with CF_3SO_3H and C_6H_6

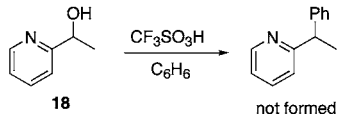
entry	starting material	product	yield[a]
(1)	 **1**	 **7**	89%
(2)	 **2**	 **8**	98%
(3)	 **3**	 **9**	90%
(4)	 **4**	 **10**	95%
(5)	 **5**	 **11**	97%
(6)	 **6**	 **12**	0 °C: 77%
		 **13**	25 °C: 56%; 0 °C: 5%; 25 °C: 26%

[a] Isolated yields of purified products.

tion)−protonation reaction steps rather than via 1,2-hydride shifts.[6] The migration of the charge is evidently driven by the formation of the benzylic-type carbocation, as well as the increasing separation of the two positive charge centers. The importance of increasing charge separation is seen in the reaction of compound **5,** which ionizes in superacid to initially generate a 1,5-dication having benzylic stabilization. Despite the benzylic stabilization, charge migration produces the 1,6-dication (also benzylic), and product **11** is obtained in good yield. The thiazole system (**6**) gives both the rearrangement (**13**) and substitution (**12**) products, and the relative ratio of the two products varies with temperature. However if compound **6** is reacted with CF_3SO_3H for 1 h and then C_6H_6 is added, the charge migration product (**13**) is formed exclusively. This suggests that the rearrangement product (**13**) is the thermodynamically favored product, whereas product **12** is the kinetically favored product. When the dicationic intermediates leading to products **12** and **13** are compared, the rearrangement involves the isomerization of the 1,3-dication to the 1,4-dication. Ab initio calculations were done on the intermediates (**14** and **15**), and the calculations estimate that dication **15** is significantly more stable than dication **14**. The geometry optimized structure (**14**) shows neighboring group participation by a phenonium ion type of interaction; however, the 1,3-dication (**14**) is about 16 kcal/mol less stable than the 1,4-dication (**15**) at the B3LYP 6-311G**// B3LYP 6-311G** level of theory.[7] Nevertheless, the phenonium ion stabilization may provide important anchimeric assistance for the ionization of the alcohol to the dicationic intermediate. This is also evident from the observed reactivity differences between compound **16** and compound **18**: ionization of **16** occurs readily and gives the arylated product (**17**) almost quantitatively (eq 1), whereas compound **18** does not give the substitution product under similar conditions (eq 2), but instead starting material **18** is recovered.


14 **15**


16 **17** (1)

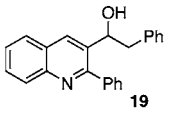
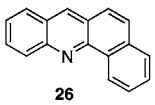
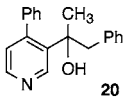
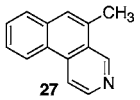
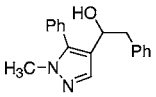
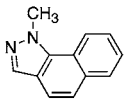
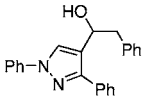
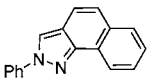
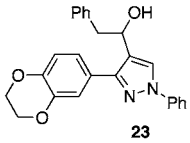
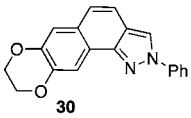
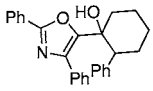
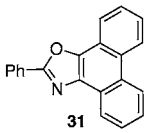
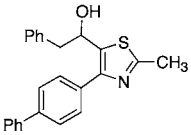
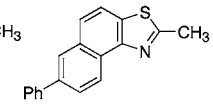

18 not formed (2)

When appropriately substituted *N*-heterocycles are reacted with superacidic CF_3SO_3H, a cyclization gives aza-polycyclic aromatic compounds from loss of water and benzene (Table 2). For example, this conversion gives benz[*c*]acridine (**26**) in one step from the reaction of the substituted quinoline (**19**) and CF_3SO_3H (entry 1). Other aza-polycyclic compounds prepared by this method include the benz[*f*]isoquinoline (**27**), the benz[*g*]indazole (**29**), and the benz[*e*]imidazole (**28**). The conversions are thought to involve several types of dicationic intermediates (Scheme 1). In the case of compound **20**, protonation of the pyridine ring and alcohol group leads to the 1,4-dication (**34**), and this is followed by charge migration to give the 1,5-dication (**35**). Cyclization toward the phenyl group then leads to the formation of the new ring. Elimination of benzene occurs by the initial *ipso*-protonation to form dication **(37)**, with subsequent loss of benzene and a proton to generate the benz[*f*]isoquinoline system. On the basis of this mechanism, we sought to determine if a larger ring system could be prepared by a cyclization involving a phenyl-substituted cyclohexyl group (entry 6, Table 2). When compound **24** is reacted with CF_3SO_3H and the product then aromatized with DDQ, the phenanthro[9,10-*d*]oxazole system (**31**) is produced in fair yield. Presumably, ionization of compound **24** in the superacid also leads to dication formation, charge migration, cyclization involving the cyclohexyl cation, and benzene elimination.

(6) As suggested by a reviewer of this manscript, the deprotonation−protonation may be more important for systems giving a double bond conjugated to a pair aromatic systems (such as entry 3), while direct hydride shift (as a mode of charge migration) may operate in other systems not having the benefit of *trans*-stillbene-type conjugation.

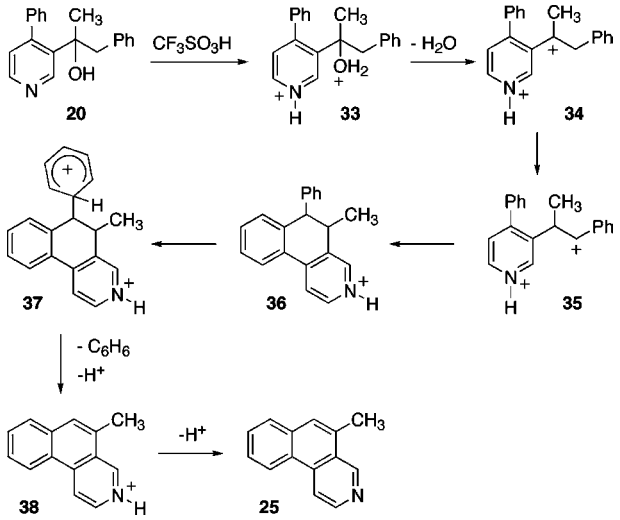
(7) For details regarding the computational results, see Supporting Information.

Table 2. Yields of Aza-polycyclic Aromatic Compounds from the Reactions of Compounds **19**−**24** with CF_3SO_3H at 25 °C

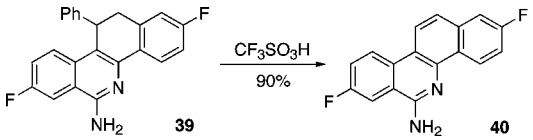
entry	starting material	product	yield[a]
(1)	 **19**	 **26**	63%
(2)	 **20**	 **27**	93%[b]
(3)	 **21**	 **28**	57%
(4)	 **22**	 **29**	86%
(5)	 **23**	 **30**	60%
(6)	 **24**	 **31**	56%[c]
(7)	 **25**	 **32**	41%

[a] Isolated yields of purified products. [b] Reaction performed at 50 °C. [c] Cyclization step followed by reaction with DDQ.

Scheme 1. Proposed Mechanism



The utility of the benzene elimination step is shown in the preparation of a substituted benzo[*c*]-phenanthrene (**40**, eq 3). Several benzo[*c*]phenanthrenes are known for their



(3)

anticancer properties and have been extensively studied by medicinal chemists.[8] Recently, Clement and co-workers described a convenient method for the preparation of dihydro-benzo[*c*]phenanthrenes having pendant aryl groups.[9] Using this method, 5-fluoro-2-methyl-benzonitrile was reacted with benzaldehyde to give the phenyl-substituted product (**39**). Reaction of product **39** with CF_3SO_3H gives the substituted benzo[*c*]phenanthrene (**40**) in good yield. The benzene elimination step likely involves a triprotonated intermediate having the ring nitrogen, as well as the amino and phenyl groups, protonated by the superacid.

The conversions of compounds **19**−**25** to the respective aza-polycyclic aromatic compounds represents a new route to these types of products and involves two novel reaction steps: separation of the two positive charge centers in the initially formed dications and the superacid-promoted elimination of benzene. As in the dicationic reactions with benzene (Table 1), the conversions leading to aza-polycyclic aromatic compounds may involve phenonium ion assistance in forming the initial carbocationic intermediate (**33** → **34**). Charge migration is driven by the increased separation of the charge centers and the formation of the benzylic type of carbocation. With respect to the superacid-promoted elimination of benzene, *ipso*-protonation of aryl groups is a known route to carbocation intermediates (i.e., solvation of tetraphenylmethane in strong acid leads to the formation of the trityl cation).[10] To best of our knowledge, elimination of benzene via *ipso*-protonation has not been described previously in the synthetic literature,[11] although similar conversions have been proposed in the superacid-promoted depolymerization of coals.[12] The driving force for this process is likely the generation of the extended aromatic systems in the aza-polycycic aromatic products (**26**−**32** and **40**). The scope of this new chemistry is presently being explored.

Acknowledgment. The financial support of the NIH-NIGMS (GM071368-01) is greatly appreciated. The Department of Chemistry at NIU is thanked for the undergraduate

(8) Nyangulu, J. M.; Hargreaves, S. L.; Sharples, S.; Mackay, S. P.; Waigh, R. D.; Duval, O.; Mberu, E. K.; Watkins, W. M. *Bioorg. Med. Chem. Lett.* **2005**, *15* (8), 2007. (b) Vogt, A.; Tamewitz, A.; Skoko, J.; Sikorski, R. P.; Giuliano, K. A.; Lazo, J. S. *J. Biol. Chem.* **2005**, *280* (19), 19078. (c) Harayama, T. *Heterocycles* **2005**, *65*, 697.

(9) Clement, B.; Weide, M.; Wolschendorf, U.; Kock, I. *Angew. Chem., Int. Ed.* **2005**, *44*, 635.

(10) Fonken, G. J. *J. Org. Chem.* **1963**, *28*, 1909.

(11) See, however: (a) Koltunov, K. Yu.; Prakash, G. K. S.; Rasul, G.; Olah, G. A. *Heterocycles* **2004**, *62*, 757. (b) Necula, A.; Racoveanu-Schiketanz, A.; Gheorghiu, M. D.; Scott, L. T. *J. Org. Chem.* **1995**, *60*, 3448.

(12) Shimizu, K.; Ikuo, I. *Energy Fuels* **1998**, *12*, 115.

research excellence award (P.J.K.). This manuscript is dedicated to the fond memory of Professor Roland E. Lehr.

Supporting Information Available: Experimental procedures and characterization data, including ^{1}H and ^{13}C NMR data spectra and mass spectra data, and computational data and methodology. This material is available free of charge via the Internet at http://pubs.acs.org.

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