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A DIAMINE-EXCHANGE REACTION OF DIHYDROPYRAZINES

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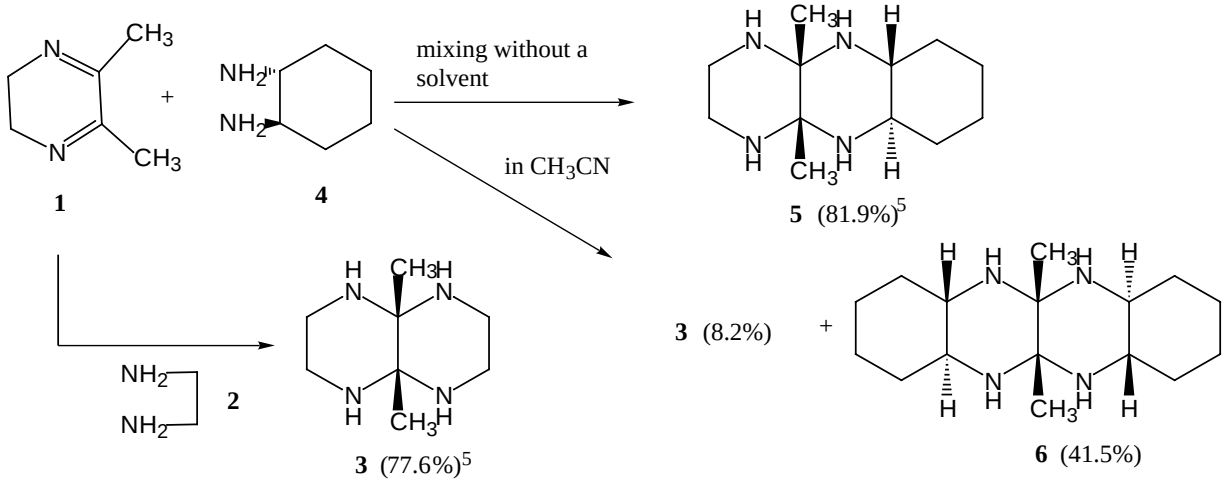
Abstract - Dihydropyrazines reacted with 1,2-diamines to form tetraazadecalins as intermediates, and then the reaction proceeded forward to dissociate into alternate dihydropyrazine and diamine, or backward to dissociate into the starting materials in certain equilibrium. The product distribution is controlled by diamine-exchange equilibrium reaction. The various equilibrium reactions were analyzed by NMR spectroscopy

In our continuous studies on dihydropyrazines (DHPs), we have elucidated certain new phenomena namely, that DHPs displayed DNA strand-breakage activity,[1] transformed to a dimeric compound[2,3] and generated certain carbon-centered radicals[4] in a buffer solution. Further, in a previous paper[5] we have shown a new reaction wherein DHPs reacted with 1,2-diamines to give tetraazadecalins (TADs). In the study, it was made clear that TADs were not the final products but intermediates in certain solvent such as $CHCl_3$. Namely, DHPs reacted with 1,2-diamines to give alternate DHPs and diamines *via* a tetraazadecalin (TAD) intermediate. In this communication, we wish to show the renewed reaction as a characteristic feature of DHPs.

Scheme 1



For example, 2,3-dihydro-5,6-dimethylpyrazine (**1**)[1] reacted with ethylenediamine (**2**) to give *cis*-4a,8a-dimethyltetraazadecalin (**3**)[5] which dissociated into the starting materials in CH_3OH or $CHCl_3$. However, in CH_3CN or $(C_2H_5)_2O$, the reassociation to **3** was observed at a low temperature. The stability

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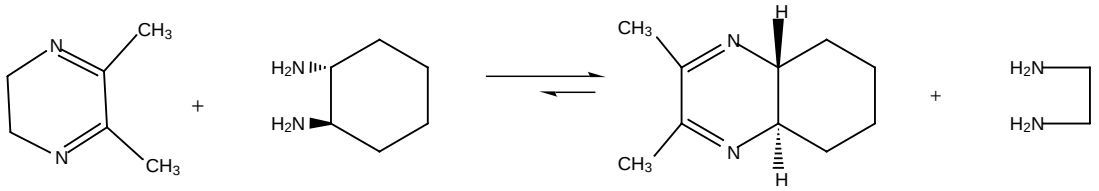
depending on the nature of the solvents was confirmed by the fact that **3** could be recrystallized from CH_3CN or $(C_2H_5)_2O$. On the other hand, **1** reacted with *trans*-1,2-diaminocyclohexane (**4**) to give *trans*-2.3-tetramethylene-*cis*-4a,8a-dimethyl-1,4,5,8-tetraazadecalin (**5**)[5] on mixing without a solvent, but the reaction in CH_3CN gave *trans*-2,3-*trans*-6,7-bis(tetramethylene)-*cis*-4a,8a-dimethyl-1,4,5,8-tetraazadecalin (**6**)[5] together with **3** (see Scheme 1). These results revealed that the diamine-exchange reaction proceeded in the solvent and the products were separated by the low solubility to the reaction solvent. Unsymmetric compounds such as **5** and *N*-methyl-*cis*-4a,8a-dimethyl-1,4,5,8-tetraazadecalin (**9**)[5] mentioned below showed higher solubility than those of TADs having a symmetric structure as **3** and **6**. Therefore, in a sparingly soluble solvent, the precipitates may separate out. The diamine-exchange reaction was confirmed as follows. On the NMR spectrum of the reaction mixture of **1** and **4** in $CHCl_3$, the formation of *cis*-2,3-dimethyl-5,6,7,8,9,10-hexahydroquinoxaline (**7**)[1] and **2** was recognized (Scheme 2). When the crystal product (**5**) was dissolved in $CDCl_3$ at room temperature, the formation of **2** and **7** together with **1** and **4** was observed by the NMR analysis. In the NMR tube experiment, the reaction mixture of **1** and **4** rapidly reached a state of equilibrium within 24 h. The proportion of **7** to the starting material **1** was about 80%. The reaction of **7** with **2** reached an equilibrium after 48 h, though the exchange was slower than the reaction of **1** with **4**. The assessment of the signal area of the NMR spectrum indicated that the equilibration inclined to the formation of **7**.

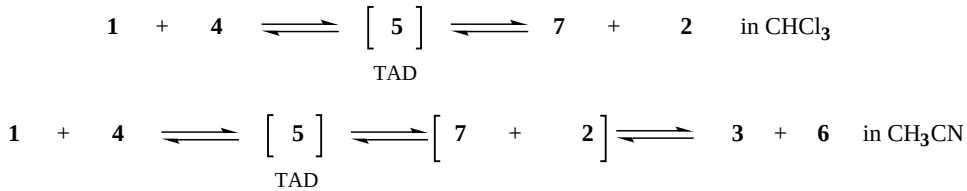
Scheme 2



1 (20%) **4** **7** (80%) **2**

Consequently, total reaction process is summarized in Scheme 3, because the TAD (**5**) formed as an intermediate was not able to exist in a solvent and also the reactions (**4** + **7** --> **6** and **1** + **2** --> **3**) proceeded in CH_3CN.

Scheme 3

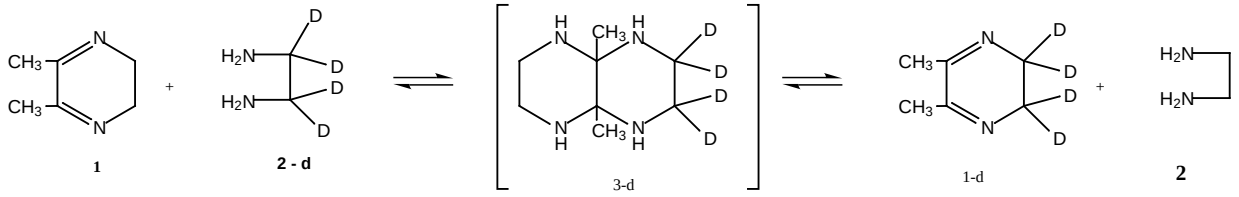


The facile dissociation of TADs in $CHCl_3$ is considered to be due to the Cl_3 C-H--X type hydrogen bond formation[6] between $CHCl_3$ and TADs similar to the O-H--X type hydrogen bond in CH_3OH. As described above, the TAD (**6**) is more stable than **3** or **5**. This stability may be attributed to the conformational rigidity of the tetrahydropyrazine ring condensed with a cyclohexane ring. In the transition state (**6** --> **4** +**7**), the deformation from nonplanar GS to planar TS is assumed to be energetically less favorable. The PM3-calculated heat of reaction support this assumption. The heat of reaction for the formation reaction of **6** is 15 kcal/mol, whereas those of **3** and **5** are 10 and 12 kcal/mol, respectively. The hydrogen bond may play a leading role in both the dissociation reaction and stabilization of the substrates, affecting the relative stability of the equilibrium reactions.

1 + **2** --> **3** 10.1 kcal/mol exothermic
4 + **7** --> **6** 15.5 kcal/mol exothermic
1 + **4** --> **5** 12.8 kcal/mol exothermic
7 + **2** --> **5** 12.8 kcal/mol exothermic

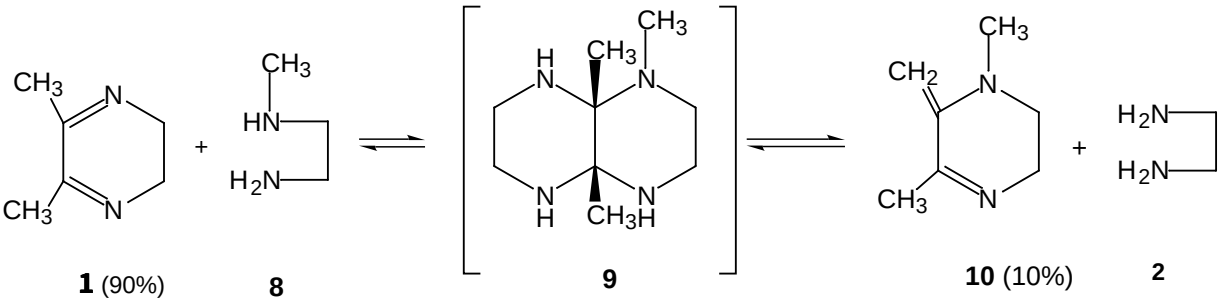
Definitive evidence for the diamine-exchange reaction was obtained as shown in Scheme 4. The reaction of **1** and ethylene-d_4-diamine (**2-d**) in $CDCl_3$ at room temperature displayed the approximately 50% exchange of diamine.

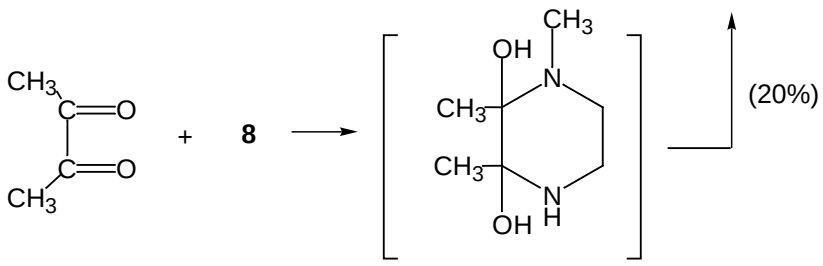
Scheme 4



In the TAD formation reaction, the reaction of **1** with **2** or *N*-methylethylenediamine (**8**) occurred, but the reaction with *N,N'*-dimethylethylenediamine did not proceed.
The reaction of **1** with **8** in $(C_2H_5)_2O$ or CH_3CN gave an *N*-methyl-TAD derivative; however, the reaction in $CHCl_3$ was revealed to form a new compound, *N*-methyl-2-methylene-3-methyl-1,4-diazacyclohexan-3-ene (**10**) which was also obtained from the reaction of 2,3-butanedione with **8**. The formation of *N*-methyl-*cis*-4a,8a-dimethyl-1,4,5,8-tetraazadecalin (**9**)[5] was confirmed in the reaction of **1** with **8** and the reaction of **10** with **2** (Scheme 5). Compound (**10**) represented DNA strand-breakage activity and generated carbon-centered radicals as well as DHPs.

Scheme 5

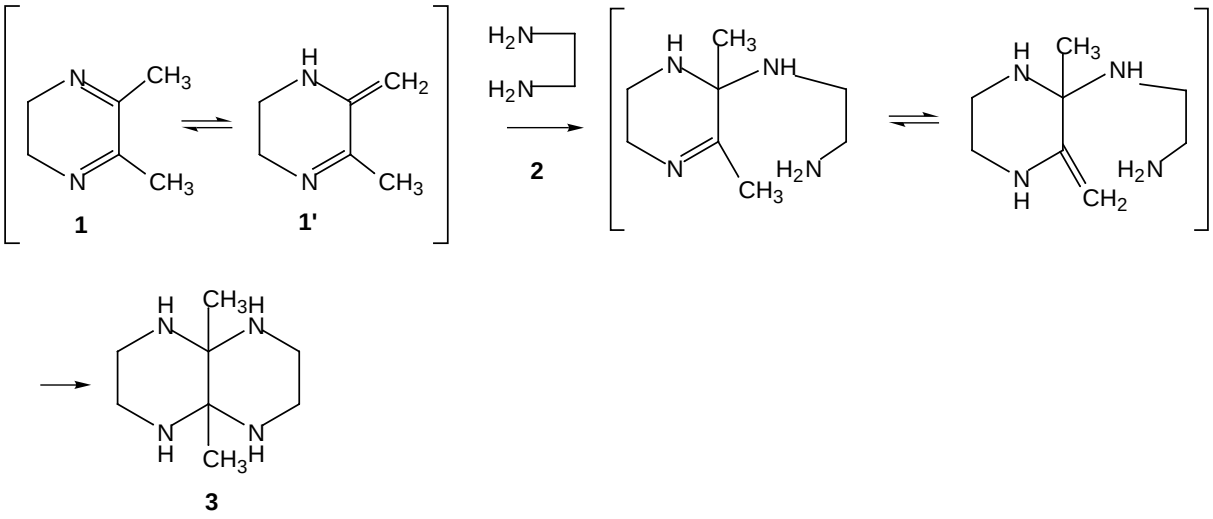




The occurrence of the reaction (**10** + **2** --> **9**) indicates that an intermediate (**10**) was formed and reacted with **2** to give **9**. This indicates that the reaction behavior of dimethyl-substituted dihydropyrazines differs from that of non-substituted dihydropyrazines, and the dissociation reaction (stability of the products) is also affected by the dimethyl groups. On the basis of these results, the reaction mechanism can be described as shown in Scheme 6. The formation of **1'** is supported by the isolation of the dimeric compound of the isomer (**1'**)[3] of **1**.

The diamine-exchange phenomenon was observed only in the reaction of 1,2-dimethyldihydropyrazine with 1,2-diamine. As shown in a previous paper,[7] *trans*-fused TADs were very stable, whereas *cis*-fused TADs obtained by us were unstable. It is presumed that the lability was due to not only the strain of the *cis*-fused ring owing to the presence of the angularly substituted methyl groups but also the participation of the methyl groups described above.

Scheme 6



The ESR study of DHPs and TADs revealed the generation of certain carbon-centered radicals. The signal pattern was approximately identical between **1** and **3**. While the signal intensity of **3** was stronger than that of **1**. The difference in the signal intensity between **1** and **3** is due to the presence of ethylene diamine (**2**), because **3** dissociated instantly into **1** and **2** in a solvent. Thus, as DHPs are prone to change to radicals, it is suggested strongly that certain phenomena of DHPs mentioned at the beginning might proceed in a radical reaction. Detailed research on this point is in progress.

ACKNOWLEDGMENT

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