Superacid-Promoted Additions Involving Vinyl-Substituted Pyrimidines, Quinoxalines, and Quinazolines: Mechanisms Correlated to Charge Distributions

ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · JUNE 2011

Impact Factor: 12.11 · DOI: 10.1021/ja202557z · Source: PubMed

5 AUTHORS, INCLUDING:

Douglas A. Klumpp
Northern Illinois University
93 PUBLICATIONS **1,105** CITATIONS

Published in final edited form as:
J Am Chem Soc. 2011 June 8; 133(22): 8467–8469. doi:10.1021/ja202557z.

Superacid-promoted additions involving vinyl-substituted pyrimidines, quinoxalines, and quinazolines: mechanisms correlated to charge distributions

Yiliang Zhang, **Matthew R. Sheets**, **Erum K. Raja**, **Kenneth N. Boblak**, and **Douglas A. Klumpp**
Northern Illinois University, Department of Chemistry and Biochemistry, DeKalb, Illinois 60115

Abstract

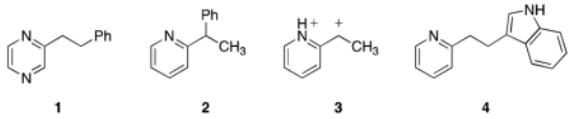
The superacid-promoted reactions of vinyl-substituted *N*-heterocycles have been studied. Diprotonated pyrimidines, quinoxalines, and quinazolines exhibit an unusual regioelectronic effect that controls the type of addition reaction observed. Depending on the ring position of the vinyl-substituent, either conjugate addition or Markovnikov addition occurs. The mode of addition has been shown to correlate well to NBO calculated charges.

Among pharmaceutical substances, the *N*-heterocycles comprise an important class.[1] A recent survey found that more than 70% of the top selling proprietary drugs contain *N*-heterocycles in their structures.[2] As such, there is significant value in synthetic chemistry leading to functionalized *N*-heterocycles. The conjugate or Michael additions involving vinyl-substituted *N*-heterocycles have been useful reactions in the preparation of substituted heterocycles, including several biologically active products.[3] These reactions generally involve the use of fairly strong nucleophiles (thiols, amines, and enolate ions) with substrates, such as 2-vinylpyridine.[4] While some of these conjugate additions occur through the prior formation of the pyridinum-type ion, many are thought to involve nucleophilic attack on the uncharged 2-vinylpyridine. The conjugate addition reactions are known to be sensitive to regioelectronic effects. For example nucleophiles do not react as readily with 3-vinylpyridine,[3c] an observation most often explained using resonance structures.[5]

Recently, the superacid-promoted (addition of benzene to vinylpyrazine was reported, with the addition product **1** formed in high yield (92%).[6] This is contrasted with the product (**2**) from 2-vinylpyridine under similar reaction conditions.[7] These results suggest two types of addition mechanisms operating: a conjugate addition in the case of vinylpyrazine and a Markovnikov-type addition with 2-vinylpyridine (involving dication **3**). Several factors appear to be involved in determining which reaction pathway is preferred, most importantly electrophilicity of the vinyl group, nucleophile strength, and acid strength. Thus, the stronger nucleophile indole undergoes conjugate addition with 2-vinylpyridine in the weakly acidic CH_3CO_2H and compound **4** is produced.[8] Prompted by these earlier results, we have sought to further examine the chemistry of the vinyl-substituted diazines and their ring-fused derivatives. In this Communication, we describe the results of these studies and a correlation between charge distributions and the tendency for conjugate addition.

Correspondence to: Douglas A. Klumpp.

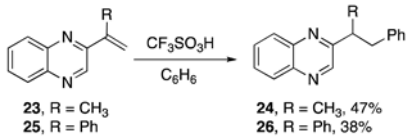
Supporting Information Available: Detailed experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra for new compounds, ^{13}C NMR spectra for ions **29** and **31**, computational methods and results.



1 2 3 4

A series of vinyl-substituted heterocycles was prepared and reacted with benzene and superacidic CF_3SO_3H (Table 1). The vinyl-substituted derivatives were prepared from the corresponding heterocyclic chloride or bromide and tributylvinyltin, using tBu_3P and $Pd_2(dba)_3$ catalyst.[9] When the vinyl group is located at the 2- or 4-positions on the pyrimidine ring, the conjugate addition products are observed (entries 1 and 2). In the case of compound **6**, reaction with benzene is preferred over intramolecular reactions at the phenyl group.[10] Interestingly, Markovnikov-type addition occurs when the vinyl group is at the 5-position of the pyrimidine ring (entries 3 and 4). The quinoxaline derivatives also show the divergent chemistry: a vinyl group at the 2-position leads to conjugate addition (entry 5) while at the 6-position, Markovnikov addition is observed (entry 6). Similar results are observed with the quinazoline derivatives (entries 7, 8, and 9). The relatively low yield of product **22** is primarily due to competing quinazoline-ring cleavage reactions in the superacid.

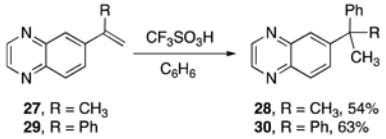
Besides vinyl-groups, propenyl- and styryl-groups show similar characteristics. Our previous study demonstrated that propenyl-and styryl-substituted pyrazine tend to undergo conjugate addition with benzene in superacid.[6] In the quinoxaline series, substituents in the 2-position undergo also conjugate addition (eq 1). Markovnikov addition is observed when the propenyl- and styryl-groups are in the 5-position (eq 2). These trends parallel the chemistry observed with the vinyl substituted quinoxalines (**9** and **10**): groups in the 2-position undergo conjugate addition and groups in the 5-position give Markovnikov addition products.



23, R = CH_3
25, R = Ph

24, R = CH_3, 47%
26, R = Ph, 38%

(1)



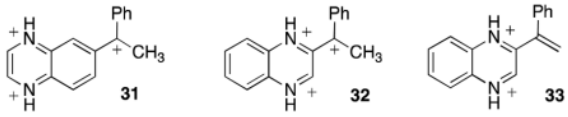
27, R = CH_3
29, R = Ph

28, R = CH_3, 54%
30, R = Ph, 63%

(2)

Among the observations from the above studies, it is clear that certain positions on the *N*-heterocycles tend to favor conjugate-type over Markovnikov-type addition. It is also obvious that this is a strong directing effect, as demonstrated by the experiments with the styryl-substituted quinoxaline **25**. Despite the potential to form a benzylic carbocation center, olefin protonation appears to be significantly disfavored. Thus, intermediate **31** is formed, but **32** cannot be formed (which would give the Markovnikov product). In order to test this hypothesis, compounds **25** and **29** were dissolved in superacid and studied by low temperature NMR (Figure 1). When compound **25** is reacted in FSO_3H-SbF_5 (4:1) in

SO_2ClF at −50°C, only the diprotonated species **33** is observed (Spectrum A). Analysis of the solution by DEPT confirms the presence of the olefinic CH_2 carbon. In contrast, a solution of compound **29** in FSO_3H-SbF_5-SO_2ClF gives a spectrum consistent with the formation of trication **31** (Spectrum B), including a carbocationic resonance (δ 223) and a methyl group resonance (δ 31). Analysis by DEPT and APT experiments also confirms the structural assignment of carbocation **31**. The ^{13}C NMR spectrum for **31** also shows a signal for each carbon atom, indicating that rotation of the phenyl group is slow. This is likely the result of extensive carbocation charge delocalization into the phenyl ring. Although FSO_3H-SbF_5 (4:1) is considerably more acidic than CF_3SO_3H, the NMR results are in accord with the observed addition reactions. The styryl group in **33** is not protonated in superacid, so the Markovnikov product cannot form. When the olefin group can be protonated and the carbocation is formed, then Markovnikov addition is observed.



To further understand this chemistry, theoretical calculations were done on the diprotonated heterocycles (Figure 2).[11] Calculations were done at the 6-311G (d,p) level using MP2 and B3LYP computational models. Natural bond order analysis was done to assign charges. We have found a very good correlation between the relative charges at the ring carbon atoms versus the type of observed addition chemistry. For example, the diprotonated pyrimidine ring (**34**) shows significant positive charge values at the 2- and 4,6-positions, while the 5-position shows a negative charge value. The positive NBO charges correspond to highly electron deficient sites on the ring.[12] Clearly, this should inhibit formation of an adjacent carbocation (from protonation of the vinyl group) and it should also increase the tendency for conjugate addition with the arene nucleophile. Thus, conjugate addition (CA) is observed with 2- and 4-vinylpyrimidines and benzene. A relatively high degree of electron density occurs at the 5-position of the ring. This evidently facilitates protonation of the vinyl group and formation of the carbocation intermediate. This leads to the Markovnikov addition (MA) product. The calculations were also done with the vinyl-substituted heterocycles (**35** and **36**) and these structures exhibited similar charge distributions. Both the quinazoline and quinoxaline systems (**37** and **38**) showed the same trend as the pyrimidine series. These *N*-heterocyclic systems give Markovnikov addition products at electron rich positions and conjugate addition products at electron deficient position.

These studies demonstrate the importance of charge distributions in controlling the chemistry of *N*-heterocycles. Diprotonated *N*-heterocycles (pyrazines, pyrimidines, quinoxalines, and quinazolines) are shown to exert very powerful regioelectronic effects at certain ring positions. NMR experiments have shown that these effects drastically influence the basicity of substituent styryl groups. The relatively high amount of positive charge leads to conjugate addition with the weak nucleophile benzene, making this chemistry analogous to the superelectrophiles described by Olah.[13] Other ring positions are clearly not as electron deficient and this leads to a completely different reaction course. The olefinic groups at these sites tend to undergo Friedel-Crafts-type chemistry via carbocationic intermediates. Functionalized *N*-heterocycles are often prepared by synthetic reactions at side chains or substituent groups. Our results have shown that such chemistry may be significantly impacted by localized charges within the *N*-heterocycles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We gratefully acknowledge the support of the National Science Foundation (CHE-0749907) and the NIH-National Institute of General Medical Sciences (GM085736-01A1). We thank Professors Peter R. Schreiner and Thomas M. Gilbert for helpful discussions.

References

1. Kleemann, E.; Kutscher, R. Pharmaceutical Substances. Thieme; Stuttgart: 2009.
2. Based on annual sales of drugs in the year 2009, see: http://www.drugs.com/top200.html; downloaded March 12, 2011.
3. a Raux E, Klene J, Blake A, Saczewski J, Strekowski L. Molecules. 2010; 15:1973. [PubMed: 20336026] b Burns AR, Kerr JH, Kerr WJ, Passmore J, Paterson J, Paterson LC, Watson AJB. Org Biomol Chem. 2010; 8:2777. [PubMed: 20424795] c Schaaf GM, Mukherjee S, Waterson AG. Tetrahedron Lett. 2009; 50:1928.d Han X, Civiello RL, Mercer SE, Macor JE, Dubowchik GM. Tetrahedron Lett. 2009; 50:386.e Gimbert C, Lumierres M, Marchi C, Moreno-Manas M, Sebastian, Vallribera A. Tetrahedron. 2005; 61:8598.f Lumbierres M, Marchi C, Moreno-Manas M, Sebastian, Vallribera A, Lago E, Molins E. Eur J Org Chem. 2001:2321.g Fellahi Y, Dubois P, Ombetta-Goka JE, Chaumont JP, Frangin Y. Eur J Med Chem. 1995; 30:633.h Øveràs AT, Bakkestuen AK, Gundersen L-L, Rise F. Acta Chem Scand. 1997; 51:1116.i Samaritoni JG, Babbitt GE. J Heterocyclic Chem. 1997; 34:1263.
4. a Katritzky AR, Takahashi I, Marson CM. J Org Chem. 1986; 51:4914.b Chung JYL, Hughes DL, Zhao D, Song Z, Mathre DJ, Ho G-J, McNamara JM, Douglas AW, Reamer RA, Tsay F-R, Varsolona R, McCauley J, Grabowski EJJ, Reider PJ. J Org Chem. 1996; 61:215.c Danishefsky S, Cain P, Nagel A. J Am Chem Soc. 1975; 97:580.d Logothetis AL. J Org Chem. 1969; 29:1834.
5. Doering WE, Weil RAN. J Am Chem Soc. 1947; 69:2461.
6. Zhang Y, Briski J, Zhang Y, Rendy R, Klumpp DA. Org Lett. 2005; 7:2505. [PubMed: 15932234]
7. Zhang Y, McElrea A, Sanchez GV Jr, Klumpp DA, Do D, Gomez A, Aguirre SL, Rendy R. J Org Chem. 2003; 68:5119. [PubMed: 12816465]
8. Gray AP, Archer WL. J Am Chem Soc. 1957; 79:3554.
9. Littke AF, Schwarz L, Fu GC. J Am Chem Soc. 2002; 124:6343. [PubMed: 12033863]
10. It is not clear if the 2-phenyl group on **6** influences the type of addition chemistry observed (Markovnikov or conjugate addition).
11. Frisch, MJ.; Trucks, GW.; Schlegel, HB.; Scuseria, GE.; Robb, MA.; Cheeseman, JR.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, GA.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, HP.; Izmaylov, AF.; Bloino, J.; Zheng, G.; Sonnenberg, JL.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, JA., Jr; Peralta, JE.; Ogliaro, F.; Bearpark, M.; Heyd, JJ.; Brothers, E.; Kudin, KN.; Staroverov, VN.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, JC.; Iyengar, SS.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, NJ.; Klene, M.; Knox, JE.; Cross, JB.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, RE.; Yazyev, O.; Austin, AJ.; Cammi, R.; Pomelli, C.; Ochterski, JW.; Martin, RL.; Morokuma, K.; Zakrzewski, VG.; Voth, GA.; Salvador, P.; Dannenberg, JJ.; Dapprich, S.; Daniels, AD.; Farkas, Ö.; Foresman, JB.; Ortiz, JV.; Cioslowski, J.; Fox, DJ. Gaussian 09, Revision B.01. Gaussian, Inc; Wallingford CT: 2009.
12. Weinhold, F. Encyclopedia of Computational Chemistry. Schleyer, PvR; Allinger, NL.; Clark, T.; Gasteiger, J.; Kollman, PA.; Schaefer, HF., III; Schreiner, PR., editors. Vol. 3. John Wiley & Sons; Chichester, UK: 1998. p. 1792-1811.
13. Olah, GA.; Klumpp, DA. Superelectrophiles and Their Chemistry. Wiley; New York: 2008.

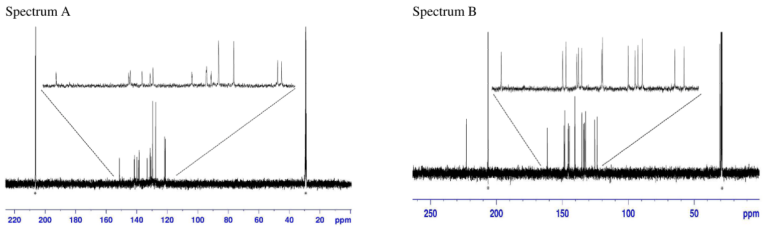


Figure 1.

Low temperature ^{13}C NMR spectrum of dication **33** (Spectrm A) and trication **31** (Spectrum B) in FSO_3H-SbF_5-SO_2ClF solution at −50°C (d_6-acetone external standard indicated by *).

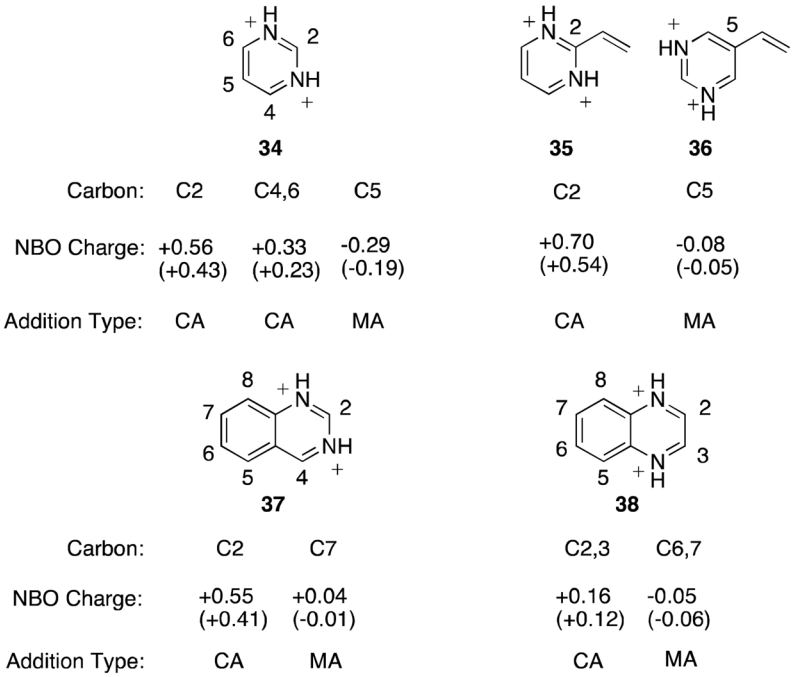
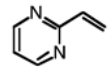
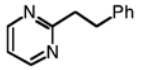
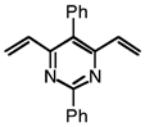
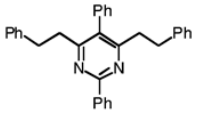
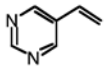
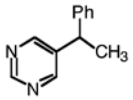
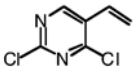
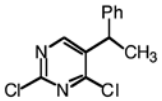
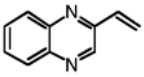
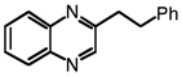
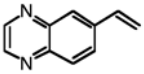
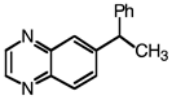
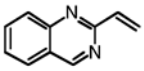
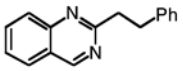
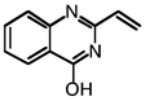
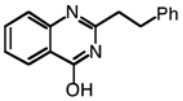
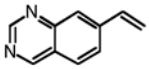
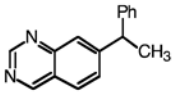


Figure 2.

MP2 6-311G(d,p) calculated NBO charges for carbon atoms in diprotonated *N*-heterocycles **34–38** and the types of addition chemistry observed (CA – conjugate addition, MA - Markovnikov addition; B3LYP 6-311G (d,p) calculated NBO charges in parentheses).

Table 1

Products and yields from the reactions of vinyl-substituted *N*-heterocycles (**5–13**) with C_6H_6 in CF_3SO_3H.

entry	olefin	product	yield
(1)	 **5**	 **14**	47%[a]
(2)	 **6**	 **15**	88%[a]
(3)	 **7**	 **16**	86%[a]
(4)	 **8**	 **17**	53%[a]
(5)	 **9**	 **18**	74%[b]
(6)	 **10**	 **19**	58%[b]
(7)	 **11**	 **20**	92%[a]
(8)	 **12**	 **21**	45%[b]
(9)	 **13**	 **22**	33%[a]

[a] Reaction done at 25°C.

[b] Reaction done at 80°C.