# Studies on Hetero-Cage Compounds. II.[1] p$K_a$ Studies on the 3,10-Diazabicyclo[4.3.1]decane System

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The p$K_a$ values of pseudopelletierine (**1**), 10-methyl-3,10-diazabicyclo[4.3.1]decan-4-one (**2**), 10-methyl-3,10-diazabicyclo[4.3.1]decane (**3**), 6,8-*exo*-ethanopseudopelloetierine (**4**), 7,9-*exo*-ethano derivatives **5** and **6** of **2** and **3** were measured potentiometrically in water-methyl cellosolve (20 : 80 v/v) at 20°C. The conformational problems in the 3,10-diazabicyclo[4.3.1]decane system were discussed based on the observed p$K_a'$ (p$K_{mcs}$) values. The characteristic conformational behavior of the monocation (**7**) of **3** was suggested by the higher value of its p$K_{mcs}$ than of **6**.

In a previous publication,[1] we described the synthesis of 10-methyl-3,10-diazabicyclo[4,3.1]decane (**3**) and its 7,9-*exo*-ethano derivative (**6**) by lithium aluminum hydride reduction of 10-methyl-3,10-diazabicyclo[4.3.1]decan-4-one (**2**) and its 7,9-*exo*-ethano derivative (**5**) respectively, both of which were obtained by the Schmidt reaction of pseudopelletierine (**1**) and 6,8-*exo*-ethanopseudopelletierine (**4**), respectively. From the chemical behavior toward methyl iodide and from the NMR spectra, it was shown that the *N*-methyl pyramidal inversion[2] in **3** is allowed, while that in **6** is prohibited by the steric hindrance due to the 7,9-*exo*-ethano bridge, and the *N*-methyl group is forced to take an *anti*-orientation.[3] In this paper, we wish to describe the results of the p$K_a$ studies on these systems.

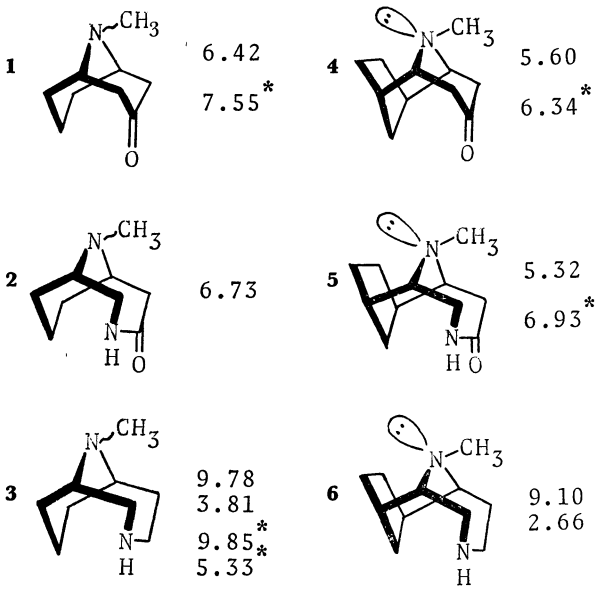



Fig. 1. p$K_{mcs}$ of **1**—**6** (* in water) at 20°C.

The apparent p$K_a$ values of the amines **1**—**6** were measured potentiometrically in water - methyl cellosolve (20 : 80 v/v) at 20°C. The obtained values (p$K_{mcs}$) are summarized in Fig. 1, in which the values in water (p$K_a$) are also shown for **1**, **3**, **4**, and **5**.

The p$K_{mcs}$ value of pseudopelletierine was 6.42 which is larger than the value (5.60) of its *exo*-ethano derivative (**4**). The p$K_{mcs}$ value (6.73) of the lactam **2** was also larger than that (5.32) of the corresponding *exo*-ethano lactam **5**. This suggests that the basicity of the *t*-amine is reduced as much as 0.82—1.41 p$K$ unit by the presence of the ethano bridge. This can be ascribed to the more crowdedness in the conjugate acids of **4** and **5** than in those of **1** and **2**. A somewhat similar effect of the steric demand on the amine basicity was also recognized by other workers.[4]

The p$K_{mcs}$ value of **2** was 0.31 larger than that of the ketone **1**, while the value of the ethano-lactam **5** was 0.28 smaller than that of the ethano ketone **4**. This suggests a contradictory effect of the lactam group on the *tert*-amine basicity in **1**—**2** and **4**—**5** series. However, examination of the values of **4** and **5** in water indicates that **5** is a stronger base than **4**. Thus, the basicity of the *t*-amines **2** and **5** might be strengthened by the presence of the lactam group instead of the carbonyl group in **1** and **4**.[5,6]

The tricyclic diamine **6** had two p$K_{mcs}$ values (9.10 and 2.66). In the NMR data of mono salt (**10**)

1) Part I: T. Sasaki, S. Eguchi and T. Kiriyama, *J. Org. Chem.*, **36**, 2061 (1971).

2) For recent reviews on the pyramidal inversion, see a) H. Kessler, *Angew. Chem.*, **82**, 237 (1970); b) A. Lauk, L. C. Allen, and K. Mislow, *ibid.*, **82**, 453 (1970).

3) The prefix *anti* refers to direction with respect to the ethano bridge.

4) For example, see a) H. O. House, P. P. Wickham, and H. C. Müller, *J. Amer. Chem. Soc.*, **84**, 3139 (1962); b) L. A. Paquette and J. W. Heimaster, *ibid.*, **88**, 763 (1966).

5) The basicity promoting effect of the lactam group could be explained by inductive and field effects as well as the ring-size effect. *Cf.* The p$K_a$ value of acetamide (−1.40, 18°C) and cyclohexanone (−6.8, 25°C); J. T. Edward, S. C. R. Meacock, *J. Chem. Soc.*, **1957**, 2000; H. J. Campbell and J. T. Edward, *Can. J. Chem.*, **38**, 2109(1960). For a review on the electronic effects, see C. K. Ingold,"Structure and Mechanism in Organic Chemistry," 2nd Ed., Cornell University Press (1969), Chapter II.

6) The fact that the p$K_{mcs}$ value of **5** is smaller than that of **4** could be explained by the steric hindrance in the solvation. For a similar effect of a carbonyl group on acetolysis rates of 2,6-bridged bicyclo[2.2.1]heptyl and bicyclo[2.2.2]octyl tosylates strengthened by the steric hindrance of the solvation, see R. M. Moriarty, C. R. Romain, and T. O. Lovett, *J. Amer. Chem. Soc.*, **89**, 3927 (1967).

of **6** with trifluoroacetic acid, the chemical shifts of $C_2$- and $C_4$-methylene protons adjacent to the *s*-amino group were more deshielded compared to $C_1$- and $C_6$-methine protons adjacent to the *t*-amino group.[1] This indicates that the first equivalent of the acid is neutralized by the *s*-amino group in **6** rather than by the *t*-amino group. Hence, the value 9.10 is assigned to $pK_{mcs}$ of the *s*-amino group in **6**, and 2.66 to that of the *t*-amino group. The much smaller value (2.66) of the *t*-amino group in **6** than the values 5.32 and 5.60 of the *t*-amino group in **4** and **5** is apparently explained by the strong inductive- and field-effects of the $-NH_2^+$ group.[5] The assignments are compatible with the fact that the $pK_a$ values of *t*-amines are smaller than those of the corresponding *s*-amines in several monocyclic amines such as pyrrolidine, *N*-methylpyrrolidine, piperidine, *N*-methylpiperidine, morpholine, and *N*-methylmorpholine as summarized in Fig. 2.[7]

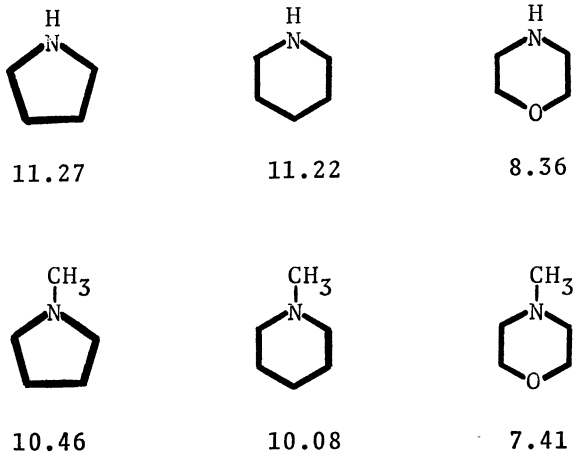
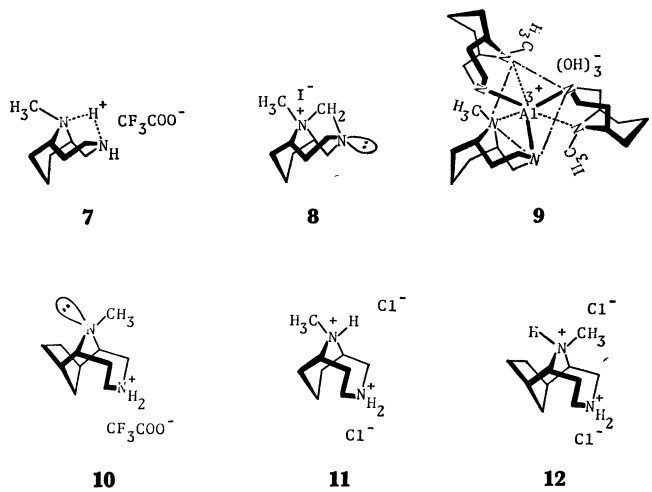
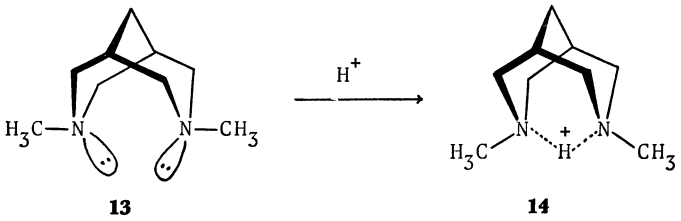



Fig. 2. $pK_a$ of cyclic amines (in water at 25°C).

On the other hand, bicyclodiamine **3** had two $pK_{mcs}$ values (9.78 and 3.81), in which a larger one could be assigned to the *s*-amino group and a smaller one to the *t*-amino group analogously to **6** and other monocyclic *s*- and *t*-amines. The larger $pK_{mcs}$ value of the *s*-amino group in **3** than that in **6**, and the greatly decreased value of the *t*-amino group in **3** compared to **1** and **2** suggest that the monocation of **3** should be more stable than that of **6** for some steric reasons. An inversion of the homopiperazine ring to a boat form is possible in **3**, while in **6**, the presence of the 8,9-*exo*-ethano bridge fixes the N–$CH_3$ group in *anti*-direction, the inversion of the homopiperazine ring thus, being prohibited. Hence, the monocation of **3** can exist in such a conformation as **7** where the piperazine ring takes the chair-form and the homopiperazine ring takes the boat-form as evidenced by the NMR data of compounds **7** and **9**.[1] A similar




but more drastic conformational effect on the amine basicity has been reported on the bispidine system.[8] *N,N*-Dimethylbispidine (**13**) has a very large $pK_a$ value such as 11.88. This is 1.8 $pK$ unit larger than *N*-methylpiperidine. The stabilizing factors of the monocation might be involved in a very stable adamantane-like conformation such as **14**.




In the bicyclodiamine **3**, the stabilizing effect of the monocation by the *t*-amino group can be fulfilled only by inverting its chair-homopiperazine ring to a boat-homopiperazine ring leading to a strained 1,5-diazabicyclo[3.2.1]octane ring structure instead of a strain-free adamantane form[9] in bispidine **13**. Hence, the increase in the $pK_{mcs}$ value from 9.10 of **6** to 9.78 of **3** is reasonably moderate compared to that of *N*-methylpiperidine to bispidine. Furthermore, the decrease in the second $pK_{mcs}$ value (3.81) or the difference between the two $pK_{mcs}$ values (9.78 and 3.81) seems smaller than that in **13**,[10] but larger than that in piperazine whose $pK_a$ values are reported to be 9.82 and 5.68 at 20°C.[11,12] The abnormally smaller value (2.66) of the *t*-amino group in **6**, how-

7) a) S. Searles, M. Tamres, F. Block, and L. A. Quarterman, *J. Amer. Chem. Soc.*, **78**, 4917(1956); b) "Handbook of Organic Structural Analyses," Ed. by Y. Yukawa, W. A. Benjamin, Inc., New York, N. Y. (1965), p.p. 584–613.

8) J. E. Douglass and T. B. Ratliff, *J. Org. Chem.*, **33**, 355 (1968).

9) Strictly speaking, adamantane is not strain-free, *cf*, P. v. R. Schleyer, J. E. Williams, and K. R. Blanchard, *J. Amer. Chem. Soc.*, **92**, 2377 (1970).

10) The second $pK_a$ value is not reported but even the disalt formation is described to be difficult; Ref. 8.

11) The $pK_a$ value of homopiperazine does not seem to have been reported.

12) G. Schwarzenbach, B. Maissen, and H. Ackermann, *Helv. Chim. Acta*, **35**, 2333 (1952).

ever, is explained by both the electronic effects of $-NH_2^+$ group and the above described steric hindrance of the *exo*-ethano bridge.

A homopiperazine ring seems to be one of the smallest membered ring of diazacyclic compounds that can afford a stable monocation form with one equivalent of acid. Investigation[13] on the proton exchange rate and the *N*-pyramidal inversion rate in *N,N*-dimethylpiperazine monohydrochloride discloses no intermediate formation of a 1,4-diazabicyclo[2.2.1]heptane type monocation in the conversion of *trans*- to *trans**-*N,N*-dimethylpiperazine monohydrochloride, though an organometallic complex formation of bicyclo[2.2.1]heptane skeleton is reported on *N,N*-dimethylpiperazine.[14]

Finally, the stereochemistry of the quaternization in **3** might be discussed briefly.[15] The fact that the basicity of the *s*-amino group is stronger than that of the *t*-amino group in **3**, and the formation of tricyclic diazaundecanium iodide (**8**) from **3** and methylene iodide is facile[1] supports the view that an approach of a proton or methylene iodide from an upper side of the homopiperazine ring in **3** (Fig. 3, A) is more favored to that from a lower side (Fig. 3, B), even if the homopiperazine ring takes a pseudo-chair (a flattened-chair) form due to the steric repulsion between $C_8$-methylene and $-NH-CH_2-$ groups.[16]

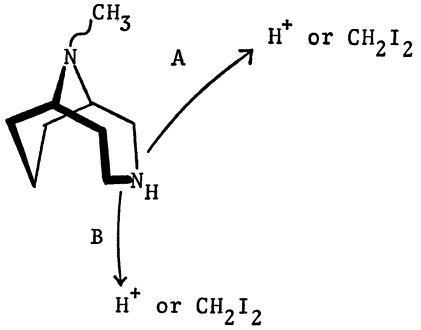



Fig. 3.

## Experimental

p$K_a$ measurements were carried out by titrating potentiometrically in an 80% methyl cellosolve-hydrochloric acid solution of each amine ith 0.1 N potassium hydroxide at 20°C. Titration was performed on a Radiometer Model TTl. The 80% methyl cellosolve solution consisted of 4.0 m*l* of methyl cellosolve, 0.6 m*l* of 0.1 N hydrochloric acid, 0.4 m*l* of water, and *ca.* 1.2 mg of each amine.

All the amines used had reported physical constants: pseudopelletierine (**1**), mp 63—65°C (sealed tube) (lit,[17] 63—64°C); 10-methyl-3,10-diazabicyclo[4.3.1]decan-4-one (**2**), mp 164—166°C (lit,[18] 164—166°C); 10-methyl-3,10-diazabicyclo[4.3.1]decane (**3**), mp 43—46°C (sealed tube) (lit,[1] 43—46°C); 6,8-*exo*-ethanopseudopelletierine (**4**), mp 100—102°C (lit,[4b] 103—104°C); 7,9-*exo*-ethano-10-methyl-3,10-diazabicyclo[4.3.1]decan-4-one (**5**), mp 154°C (lit,[1] 154°C); 7,9-*exo*-ethano-10-methyl-3,10-diazabicyclo[4.3.1]-decane (**6**), mp 66—69°C (sealed tube) (lit,[1] 66—69°C).

The authors express their appreciation to Prof. T. Goto and Dr. Y. Kishi for the p$K_a$ measurements.

13) J. L. Sudmeier and G. Occupati, *J. Amer. Chem. Soc.*, **90**, 154 (1968).

14) For example, see G. E. Ryschkewitsch, *ibid.*, **91**, 6535 (1969).

15) a) For a recent review on the quaternization of *t*-amines, see A. T. Bottini, "Selective Organic Transformations," Vol. 1, Ed. by B. S. Thyagarajan, Wiley-Interscience, New York, N. Y. (1970), p.p. 89–142; b) D. R. Brown and J. McKenna, *J. Chem. Soc., B*, **1969**, 570.

16) For a similar repulsion in bicyclo[3.3.1]nonane system, see N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tyminski, and F. A. Van-Catledge, *J. Amer. Chem. Soc.*, **90**, 1199 (1968).

17) Organic Syntheses, Coll. Vol. IV, 1963, p. 816.

18) L. A. Paquette and J. W. Heimaster, *J. Amer. Chem. Soc.*, **88**, 763 (1966).