The Role of the Nitrogen Atom in the Hydrogenation of Piperidinones and Methylenepiperidines

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Dimethylpiperidinones and dimethylmethylenepiperidines have been hydrogenated over several Group 8, 9 and 10 transition metal catalysts and the stereochemistry of the products compared with those of the carbocyclic analogues. The results obtained suggest that intramolecular interactions between the nitrogen lone pair and the unsaturated bond play a major role in determining the stereochemistry of hydrogenation.

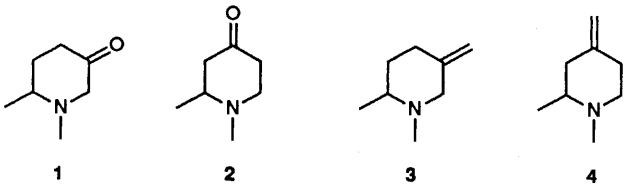
The high stereoselectivity observed in enzymatic reactions is known to be the result of intramolecular non-covalent bonding interactions in the substrate and intermolecular ones between substrate and enzyme. As one of the applications of such weak non-bonding interactions in a highly selective enzymatic reaction to a catalysed one, we are currently exploring how heteroatoms, which are remote from the reaction site of the molecule, participate in the stereochemistry of hydrogenation.[1] Our study has now been extended to piperidinones and methylenepiperidines in order to examine the role of the nitrogen atom in the hydrogenation of exocyclic unsaturated bonds.

The stereochemistry of the hydrogenation of an unsaturated bond is frequently controlled by a heteroatom in the molecule. For instance, in allylic alcohols and ethers, addition of hydrogen to the unsaturated bond occurs from the same side as the oxygen atom of the hydroxy or alkoxy group.[2] When a nitrogen atom is introduced as a heteroatom into the molecule, a similar effect was found in the hydrogenation.[3] This is known as a 'directing effect'[2] or an 'anchor effect'.[3] In some cases, however, this effect does not necessarily appear. In the case of cyclic allylic ethers in which oxygen atom(s) are placed at a suitable position, the stereochemistry of the hydrogenation is such that the addition of hydrogen to the double bond has been found to occur predominantly from the opposite side to the oxygen lone pair.[1]

Results and Discussion

In order to investigate the role of a nitrogen atom, which has a higher basicity than an oxygen atom in a ring in the hydrogenation, 1,6-dimethylpiperidin-3-one (**1**), 1,2-dimethylpiperidin-4-one (**2**), and 1,6-dimethyl-3- (**3**) and 1,2-dimethyl-4-methylenepiperidine (**4**) (Fig. 1) were hydrogenated in ethanol over several Group 8, 9 and 10 transition metal catalysts, and the results were compared with those for the carbocyclic analogues. The results of the hydrogenation are summarised in Table 1.

The stereochemistry of the hydrogenation of cyclohexanones and methylenecyclohexanes over Group 8, 9 and 10 transition metal catalysts has been investigated in detail and was interpreted in terms of the Horiuti–Polanyi mechanism which is one of the most satisfactory theories.[4] The change in the product-controlling step, depending on the catalyst, coincides with a change in the ratio of the products. The Horiuti–Polanyi formulation of the mechanism of hydrogenation of unsaturated bonds may be represented by four elementary reactions; dissociation of hydrogen, adsorption of the substrate on the catalyst, first hydrogen transfer to the adsorbed species, and second hydrogen transfer to the half-hydrogenated intermediate. The proportion of each of the stereoisomeric products formed will depend upon which of the elementary reactions is a product-controlling step, because the geometry and/or composition of the several possible transition states differ from one another. When the product-controlling step is the adsorption of the substrate on the catalyst or the first hydrogen transfer from the catalyst to the adsorbed species, the stereochemistry of the reaction is controlled by the interaction between the substrate and the catalyst. On the other hand, when the product-controlling step is the second hydrogen transfer from the catalyst to the half-hydrogenated species, the stereochemistry is controlled by the relative stabilities of the two epimeric half-hydrogenated species.



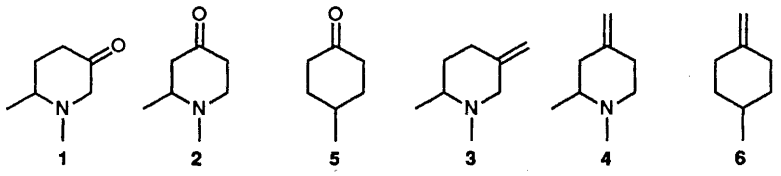
1 2 3 4

Fig. 1 Structures of substrates **1**–**4**

During the hydrogenation of simple unhindered cyclohexanones and methylenecyclohexanes, the introduction of the hydrogen generally occurs from the less hindered equatorial side to the exocyclic double bond, and axial hydroxy or methyl products are predominant. This means that the stereochemistry of the hydrogenation is determined by the relative ease of the two modes of adsorption of the exocyclic double bond of the cyclohexane ring. Since the product-controlling step over a Pd catalyst is known to be the second hydrogen transfer step from the catalyst to the half-hydrogenated intermediate,[5] different stereochemistry was observed in some cases. The product-controlling step over a Ni catalyst is not yet accurately known.[6]

In the hydrogenation of **1** and **3** whose exocyclic double bonds are placed at the β-position to the nitrogen atom, the hydrogen is preferably introduced from the equatorial side except in the case of the Pd and Ni catalysts. On the other hand, in the hydrogenation of **2** and **4**, whose exocyclic double bonds are placed at the γ-position to the nitrogen atom, the hydrogen addition generally occurred from the axial side of the molecule. The equatorially substituted products were predominant. These results are compared with those of 4-methylcyclohexanone (**5**) and 4-methylmethylenecyclohexane (**6**). In the hydrogenation of **1** and **3** more of the axial products were generally formed than for the carbocyclic compounds. During the hydrogenation of **2**

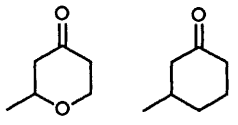
Table 1 The hydrogenation of dimethylpiperidinones, dimethylmethylenepiperidines and corresponding carbocyclic compounds **1**–**6**



		Hydrogen addition from equatorial side (%)					
Catalyst	Weight/mg	**1**	**2**	**5**	**3**	**4**	**6**
PtO_2	2.5	68	17	34[a]	75	32	64[b]
Pt–carbon	25	58	15	53	64	14	62[b]
Pt–black	2.5	76	19	63[a]	64	29	62
Ru–carbon	25	93	43	84[c]	78	42	77
Rh–carbon	25	55	33	84[a]	69	40	61[b]
Rh–black	2.5	80	45	75[a]	85	29	84[c]
Pd–carbon	25	6	11	44[a]	43	16	26[b]
Pd–black	2.5	30	13	58[a]	38	15	59[c]
Raney Ni	100	34	31	65[a]	30	20	45[a]
Raney Co	250	68	45	62	56	16	37

[a] S. Mitsui, H. Saito, Y. Yamashita, M. Kaminaga and Y. Senda, *Tetrahedron*, 1973, **29**, 1531. [b] S. Mitsui, K. Gohke, H. Saito, A. Nanbu and Y. Senda, *Tetrahedron*, 1973, **29**, 1523. [c] The results of hydrogenation of 4-*tert*-butylmethylenecyclohexane; ref. 1(*c*).

Table 2 The hydrogenation of 2-methyltetrahydropyran-4-one **7**



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		Hydrogen addition from equatorial side (%)	
Catalyst	Weight/mg	**7**	3-Methylcyclohexanone
PtO_2	2.5	8	77[a]
Pt–carbon	25	8	29
Ru–carbon	25	38	41[a]
Rh–carbon	25	62	88[a]
Pd–carbon	25	35	40[a]
Raney Ni	100	26	52[a]
Raney Co	250	26	79

[a] S. Mitsui, H. Saito, Y. Yamashita, M. Kaminaga and Y. Senda, *Tetrahedron*, 1973, **29**, 1531.

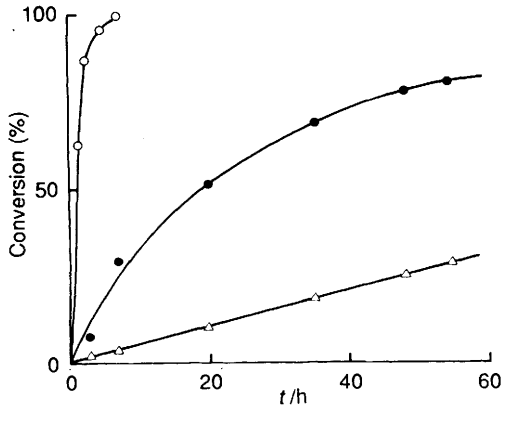


Fig. 2 Relative reactivity of dimethylpiperidinones and 4-methylcyclohexanone over Rh–carbon catalyst. The product from 1,6-dimethylpiperidine-3-one (**1**) ○; 1,2-dimethylpiperidine-4-one (**2**) ●; and 4-methylcyclohexanone (**5**) △.

and **4** the equatorially substituted products were preferably produced. This is in sharp contrast to the case of carbocyclic

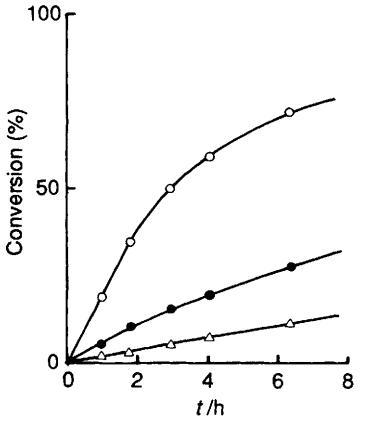
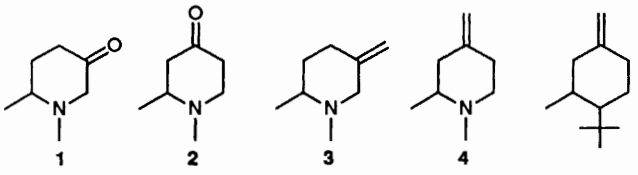


Fig. 3 Relative reactivity of dimethylmethylenepiperidines and 4-methylmethylenecyclohexane. The product from 1,6-dimethyl-3-methylenepiperidine (**3**) ○; 1,2-dimethyl-4-methylenepiperidine (**4**) ●; and 4-methylmethylenecyclohexane (**6**) △.

compounds. Since the nitrogen lone pair in the piperidine ring must preferably occupy an axial position, these results indicate that the hydrogen addition occurred preferably from the side opposite to the nitrogen lone pair in these nitrogen heterocycles. The same was true in the hydrogenation of 2-methyltetrahydropyran-4-one which is the oxygen analogue of **2** (Table 2). Hydrogen addition from the axial direction was preferred with most of the catalysts used, as was observed for the nitrogen analogues.

In order to obtain further information on the role of the nitrogen atom, the competitive hydrogenation of **1**, **2** and **5** was performed over the Rh–carbon catalyst. The mixture prepared from equimolar amounts of these three substrates was hydrogenated and the relative reactivities were determined. Plots of conversion of the substrate *versus* time are shown in Fig. 2. The order of reactivity is **1** > **2** > **5**; the relative reactivity of **1** was quite high and that of **2** was seven times as large as that of **5** in the early stages of the reaction. Again, the competitive hydrogenation of **3**, **4** and **6** in the same way as above gave results such that the order of reactivity was **3** > **4** > **6**; the relative reactivity of **3** was more than ten times as large as that of **6** while **4** was *ca.* three times more reactive than **6** (Fig. 3). These results indicate that the reactivity is

Table 3 The hydrogenation of dimethylpiperidinones and dimethylmethylenepiperidines over Rh/SiO_2 and Rh colloid catalysts



	Hydrogen addition from equatorial side (%)				
Catalyst[a]	1	2	3	4	4-*tert*-Butylmethylene cyclohexane
Rh/SiO_2					
1.0% (14Å)	92	11	70	27	65[b]
4.7% (28Å)	94	12	74	27	71[b]
14.2% (48Å)	94	9	72	23	78[b]
Rh colloid					
A	—	—	60	30	58[b]
B	—	—	60	29	80[b]

[a] Rh/SiO_2, 50 mg; colloid, substrate/catalyst 200 mol/g atom. [b] Ref. 9.

Table 4 ^{13}C chemical shifts of dimethylpiperidinones and dimethylmethylenepiperidines in $CDCl_3$ (δ)

	Compound			
Carbon	1	2	3	4
C-2	65.5	58.7	62.5	59.8
C-3	207.2	48.7	144.9	42.5
C-4	38.2	206.8	34.9	145.2
C-5	32.2	41.3	32.8	34.8
C-6	56.4	54.6	58.5	57.0
$=CH_2$	—	—	108.7	107.6
$N-CH_3$	42.4	41.5	42.5	42.9
$C-CH_3$	18.3	19.7	19.7	19.4

Table 5 Comparison of the observed and predicted sp^2 carbon resonances of dimethylpiperidinones and dimethylmethylenepiperidines

		Chemical shift		
Compound	Carbon	Observed	Calculated	Difference
1	β	207.2	208.9	−1.7
2	γ	206.8	207.2	−0.4
3	β	144.9	149.0	−4.1
4	γ	108.7	106.6	+2.1
	γ	145.2	147.3	−2.1
	δ	107.6	106.6	+1.0

greater in the nitrogen heterocycles than in the carbocyclic compounds, and in the substrate in which the nitrogen atom is closer to the unsaturated bond.

Piperidinones and methylenepiperidines were also hydrogenated over the Rh colloid [7] and the $Rh-SiO_2$[8] catalysts whose metal particle sizes are already known. The isomer distribution of the products showed no appreciable difference with respect to particle size (Table 3). It was previously reported that the stereochemistry of the hydrogenation of methylenecyclohexanes depends on the size of the metal particles of the catalyst and this was interpreted in terms of the difference in the steric interaction between the substrate and the catalyst.[9] The almost constant product distribution for the nitrogen heterocycles, irrespective of the catalyst used, indicates that the stereochemistry of the hydrogenation of the nitrogen heterocycles was not at all controlled by the particle size of the metal catalyst as has been observed for the oxygen heterocycles.[9]

In order to provide additional structural information on the nitrogen heterocycles, molecular mechanics calculations were carried out. The optimized geometries of the molecules suggested that the introduction of the nitrogen atom into the cyclohexane skeleton results in no sizeable deformation of the six-membered ring. This strongly supported the fact that the appreciable difference in the product distribution between the carbocyclic compounds and the nitrogen heterocycles is not attributable to the three-dimensional structures of the substrates during the hydrogenation.

The fact that (*a*) the unsaturated bond contained in the nitrogen heterocycles is more reactive than in the carbocyclic analogues, and (*b*) the hydrogen addition occurs less from the side having the axially oriented nitrogen lone pair than from the other side, leads to the postulation that the interaction between the nitrogen lone pair and the catalyst surface is not responsible for the stereochemistry of hydrogenation, but some other nitrogen participation is expected.

When a polar atom(s) or a group(s) such as oxygen or nitrogen are introduced into the molecule, an attractive interaction of the heteroatom, through the lone pair, with the catalyst surface has bound these atoms or groups to the catalyst surface during the hydrogenation in order to enhance the addition of hydrogen atoms from the same side of these heteroatoms. However, in some cases, this effect does not necessarily appear. The addition of hydrogen from the side opposite to the oxygen lone pair in the hydrogenation of cyclic allylic ethers such as methylene-1,3-dioxane and 3-methylenetetrahydropyran was interpreted in terms of the intramolecular interaction between the non-bonding orbital of the oxygen and the olefinic π-orbital.

The presence of a through-space interaction of such an n–π system as well as that of a non-conjugated π–π system has been found to be reflected by the ^{13}C chemical shift difference ($\Delta\delta$) between the sp^2 carbon atoms of the difunctional compounds and those of the corresponding monofunctional ones.[10] To examine the presence of an intramolecular orbital interaction in these piperidines, the ^{13}C NMR spectra were measured and the chemical shifts were tabulated in Table 4. Since simple additivity relationships for carbon chemical shifts are very useful for the prediction of the chemical shift of a certain carbon atom, the chemical shifts for the sp^2 carbons of piperidinones and methylenepiperidines were roughly calculated by using the SCS parameters from cyclohexanone methylenecyclohexane, their methylated analogues and 1,2-dimethylpiperidine.[11] These values were compared with the measured ones (Table 5). The chemical shifts of the carbonyl carbons were compared with those of the carbocyclic compounds. Introduction of a nitrogen atom into a cyclohexane ring leads to shielding of the sp^2 carbon β to the nitrogen atom by 4.1 ppm, but deshielding of the γ sp^2 carbon by 2.1 ppm in the *exo*-methylene compound, **3**. The same is true at the carbonyl carbon in dimethylpiperidinone, **1**, the shielding of which was 1.7 ppm. In the case of **2** and **4**, the shift effect on the γ sp^2 carbon was found to be −0.4 in **2**, and −2.1 in **4** and on the δ-carbon of **4** to be +1.0 ppm. These results indicate that sizeable upfield shifts were observed on the proximal sp^2 carbon and the downfield shifts on the distal sp^2 carbon by the introduction of the nitrogen atom to a six-membered ring. This suggests that electron delocalization owing to transannular effects[12] occurred in these molecules.

Hydrogen addition from the equatorial direction in high selectivity, observed in the hydrogenation of **1** and **3**, together with the results for oxacyclohexanones and methyleneoxacyclohexanes previously obtained, implies that significant control is exerted by nitrogen atom participation in the transition state for

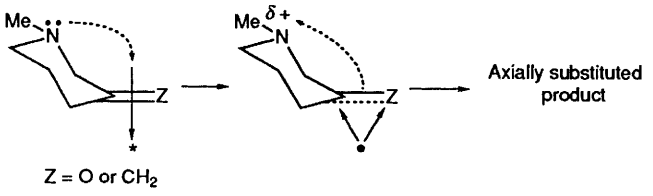


Fig. 4

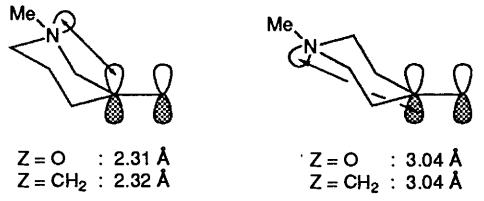


Fig. 5 The distance between n_N and $\Pi_{C=O}$ or $\Pi_{C=C}$ in the optimised structure by molecular mechanics calculations

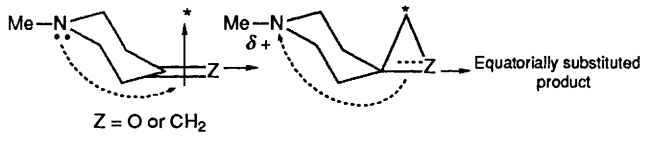


Fig. 6

the adsorption of the substrate on the catalyst. The nonbonding electrons of the nitrogen atom can stabilize any incipient charge which might result from π-donation of an unsaturated bond on the metal surface. The enhanced effective electronegativity of the nitrogen, therefore, induces back-donation from the metal surface to the π*-orbital of the unsaturated bond. As a consequence, the substrate is preferably adsorbed on the catalyst from the side, so that the ring nitrogen is inclined away from the surface of the catalyst. This leads to the formation of products in which hydrogen addition occurs from the equatorial side of the molecule (Fig. 4).

The optimized conformation of **1** and **3** based on the molecular mechanics calculation indicated that there are distances of 2.31 Å and 2.32 Å between the non-bonding orbital of the nitrogen and the π-orbital of the ring sp^2 carbon β and γ to the nitrogen atom, respectively, whereas the corresponding distances were 3.04 Å in both **2** and **4**. These values for **2** and **4** are *ca.* 1.3 times as large as those of **1** and **3** (Fig. 5). In ^{13}C NMR spectra, the shift effect on the sp^2 carbons of the introduction of the nitrogen atom to the cyclohexane ring was much less pronounced for these compounds than for **1** and **3**. Cieplak proposed, however, a theory of charge-transfer stabilization of the transition state for nucleophilic addition to a carbonyl group by an electron donor. He considered that in the nucleophilic addition to the substrate containing the heteroatom, the orbital overlap control between the nonbonding orbital of the heteroatom and the developing σ* orbital is important for the transition state stabilisation even in the 1,4-system.[13] This strongly supports the fact that the orbital overlap control of the transition stabilisation participates even in the hydrogenation of **2** and **4** in which there are relatively long distances between the non-bonding orbital of the nitrogen atom and the π-orbital of the substrate (Fig. 6).

In summary, the hydrogenation of the exocyclic double bond in monocyclic compounds which contain a heteroatom indicates that the interaction between the heteroatom and the unsaturated bond overcomes the steric interaction between the substrate and the catalyst surface, so that such intramolecular interactions play a major role in the stereochemistry of hydrogenation.

Experimental

Materials.—1,6-*Dimethylpiperidin*-3-*one* (**1**). A solution of 1,6-dimethyl-3-hydroxypyridinium *p*-toluenesulfonate (47 g, 0.17 mol) in ethanol (40 cm^3) was hydrogenated with 1.0 g of Rh–carbon catalyst at high hydrogen pressure (initial pressure 140 kg cm^{-1}) at 60 °C. After filtering off the catalyst, the solvent was removed under reduced pressure and the residue treated with dilute aqueous sodium hydroxide. The mixture was extracted with diethyl ether and the extracts were dried with sodium sulfate, concentrated and distilled to give 1,6-dimethylpiperidin-3-ol (b.p. 90–92 °C/19 mmHg, yield 72 g, 84%).[14] 1,6-Dimethylpiperidin-3-ol (2 g, 16 mmol) was dissolved in acetone (80 cm^3) at 0 °C. A slight excess of Jones' reagent (13 cm^3) was added and the mixture was stirred for 24 h at room temperature. Saturated sodium hydrogensulfite solution was added and acetone was removed at reduced pressure. The solution was basified with 30% aqueous sodium hydroxide and extracted with $CHCl_3$. The extracts were dried and distilled to give **1** (b.p. 68–73 °C/13 mmHg, yield 7 g, 35%).[15]

1,2-*Dimethylpiperidin*-4-*one* (**2**). Ethyl acrylate (45 g, 0.45 mol) and methyl β-methylaminobutyrate (62 g, 0.45 mol), which was prepared from methylamine and methyl crotonate, were left standing for 14 days at room temperature. Fractional distillation gave β-ethoxycarbonylethyl-β-ethoxycarbonylisopropylmethylamine (b.p. 120–130 °C/1 mmHg, yield 68 g, 62%). To a stirred mixture of benzene (200 cm^3) and of sodium hydride (5.6 g, 0.23 mol) was added β-ethoxycarbonylethyl-β-ethoxycarbonylisopropylmethylamine (43 g, 0.18 mol) and the contents of the flask were heated under reflux for 3 h. The reaction mixture was cooled to 0 °C and was extracted with 15% aqueous HCl. After the extracts had been heated for 4 h, the solution was basified with aqueous NaOH and was extracted with $CHCl_3$. The extracts were dried, concentrated and distilled to give **2** (b.p. 82–87 °C/22 mmHg, yield 9.88 g, 44.8%).[16]

Dimethylmethylenepiperidines **3** and **4**. Wittig reaction of the corresponding piperidinones was performed using sodium hydride as base by the method of Corey *et al.*[17] The products were taken up from the reaction mixture by distillation in reduced pressure. Redistillation gave 1,6-dimethyl-3-methylenepiperidine (b.p. 95–100 °C, yield 2.26 g, 36.4%) and 1,2-dimethyl-4-methylenepiperidine (b.p. 90–94 °C, yield 1.45 g 32.1%).[16]

2-*Methyltetrahydropyran*-4-*one* (**7**). A mixture of but-3-en-1-ol (9.8 g, 0.14 mol), acetaldehyde (5.91 g, 0.14 mol) and 20% aqueous sulfuric acid (16.2 g) was heated for 52 h at 80–85 °C. The cooled mixture was neutralized and extracted with diethyl ether. The organic layer was dried and distilled to give 2-methyltetrahydropyran-4-ol (b.p. 89–92 °C/20 mmHg, yield 13.6 g 83.7%). 2-Methyltetrahydropyran-4-ol (6.6 g, 0.06 mol) was oxidised by pyridinium chlorochromate to give **7** (b.p. 68–71 °C/25 mmHg, yield 4.8 g, 74.2%).[18]

Catalytic Hydrogenation.—The substrate (0.5 mmol) was stirred under a hydrogen atmosphere in ethanol (3 cm^3) at room temperature over a weighed catalyst. The reaction was followed by gas chromatography, by analysing aliquots of the reaction mixture at appropriate time intervals. Competitive hydrogenation was performed as follows; mixtures of equimolar amounts (0.5 mmol) of these three ketones or *exo*-methylene compounds were hydrogenated in ethanol (3 cm^3) at room temperature over Rh–carbon catalyst (25 mg). The reaction was followed by gas chromatography by analysing aliquots of the reaction mixture at appropriate time intervals.

NMR and Gas Chromatographic Analyses.—^{13}C NMR spectra were obtained with a JEOL JNM FX-90-Q instrument operating at 22.53 MHz in the pulse Fourier mode. Gas chromatographic analyses were performed on a Shimadzu

model GC-8AIF with OV-1 chemical bonded silica capillary column (0.25 mm × 25 m) at column temperature 80 °C for **1**, 90 °C for **2**, 85 °C for **3** and **4**. The products were compared with authentic samples (1,6-dimethylpiperidin-3-ol,[15] 1,2-dimethylpiperidin-4-ol,[19] 1,2,5-trimethylpiperidine[20,21] and 1,2,4-trimethylpiperidine[21]).

Molecular Mechanics Calculations.—Allinger's standard MM2 program was used.[22] The calculations were performed on NEC 9801 microcomputer with 80287 coprocessor.

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