Mechanism of Isomerization of 1,2,3,4-Tetrahydroisoquinoline to 5,6,7,8-Tetrahydroisoquinoline over Raney Nickel

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The isomerization of 1,2,3,4-tetrahydroisoquinoline to 5,6,7,8-tetrahydroisoquinoline proceeded over Raney nickel at *ca.* 200 °C under hydrogen and nitrogen pressure in a closed reactor. Based on kinetic analyses and quantum chemical calculations we propose that the isomerization proceeds through a series of consecutive steps where dehydrogenation and hydrogenation take place in an alternate manner. The isomerization is initiated by dehydrogenation at the C-1 and N positions of 1,2,3,4-tetrahydroisoquinoline to form 3,4-dihydroisoquinoline which, in turn, is rehydrogenated into 3,4,6,7-tetrahydroisoquinoline and 3,4,5,6,7,8-hexahydroisoquinoline. The hexahydroisoquinoline is finally dehydrogenated into the isomerized product. No extra hydrogen appears to be required for the isomerization. Under a nitrogen stream in an open reactor, the selective formation of isoquinoline occurred.

In our previous paper[1] kinetic analysis of the hydrogenation of isoquinoline (**3**) over Raney nickel (R–Ni) indicated that the initial product, 1,2,3,4-tetrahydroisoquinoline (**1**), was isomerized into 5,6,7,8-tetrahydroisoquinoline (**2**) prior to giving the final product, decahydroisoquinoline (**4**). This isomerization is very interesting from an industrial viewpoint as well as in the area of theoretical research since compound (**2**) is an important pharmaceutical intermediate.[2,3] The substrate (**1**) is readily obtained as an initial hydrogenation product of isoquinoline (**3**) over Ni or Cu–Cr catalysts.[4,5] Therefore, the preparation of compound (**2**) from isoquinoline (**3**) *via* compound (**1**) using this isomerization constitutes a simple and practical method, when compared with the other available methods.[4,6–8] The reaction involves a four-hydrogen migration from one ring to the other, which appears to require a number of steps.

The purpose of our present study is to clarify some principal steps in the isomerization reaction. The kinetic analyses and quantum chemical calculations on the starting material and related hypothetical intermediates in a series of competitive consecutive reactions were carried out.

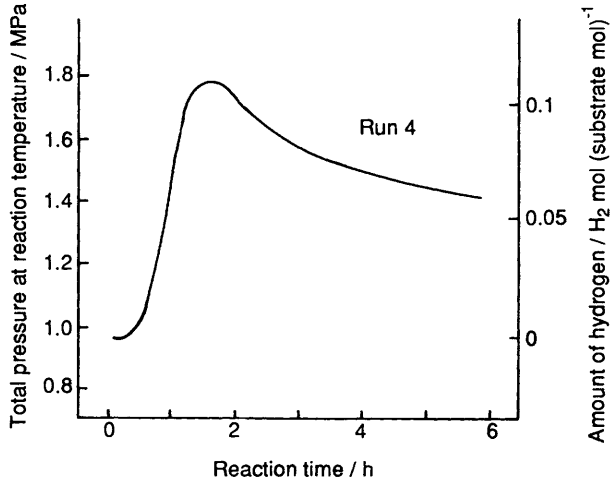


Figure 1. Pressure changes and hydrogen evolution in the reaction of (**1**) over R–Ni under N_2 pressure in a closed reactor.

Results and Discussion

Reactivities of 1,2,3,4-*Tetrahydroisoquinoline* (**1**).—Table 1 summarizes the reaction of compound (**1**). The substrate (**1**) yielded 5,6,7,8-tetrahydroisoquinoline (**2**), isoquinoline (**3**), and decahydroisoquinoline (**4**) as major products. In addition, unidentified dihydro- and hexahydro-isoquinoline (U-1 and U-2, respectively) were found in small amounts by GC–MS. 'Others' in Table 1 contained *N*-methylisoquinolines, an unidentified tetrahydroisoquinoline, and decomposition and condensation products, the total amounts of which were 5% at the most.

The product distribution was influenced by the type of atmosphere and the magnitude of its pressure in the reactor. Under low hydrogen pressure (run 1) compound (**1**) was very selectively isomerized into compound (**2**). Under high hydrogen pressure (run 2), however, the formation of compound (**4**) was accelerated and the yield of compound (**2**) was decreased. Dehydrogenation of compound (**1**) was quick and almost complete to give isoquinoline (**3**) in a nitrogen stream (run 3). In contrast, compound (**2**) was a principal product, obtained in high yield, together with compound (**3**) as a minor product under nitrogen pressures of 1 and 6.1 MPa (runs 4 and 5) in a closed reactor.

The evolution of hydrogen was detected in the experiments conducted under nitrogen. The hydrogen was purged with nitrogen in the open reactor, whereas in the closed reactor the hydrogen was allowed to accumulate in order for it to react with a substrate to some extent. The total pressure change in run 4 is illustrated in Figure 1. In the early stage of the reaction (0–2 h) the pressure increased to reach a maximum, and then decreased. The amounts of hydrogen in the reactor at 2 and 6 h were calculated to be 0.11 and 0.06 mol per mol of substrate, respectively. These values were nearly equal to those estimated from the compositions of the liquid phase. Thus, in the closed reactor, there existed some hydrogen which was available for hydrogenation of the substrate.

Under a lower hydrogen pressure (1.6 MPa), compound (**1**) was exclusively converted into compound (**2**) as shown in the time-dependent product distributions for run 1 (see Figure 2). The dehydrogenated product (**3**) also formed to a small extent

Table 1. Reaction of 1,2,3,4-tetrahydroisoquinoline (1) over R–Ni (5 wt%).

Run No.	Temp./ °C	Pressure/MPa[a] N_2	H_2	Total	Time/ h	Composition (wt%) (1)	(2)	(3)	(4)	U-1	U-2	Others
1	205	0	1.6[b]	1.6	2	46.0	48.3	3.4	1.9	0.1	0.0	0.4
					6	1.3	91.2	0.1	5.9	0.1	0.1	1.5
2	205	0	10.0[b]	10.0	2.5	63.9	26.4	0.1	8.0	0.1	0.7	0.8
					5.5	27.6	41.2	0.0	29.4	0.1	0.5	1.2
3	200	0.1[c]	0	0.1	2	6.0	5.9	84.1	0.1	0.2	0.1	3.6
4	200	1.0	0.8[d]	1.0–1.8	2	42.3	46.6	8.4	1.6	0.2	0.2	0.9
					6	8.4	75.5	8.6	3.2	0.4	0.7	3.2
5	210	6.1	0.3[d]	6.1–6.4	2.5	20.7	65.5	9.0	2.4	0.3	0.4	1.6
					6	4.5	77.1	8.7	3.2	0.5	1.0	5.0
6	150	0.9	0.3[d]	0.9–2.1	1.5	93.0	3.3	3.3	0.3	0.0	0.0	0.1
					6	88.6	7.4	3.4	0.3	0.0	0.0	0.3

[a] At reaction temperature. [b] Controlled by hydrogen supply. [c] Flow system. [d] Generated from substrate (closed reactor).

Table 2. Reaction of related hydroisoquinolines over R–Ni (5 wt%) at 200 °C.

Run No.	Starting material	Pressure/MPa[b] N_2	H_2	Total	Time/ h	Composition (wt%) (1)	(2)	(3)	(4)	U-1	U-2	Others
7	(2)	0.1[c]	0	0.1	2	0.0	99.1	0.9	0.0	0.0	0.0	0.0
8	(2)	1.0	0.2[d]	1.0–1.2	2	0.0	92.2	1.0	0.4	0.0	0.3	6.1
					6	0.0	90.7	0.9	0.4	0.1	0.3	7.6
9	(3)[a]	0	1.6	1.6	2.3	48.3	43.8	6.1	0.8	0.0	0.2	0.8
					5.3	12.9	79.8	1.8	2.6	0.2	0.3	2.4
10	(4)	0.1[c]	0	0.1	2	0.0	7.1	0.2	89.7	0.0	0.2	3.0
11	(4)	1	0.5[c]	1.0–1.5	2.5	0.2	2.4	0.1	96.1	0.0	0.0	1.2
					6	0.0	2.2	0.0	95.9	0.0	0.0	1.9

[a] Temp. 205 °C. [b] At reaction temperature. [c] Flow system. [d] Generated from substrate in a closed reactor.

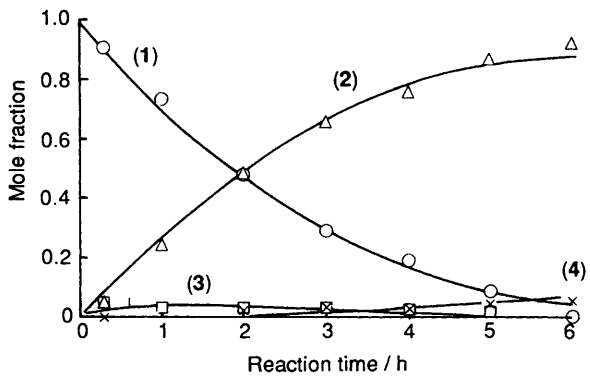


Figure 2. Product distributions for the reaction of compound (1) over R–Ni at 205 °C under 1.6 MPa H_2 pressure in a closed reactor (run 1). (1) 1,2,3,4-tetrahydroisoquinoline, (2) 5,6,7,8-tetrahydroisoquinoline, (3) isoquinoline, (4) decahydroisoquinoline.

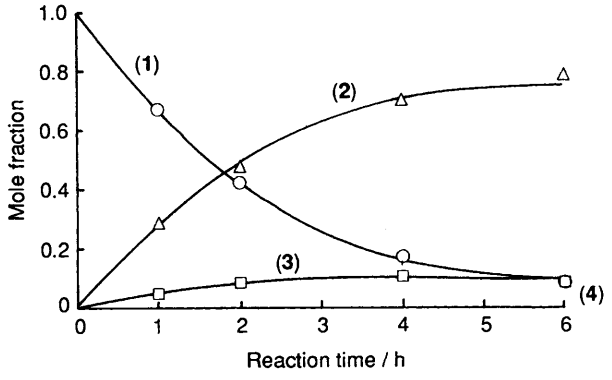


Figure 3. Product distributions for the reaction of compound (1) over R–Ni at 200 °C under 1 MPa N_2 pressure in a closed reactor (run 4). See Figure 2 caption for chemical identity of compounds (1)–(4).

at an early stage of the reaction but disappeared after 4 h. The perhydrogenated product (4) was detected only after 3 h, and gradually increased with increasing reaction time. Under high hydrogen pressure (10 MPa, run 2), the yields decreased for compounds (2) and (3), and increased for product (4).

In a closed reactor, the time-dependent product distributions under nitrogen were essentially the same as those under hydrogen. For the former case, however, isoquinoline (3) formed in significant amounts while compound (4) was produced in only a negligible amount, as illustrated in Figure 3.

Table 2 summarizes the reactivities of compounds (2), (3), and (4) as starting materials. Under a nitrogen atmosphere compounds (2) and (4) were far less reactive than compound (1). The substrate (2) was slowly but predominantly converted into 'others', with isoquinoline (3) as a minor product. Compound (4) was slowly dehydrogenated into compound (2).

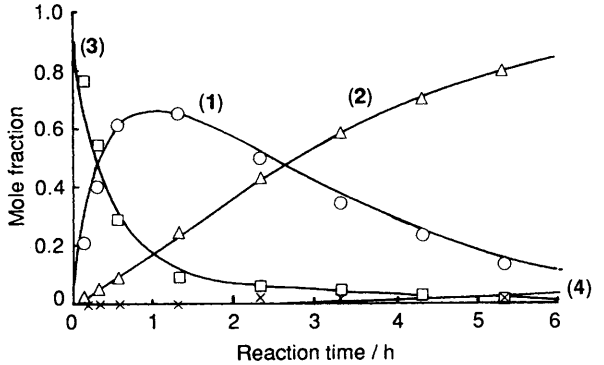
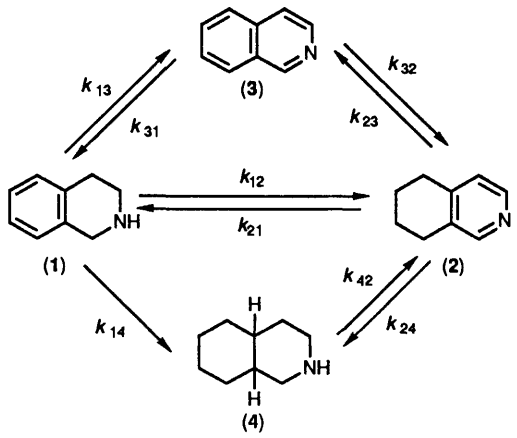


Figure 4. Product distributions for the reaction of isoquinoline (3) over R–Ni at 205 °C under 1.6 MPa H_2 pressure in a closed reactor (run 9). See Figure 2 caption for chemical identity of compunds (1)–(4).

Table 3. Rate constants for the reactions of 1,2,3,4-tetrahydroisoquinoline (1) over R–Ni (5 wt%) in a closed reactor.

Run No.	Temp./ °C	Pressure[a]/MPa			Rate constants								
		N_2	H_2	Total	k_{12}	k_{13}	k_{14}	k_{21}	k_{23}	k_{24}	k_{31}	k_{32}	k_{42}
1	205	0	1.6	1.6	0.28	0.09	0.00	0.00	0.00	0.03	3.00	0.05	0.00
4	200	1.0	0.8	1.0–1.8	0.30	0.06	0.00	0.00	0.10	0.02	0.60	0.00	0.00
5	210	6.1	0.3	6.1–6.4	0.40	0.06	0.00	0.00	0.10	0.02	0.60	0.00	0.00
6	150	0.9	0.3	0.9–1.2	0.015	0.04	0.00	0.00	0.00	0.00	2.00	0.00	0.00
9	205	0	1.6	1.6	0.23	0.12	0.00	0.00	0.00	0.02	2.90	0.05	0.00
10	190	0	1.6	1.6	0.15	0.02	0.00	0.00	0.00	0.01	3.00	0.02	0.00

[a] At reaction temperature. [b] Result of the hydrogenation of isoquinoline in a previous work.[1]



Scheme 1. Reaction network for kinetic analyses.

We postulate that isoquinoline (3) underwent hydrogenation to compound (1), followed by isomerization into compound (2) (run 9: see Figure 4).

Kinetics.—Using the simplified reaction Scheme 1, we applied the following modified Langmuir–Hinshelwood-type rate equations (1)–(4) for kinetic analyses of the present results, in which we took into account both our previous results[1] and Satterfield's report on the hydrodenitrogenation (HDN) reaction of quinoline.[9]

$$\frac{dC_1}{dt} = \frac{k_{21}(K_2/K_1)C_2 + k_{31}(K_3/K_1)C_3 - (k_{12} + k_{13} + k_{14})C_1}{C_1 + (K_2/K_1)C_2 + (K_3/K_1)C_3 + (K_4/K_1)C_4} \quad (1)$$

$$\frac{dC_2}{dt} = \frac{k_{12}C_1 + k_{32}(K_2/K_1)C_3 + k_{42}(K_4/K_1)C_4 - (k_{21} + k_{23} + k_{24})(K_2/K_1)C_2}{C_1 + (K_2/K_1)C_2 + (K_3/K_1)C_3 + (K_4/K_1)C_4} \quad (2)$$

$$\frac{dC_3}{dt} = \frac{k_{13}C_1 + k_{23}(K_2/K_1)C_2 - (k_{31} + k_{32})(K_3/K_1)C_3}{C_1 + (K_2/K_1)C_2 + (K_3/K_1)C_3 + (K_4/K_1)C_4} \quad (3)$$

$$\frac{dC_4}{dt} = \frac{k_{14}C_1 + k_{24}(K_2/K_1)C_2 - K_{42}(K_4/K_1)C_4}{C_1 + (K_2/K_1)C_2 + (K_3/K_1)C_3 + (K_4/K_1)C_4} \quad (4)$$

C_i is the mole fraction of species i, t the reaction time (h), k_{ij} the apparent rate constant (h^{-1}) of reaction $i \longrightarrow j$, and K_i/K_1 the relative equilibrium adsorption constant of species i *vs.* (1). The values of K_i/K_1 were assumed to be constant under the present experimental conditions, and the following values were employed: K_2/K_1 0.3, K_3/K_1 0.5, and K_4/K_1 0.5.[1]

The values of k_{ij} were determined by a curve-fitting procedure using the numerical method containing the Runge–Kutta–Gill routine. Table 3 summarizes the optimum values of the rate constants. Figures 2–4 show some examples for comparison of the calculated product distribution curves with the corresponding experimental data as dots (circle, *etc.*). The dots satisfactorily fit the curves. The standard deviations of calculated values for the product distributions were 1.9, 2.3, and 2.4% for runs 1, 4, and 9, respectively. The values of k_{12} were almost the same for runs 1, 4, and 9. Therefore, the hydrogen pressure had little effect on the rate constant. The values of log (k_{12}) are plotted against the reciprocal absolute temperature in Figure 5. The apparent activation energy of the isomerization was calculated to be 22.5 (±2.5) kcal mol^{-1}.*

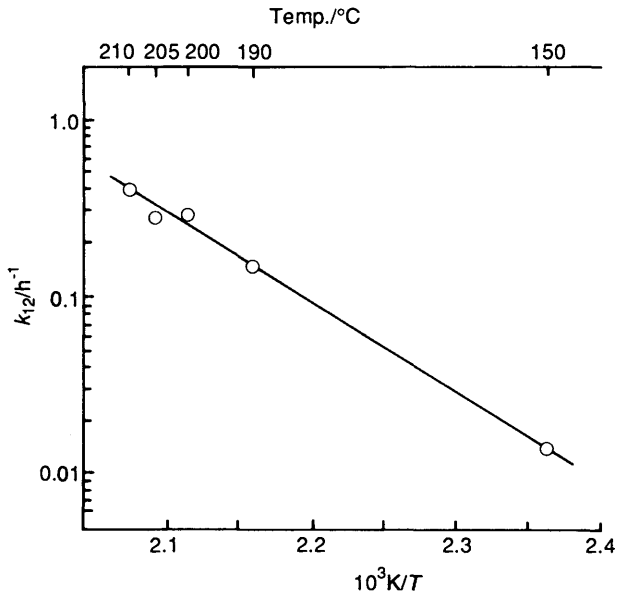


Figure 5. Arrhenius plot for the isomerization of compound (1) to compound (2).

* 1 cal = 4.184 J.

Schulz *et al.* also observed compounds (1) and (2) as intermediates of the HDN reaction of isoquinoline over NiWS–Al_2O_3 catalyst.[10] They proposed that compound (2) as well as compound (1) was formed through the hydrogenation of isoquinoline (3). The formation pathway of these two tetrahydroisoquinolines may be simplified as the following parallel reversible reactions: (1) ⇄ (3) ⇄ (2). However, this model was not applicable to our present kinetic results because the value of k_{32} was very small as shown in Table 3. We propose that compound (2) is formed mainly through the isomerization of compound (1), together with the dehydrogenation of compound (1) into isoquinoline (3), under the present conditions. This reaction pathway can be simplified as the following consecutive reversible reactions: (3) ⇄ (1) ⇄ (2). In addition, the latter consecutive reaction model is more plausible than the former parallel one upon examination of the profile of the time-dependent product distributions in Figures 3 and 4, according to Vriens's report.[11]

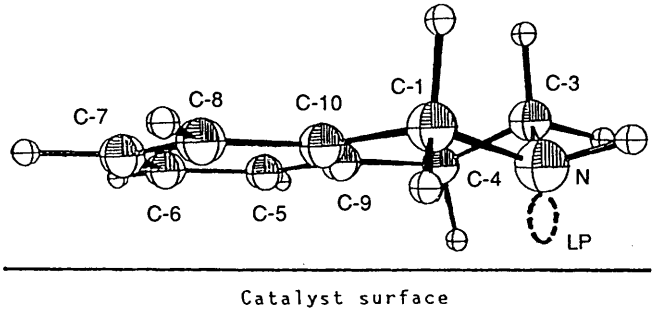


Figure 6. Optimized structure of 1,2,3,4-tetrahydroisoquinoline (1) (ORTEP projection).

Quantum Chemical Indices.—Some quantum chemical indices for isoquinoline and its derivatives were calculated by the MNDO–MO[12] on a CRAY X-MP/216 computer. The geometries of these molecules were energetically optimized at the fixed configuration of their planar aromatic ring. The optimized structure of compound (1) is illustrated in Figure 6 using the ORTEP routine.[13] The molecule was placed with the lone-pair electrons of its nitrogen atom orientated vertically towards the catalyst surface,[14,15] where the distance between compound (1) and the catalyst was not optimized. The positions of the substrate (1) and the catalyst surface seemed to be sterically preferable for the catalyst to abstract the hydrogens of the piperidine ring of compound (1) and, in turn, to hydrogenate the benzene ring of compound (1) with the abstracted hydrogens, due to both of the rings being almost simultaneously coordinated to the catalyst surface.

Several quantum chemical indices of related compounds are shown in Figures 7 and 8. The electron densities in the frontier orbitals (HOMO and LUMO, or SOMO) of the aliphatic hydrogens, and aromatic or alkenic carbons and nitrogens are given in these Figures. It is assumed that the dehydrogenation occurs most probably at the hydrogen atom having the highest frontier electron density (HOMO and LUMO),[16] although the

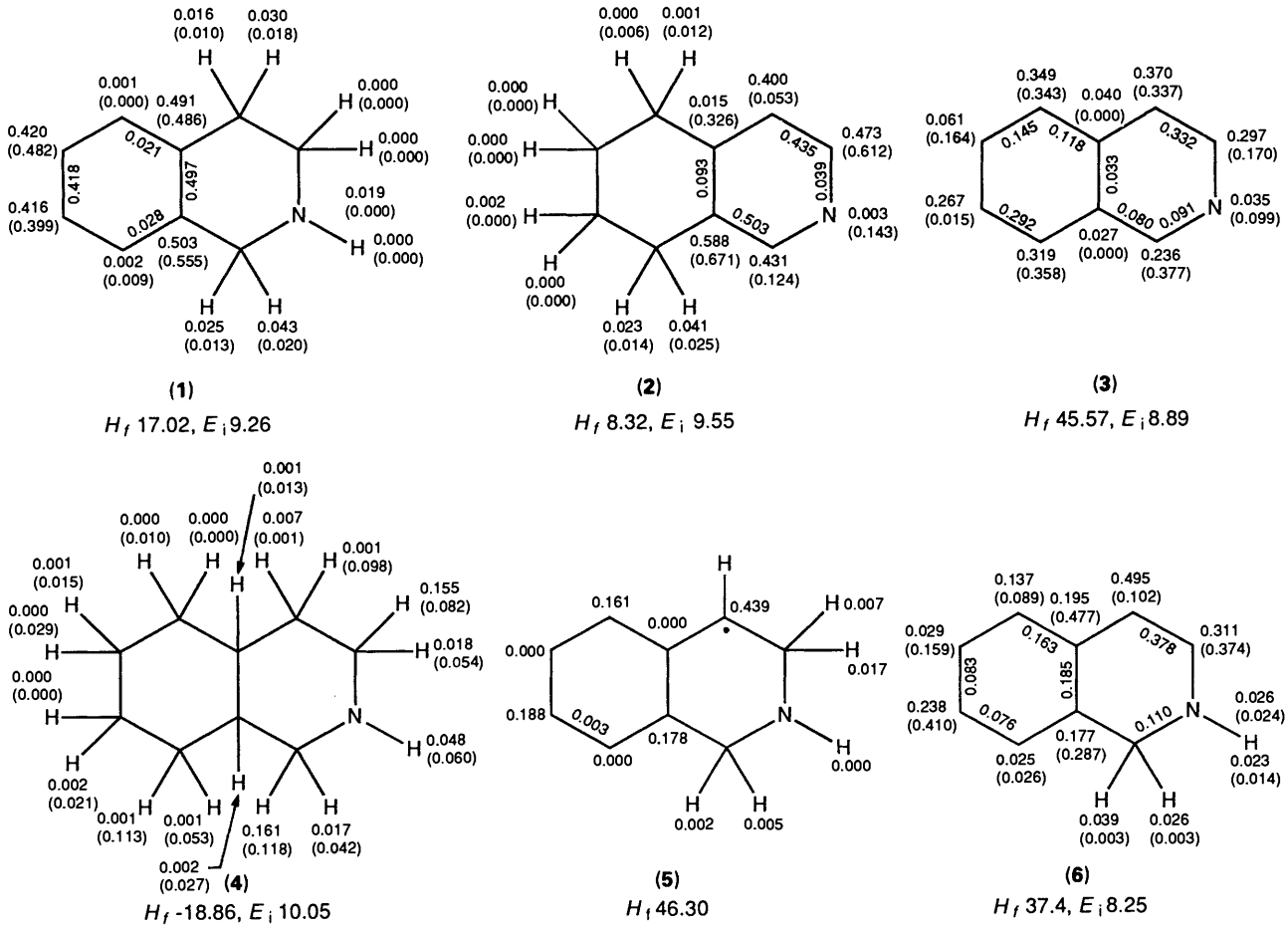


Figure 7. Quantum chemical indices of isoquinolines (1)–(6). Electron densities in HOMO and LUMO (in parentheses) are shown out of the ring, bond orders in HOMO are shown inside the ring; heats of formation (H_f, kcal mol^{-1}) and ionization potentials (E_i/eV) are given beneath.

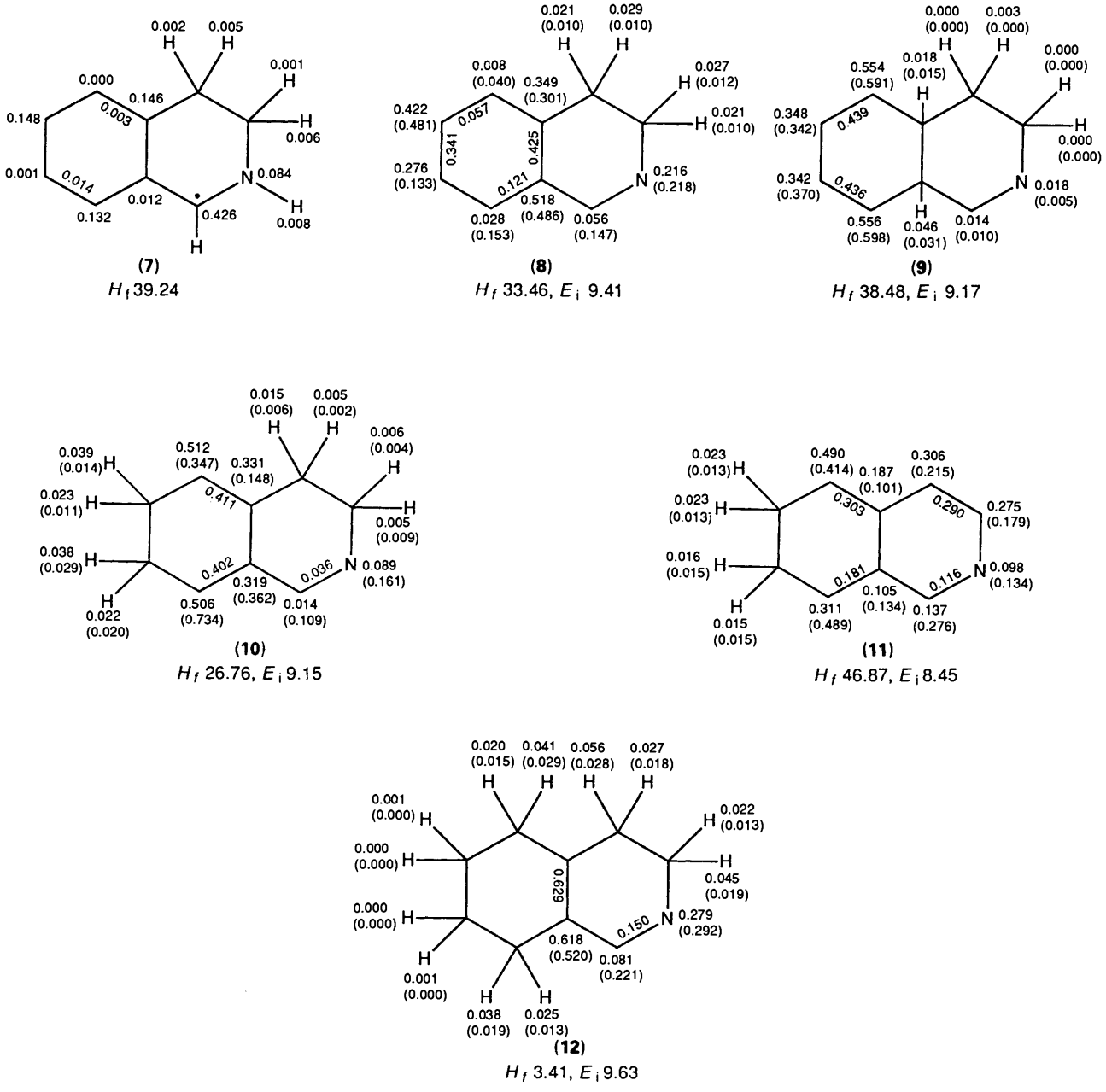
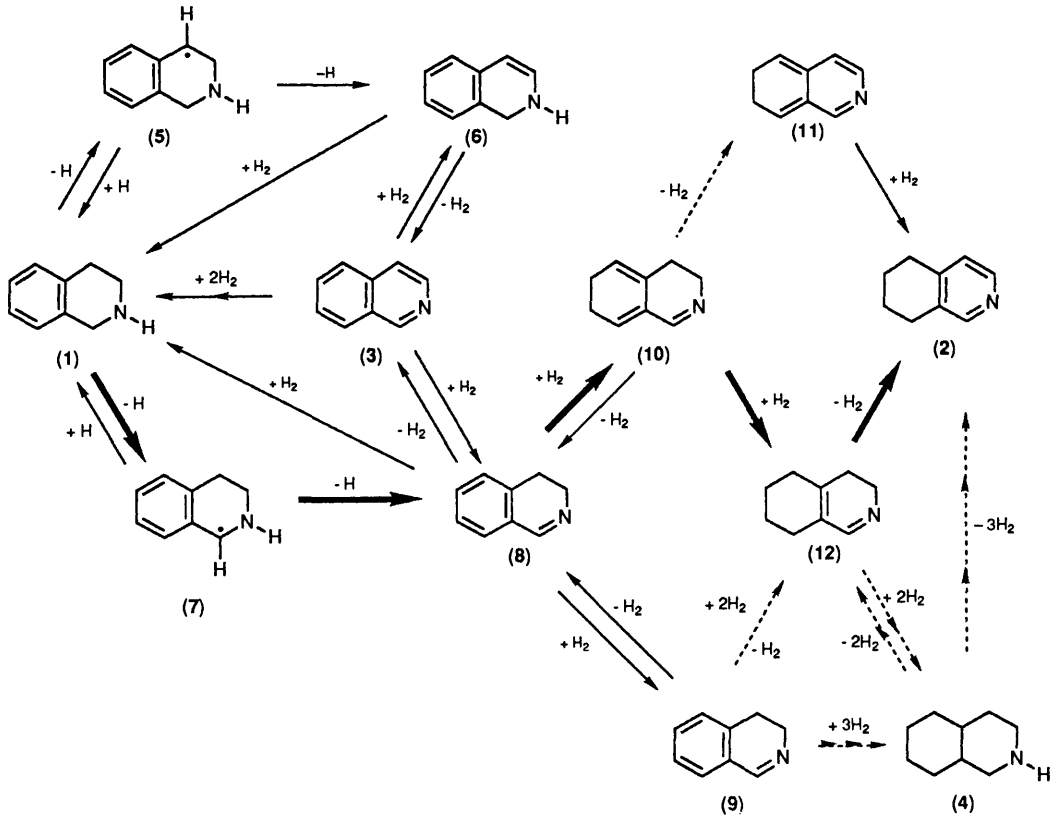


Figure 8. Quantum chemical indices of isoquinolines (7)–(12). Key to data elements is that given in the caption to Figure 7.

adsorbed forms on the catalyst surface should also be taken into account. The hydrogen atoms at the C-1 and C-4 in compound (1) have higher frontier electron densities and therefore are more reactive in hydrogen abstraction than those at C-2 and C-3. There are two possible indices for the hydrogenation reactivity. One is the frontier electron density (HOMO and LUMO)[17,18] of the sp^2-carbon and the other is the C–C bond order in the frontier orbital (π-orbital).[19] The orders of bonding combinations are also shown in the Figures. The heat of formation (H_f), also obtained from quantum chemical calculations, is an index of the thermal stability of a substrate. Generally speaking, isoquinoline derivatives are thermally stabilized by hydrogenation. The ionization potential (E_i) is another index for the intermolecular reactivity of a substrate. Substrate (2) was thus expected to be more stable than the isomer (1).

Dominant Isomerization Route.—Based on the present kinetic results and quantum chemical calculations, the most plausible steps for the isomerization of compound (1) to compound (2) are shown in Scheme 2.

The first step of the isomerization would be the partial dehydrogenation of compound (1). A hydrogen at C-4 is reactive because one of the two hydrogens has the second highest frontier electron density, and is located at the closest position to the catalyst surface as shown in Figure 6, where the lone pair of the nitrogen atom is directed towards the catalyst. One of the hydrogens at C-1 has the highest frontier electron density. Thus, compound (1) would be first converted into an intermediate radical (5) or (7) by the elimination of one of these hydrogens. The heats of elimination reactions, ΔH_f(5)–(1) and ΔH_f(7)–(1), were calculated to be 29.3 and 22.2 kcal mol^{-1}, respectively, the largest values among those calculated for a series of possible steps. The apparent activation energy for the isomerization of compound (1) to compound (2) was 22.5 kcal mol^{-1} as described above. Hence, radical (7) was a more



Scheme 2. Possible isomerization route of compound (1) to compound (2).

plausible intermediate than (5). The initial products (7) and (5) suffer elimination of their second hydrogen to form dihydroisoquinolines (8) and (6), respectively. Since the β-fission is widely assumed to proceed readily, the higher frontier electron density of hydrogen at C-3 in radical (5) and at the N atom in radical (7) may support the β-fission route in these substrates. Hydrogenation of the benzene ring of compounds (5) and (7) may not occur because they both have much lower π-electron densities and π-bond orders in the ring.

The reactivity seems very different between intermediates (6) and (8). The benzene ring in compound (6) will resist hydrogenation because of its lower π-bond order compared with the alkenic C-3–C-4 bond in the same molecule, and the strongly basic sp^3-nitrogen atom may be firmly adsorbed on the catalyst surface to hinder hydrogenation of the benzene ring.[20] Therefore, transformation of compound (6) into compound (2) will be difficult. Rehydrogenation of compound (6) may regenerate compound (1) directly or stepwise *via* isoquinoline (3). In contrast, the benzene ring in compound (8) will be more susceptible to hydrogenation because of its higher π-bond orders compared with the C-1–N double bond. A weaker poisoning effect of the sp^2-nitrogen on hydrogenation is also expected.

A possible product from hydrogenation of compound (8) is the tetrahydroisoquinoline (9) or (10), by taking into account the π-bond orders of the preceding intermediate (8). The intermediate (10) may be more preferable because compound (9) is susceptible to dehydrogenation of its tertiary hydrogens and may readily regenerate compound (8). Nevertheless, the route (8) ⟶ (9) ⟶ (12) may also participate to a limited extent owing to the high reactivities of the C-5=C-6 and C-7=C-8 double bonds of compound (9).

The last step in the isomerization is the transformation of tetrahydro- (10) to hexahydro-isoquinoline (2). The hexahydroisoquinoline (12) is the most probable intermediate leading to compound (2), according to the high reactivities of C-5 and C-8 of compound (10) for hydrogenation as shown in their frontier electron densities, the high barrier to compound (11) as shown in its heat of formation, and the reactivities of the hydrogens at C-3 and C-4 of compound (10) for dehydrogenation. In fact, a hexahydroisoquinoline was detected among the products in our present study. Unfortunately, however, the very small amount isolated did not allow us to determine its structure in detail.

In conclusion, the hydrogen-transfer isomerization of compound (1) to compound (2), both kinetically and quantum chemically, proceeds through a series of stepwise dehydrogenations and hydrogenations as illustrated by the thick arrows in Scheme 2.

Experimental

All the starting materials were 99% pure with sulphur contents <1 ppm. R–Ni N154D (containing *ca.* 50 wt% Ni) was purchased from Nikki Chemical Co., Japan. A substrate (50 g) and R–Ni (2.5 g) were charged in a 200 cm^3 autoclave. The reactor was purged five times with either pressurized hydrogen or nitrogen depending upon the experimental conditions, and then heated to a given temperature within 30 min without stirring of the contents. The reaction was started when the reactants were stirred. The temperature to be set was attained within 2 min, and was then kept steady for a given period. Aliquots of the reaction mixture (*ca.* 0.5 g) were removed periodically through a sampling valve at appropriate times, and quenched with methanol (5 cm^3). After filtration to remove the catalyst, the sample was analysed by gas chromatography.[1] The following sets of experimental conditions were examined: hydrogen pressures of 1.6 and 10 MPa and nitrogen pressures of

1 and 6.1 MPa in a closed reactor, and atmospheric pressure of nitrogen in an open reactor.

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