Conformational Study on 2-Acyl-1-alkylidene-1,2,3,4-tetrahydroisoquinolines

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The title enamide compounds can exist in either a sickle or U conformation with respect to the C=C–N–C=O conjugated moiety, where the sickle form is greatly favored. The sickle rotamers are chiral in nature in both solution and crystalline states, as proved by ^{1}H NMR and a single-crystal X-ray analyses. The molecular distortion from the standard structure occurs in such a way as to retain the amide planarity, indicating a higher significance of the $n/\pi^*_{C=O}$ orbital interaction compared to the $n/\pi^*_{C=C}$ overlapping. The pathway and interconversion rate between the rotational stereoisomers are highly dependent on the nature of the 1-alkylidene and *N*-acyl groups. The energy barrier for the stereomutation of (*Z*)-2-(*p*-bromobenzoyl)-1-(3,4-dimethoxyphenylmethylene)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline has been determined by a lineshape analysis of the ^{1}H NMR spectra.

In connection with our recent work on the asymmetric synthesis of isoquinoline alkaloids using BINAP–Ru catalyzed hydrogenation,[1] we have prepared a series of *N*-acylated 1-alkylidene-1,2,3,4-tetrahydroisoquinolines, which serve as the key precursors. The highly efficient asymmetric catalysis urged us to deeply understand the mechanism of the chiral recognition of the olefinic substrates with BINAP–transition metal complexes.[2] The enamides are an interesting class of cross-conjugated systems in which the nitrogen lone-pair electrons delocalize over the C=O and C=C bonds, presenting numerous stereochemical problems. In searching the literature for a description of the properties of the enamides, however, we noticed that little is known about their structural features.[3,4] This paper discloses detailed geometries of the uniquely functionalized olefins in solution and solid states.

Results and Discussion

We chose three classes of compounds **1**—**3** (**a**, 2-formyl; **b**, 2-acetyl; **c**, 2-*p*-bromobenzoyl; **d**, 2-pivaloyl). Compounds of type **1** are the simple 1-methylene derivatives, where the *N*-formyl compound **1a** presents a prototype. 1-Benzylidene compounds of type **2** are sterically congested because of a nonbonded interaction between the *N*-acyl group and the benzylidene moiety. Compound **3a** is the 1*E* isomer of **2a**. A comparison of the structural characteristics of simple **1a** and highly congested **2b**—**d** is particularly enlightening. This five-atom π system can exist in either a sickle or U-type conformation.

Structures in Solution Phase. The ^{1}H NMR spectrum of **1a** clearly shows the presence of the sickle and U isomers (Fig. 1). The ratio of the two components at 20—27 °C depends on the solvent, ranging from 13 : 1 (dimethyl-d_6 sulfoxide), 15 : 1 (acetone-d_6), 17 : 1 (methanol-d_4 and acetonitrile-d_3), 18 : 1 (pyridine-d_5) and 21 : 1 (benzene-d_6), to 26 : 1 (chloroform-*d*). The major isomer was assigned to be the sickle rotamer, since the spectrum taken in chloroform-*d* at 27 °C exhibited 7% NOE between the formyl proton and the cis proton of the exocyclic methylene group. This rotamer gave a triplet due to the C(3) protons at $\delta = 3.89$, a lower field than that of the minor U form, $\delta = 3.70$. This NMR observation is in full accord with an ab initio MO calculation of the simple model **4** given in Fig. 2. The result indicates that the sickle conformation is more stable than the U form by 11.6 kJ mol^{-1}, which is consistent with 6.4—8.1 kJ mol^{-1} observed by ^{1}H NMR. This conformational preference is obviously due to the lower dipole repulsion, as understood by the extreme ionic valence bond representation **5**. The calculations also suggest that both conformers are nonplanar and chiral, making the ring methylene protons diastereotopic. This nonplanarity is ascribable to a steric repulsion between COR^2 and R^1 in the enamide system of **5** (Chart 1). In solution, however, sickle-**1a** undergoes a rapid interconversion between the enantiomers, even at −70 °C, giving a time-averaged single triplet for the C(3) protons in the NMR spectrum. The 1-methylene 2-acetyl compound **1b** behaves similarly, while the minor U form (ca. 4%) is detectable only below −25 °C.

In a similar manner, the 1-benzylidene 2-formyl analogue **2a** in chloroform-*d* at 22 °C exhibited a 5—6% signal enhancement for the formyl proton upon irradiation of the C(2′) or C(6′) proton, consistent with the sickle conformation. The U conformer was undetectable even at −70 °C. The C(3) protons of **2a** gave a triplet at $\delta = 3.99$ (Fig. 1), suggesting a rapid conformational flipping.

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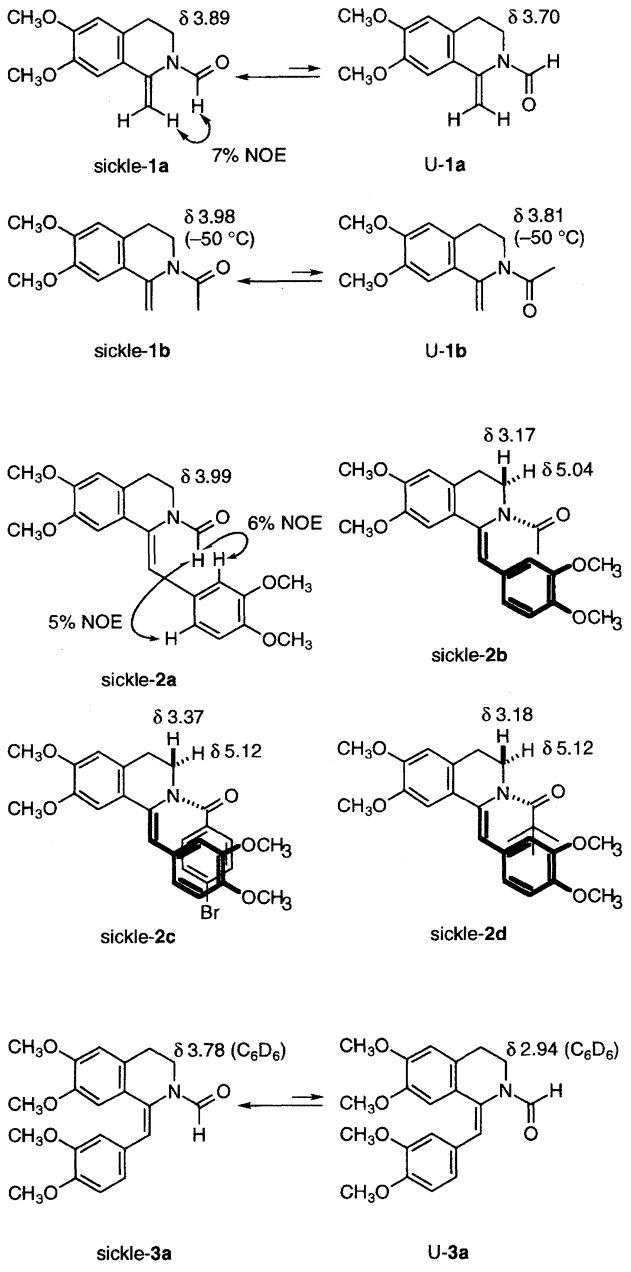

Fig. 1. ^{1}H NMR of 2-acyl-1-methylene and -benzylidene compounds **1**—**3**. All data were taken in chloroform-*d* at 20—27 °C unless otherwise specified.

More congested (1*Z*)-benzylidene compounds **2b**—**d** with a bulkier acyl group at the nitrogen behaves differently from the *N*-formyl compounds, **1a** and **2a**. The NMR spectrum of the *N*-acetyl derivative **2b**, for example, in chloroform-*d* at 21 °C, as seen with **2a**, gave a single set of signals, implying the presence of only the sickle isomer. Notably, the signals of the nonequivalent C(3) protons appeared at $\delta = 3.17$ and 5.04 (Fig. 1). The latter very low chemical shift is ascribed to an anisotropy effect of the amide oxygen, since the H–C(3)–N–C=O system is arranged approximately planar. Thus, in going from the *N*-formyl compound, **1a** or **2a**, to the acetyl derivative **2b**, the stability of the chiral structure is greatly enhanced. The *N*-*p*-bromobenzoyl and *N*-pivaloyl

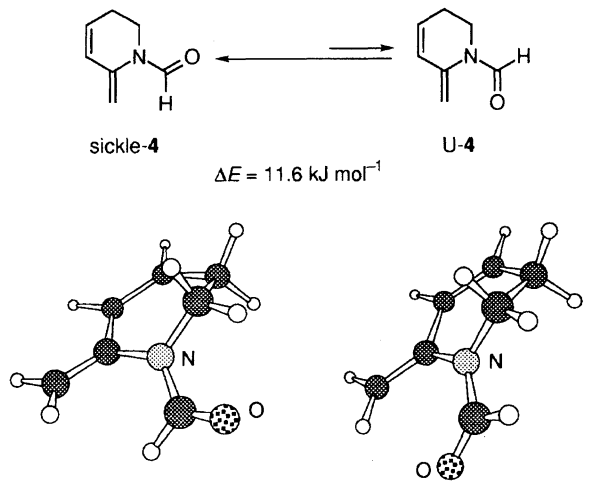

Fig. 2. Calculated structures of 1-formyl-2-methylene-1,2,5,6-tetrahydropyridine (4).

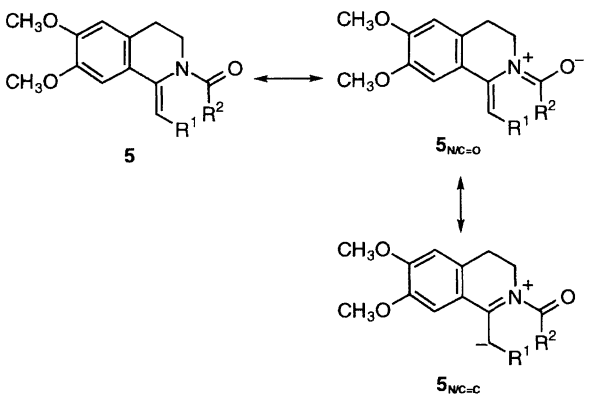

Chart 1.

compounds, **2c** and **2d**, showed similar NMR characteristics, giving the C(3) proton signals at $\delta = 3.18$—3.37 and 5.12 (Fig. 1).

The *N*-acylated (1*Z*)-benzylidene derivatives deviate from the planar structure, and are chiral. The molecular chirality of the sickle form arises mainly from compression between the benzylidene aromatic ring and the amide alkyl or aryl substituent. The 1-methylene compounds with a relatively bulky *N*-acyl group **1b** and the 1-benzylidene compound **2a**, having a small formyl group at the nitrogen, displayed intermediate NMR properties. Thus, these enamides can not be frozen to a chiral structure, even below −70 °C. The (1*E*)-benzylidene-2-formyl compound **3a** behaves similarly to the simplest compound **1a**. The ^{1}H NMR spectrum in chloroform-*d* at 20 °C indicated the presence of the sickle and U conformers in a ratio of 40 : 1.

Dynamic Equilibria. The enamide compounds **1**—**3** in principle exist as a mixture of the sickle and U conformers, where the former is considerably favorable. Although both rotamers have a nonplanar, chiral conformation, in solution the enantiomers are readily interconvertible. Thus, the dynamic behavior of the four stereoisomers of **1** and **2** is summarized in Fig. 3. The *E* enamide **3a** behaves like **1**. The ease with which a stereochemical inversion takes place is

highly dependent on the nature of the substituents. With the simplest *N*-formylated 1-methylene compound **1a**, the $S \rightleftarrows R$ stereomutation is easier than the sickle$\rightleftarrows$U interconversion. Consequently, the enantiomer interconversion occurs in the more stable sickle form. In contrast, in the congested 1-benzylidene compounds, such as **2b—d**, interconversion between the sickle enantiomers is highly unlikely. Instead, enantiomeric inversion occurs only through the NMR-undetectable U form. As shown in Fig. 4, the two diastereotopic C(4) protons of the 2-*p*-bromobenzoyl compound **2c** give separate signals at $\delta = 2.88$ and 3.09 in dimethyl-d_6 sulfoxide at 24 °C, which coallesce into a broad signal at elevated temperatures. Coalescence occuring at 100 °C suggests that the overall enantiomer interconversion takes place with a rate constant of $k_{inv} = 1.4 \times 10^2$ s^{-1} and an activation energy of $\Delta G^{\ddagger} = 74$ kJ mol^{-1}.[5] Compound **2b** behaves similarly with a coalescence temperature of 135 °C, $k_{inv} = 1.6 \times 10^2$ s^{-1}, and $\Delta G^{\ddagger} = 84$ kJ mol^{-1}.

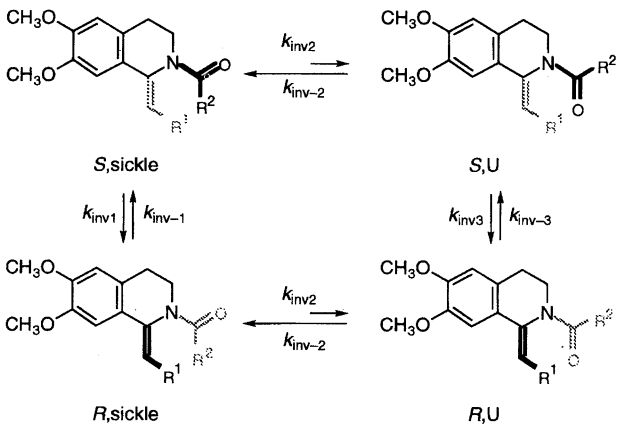

Fig. 3. Dynamic equilibration of four possible stereoisomers of (*Z*)-2-acyl-1-alkylidene-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines.

Structures in Crystalline State. A modification of the standard structure causes a molecular distortion. This structural change generally occurs in such a way as to mitigate the steric strain while maintaining electron delocalization. Figure 5 illustrates the detailed solid-state molecular structures of certain 1-benzylidene compounds determined by X-ray crystallographic studies.[1a] The enamides (**2a**, **2c**, and **2d**) all have sickle structures in the solid state, as has been noted with natural (*Z*)-6,7-dimethoxy-1-(3,4-dimethoxy-2-hydroxyphenylmethylene)-2-formyl-1,2,3,4-tetrahydroisoquinoline[3a] and 5,6-dihydro-1,2-dimethoxy-6-formyl-4*H*-dibenzo[*de*,*g*]quinoline.[3b] Table 1 lists the selected structural parameters, including the C(1)–N–C=O dihedral angle (θ_1), the C=C–N–CO dihedral angle (θ_2), and the total of the three valence angles around the nitrogen atom (θ_3), and the N–CO bond length. The calculated structure of model **4** is also included for a comparison. The analysis reveals the

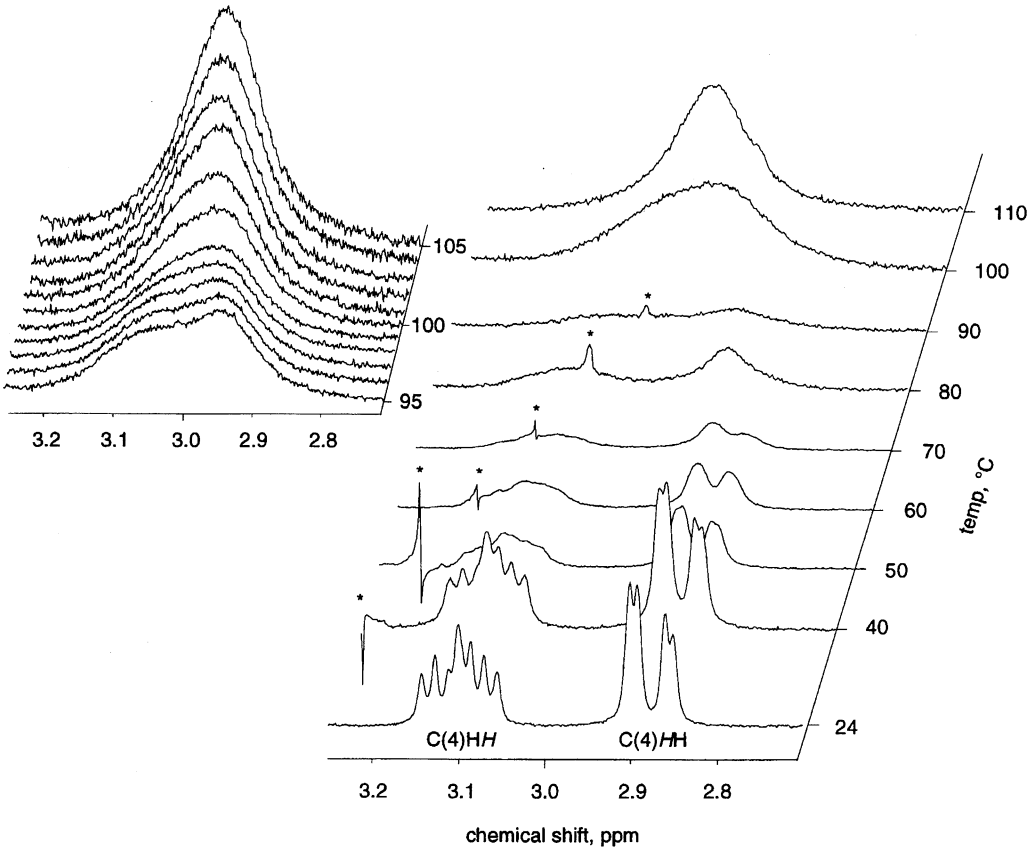

Fig. 4. Variable-temperature ^{1}H NMR spectra of a 12 mM dimethyl-d_6 sulfoxide solution (1 M = 1 mol dm^{-3}) of **2c** under irradiation of the water signals marked with asterisks.

Table 1. Selected Structural Parameters of 2-Acyl-1-alkylidene-1,2,3,4-tetrahydroisoquinolines

Compound	Dihedral angle/deg		Total valence	Bond length of
	C(1)–N–C=O (θ_1)	C=C–N–CO (θ_2)	angle of N (θ_3)/deg	N–CO/Å
Sickle-**4**[a)]	179.23	38.53	359.8	1.359
2a	175.96	53.88	360.0	1.344
2c	168.65	63.42	359.9	1.463
2d	161.47	99.49	354.1	1.368

a) Ab initio-calculated structure.

general structural characteristics of the enamides. Although all of these molecules can not be planar, conjugation of the nitrogen nonbonding orbital with the C=O orbital tends to maintain the planarity of the amide group ($\theta_1 = 161$—$179°$, $\theta_3 = 354$—$360°$), and also to shorten the N–CO bond (1.34—1.46 Å). Using the least constrained structure **4**, the calculated θ_2 value is 39°, while the θ_2 value of **2a** and **2c** increases to 54° and 63°, respectively. Furthermore, the highly crowded *N*-pivaloyl compound **2d** is greatly distorted from the unperturbed structure **4**, giving a θ_2 value of 99°. In this particular compound, the N/C=C conjugation is completely lost, whereas little nitrogen pyramidization occurs as judged from the θ_3 value of 354°. This is ascribed to the stronger $n/\pi^*_{C=O}$ orbital interaction, $\mathbf{5}_{N/C=O}$, relative to the $n/\pi^*_{C=C}$ interaction, $\mathbf{5}_{N/C=C}$. It should particularly be noted that although this molecule possesses an exceedingly large *t*-butyl group and is highly skewed, it still maintains the sickle-type, rather than the U-type, conformation at the cost of substantial *t*-butyl/aryl compression. Most importantly, the electronic factor appears to dominate over the steric effect. This view is supported by the fact that the simple *N*-acyl or *N*-aroyl piperidines, lacking the C=C bond, exhibit a very similar ^{13}C NMR chemical shift for the NC=O carbon and IR C=O stretching frequency to the enamide derivatives **2a**—**d** (Table 2).

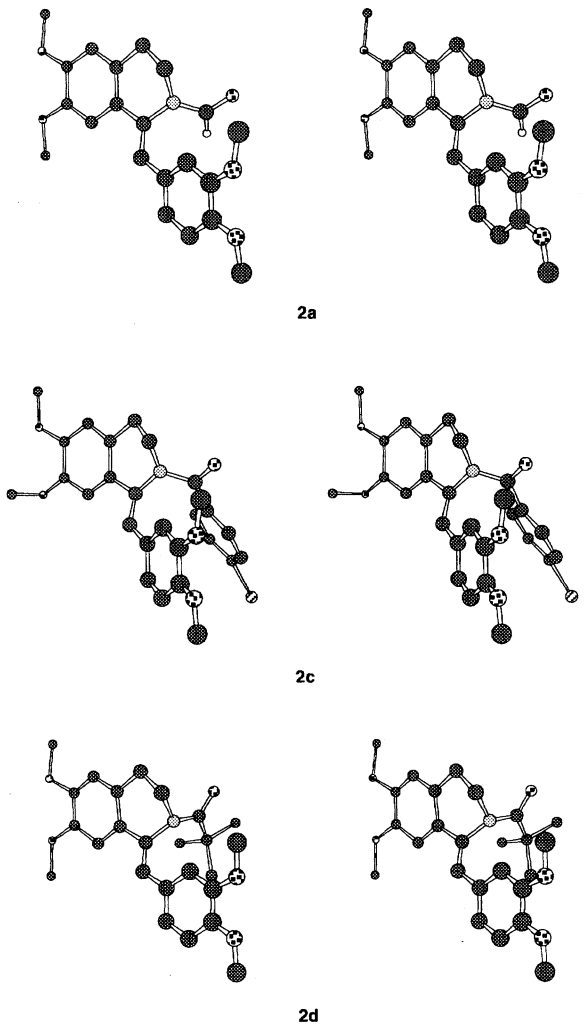

Fig. 5. Stereoviews of X-ray crystallographic structures of (*Z*)-6,7-dimethoxy-1-(3,4-dimethoxyphenylmethylene)-2-formyl-1,2,3,4-tetrahydroisoquinoline (**2a**), (*Z*)-2-(*p*-bromobenzoyl)-1-(3,4-dimethoxyphenylmethylene)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**2c**), and (*Z*)-1-(3,4-dimethoxyphenylmethylene)-6,7-dimethoxy-2-pivaloyl-1,2,3,4-tetrahydroisoquinoline (**2d**). All hydrogen atoms except for formyl proton are omitted.

Table 2. ^{13}C NMR Chemical Shift of the Carbonyl Carbon and IR Frequency of the Amide Group of the Enamides **2a—d**

Compound	^{13}C NMR, δ[a,b)]	IR/cm^{-1} [b,c)]
2a	162.66 (160.75)[d)]	1667 (1662)[d)]
2b	169.77 (168.67)[e)]	1634 (1626)[e)]
2c	168.39 (169.21)[f)]	1632 (1620)[f)]
2d	178.08 (176.03)[g)]	1622 (1605)[g)]

a) In chloroform-*d* at 21—27 °C. b) The values for the corresponding piperidine derivatives **6** are given in parenthesis. c) In chloroform at 25 °C. d) 1-Formylpiperidine. e) 1-Acetylpiperidine. f) 1-*p*-Bromobenzoylpiperidine. g) 1-Pivaloylpiperidine.

Conclusion

A systematic study of the structures of *N*-acylated 1-alkylidene-1,2,3,4-tetrahydroisoquinolines **1**—**3** revealed that these enamides exist in the sickle (stable) or U (less stable) conformation, both of which are chiral in the solution and crystalline states. The conformational stability and distribution are highly dependent on the extent of the nonbonded repulsion caused by substituents at the 1 and 2 positions. In all cases, even with very bulky substituents, the planarity of the amide moiety is retained. In solution, the chiral rotamers

readily undergo a sickle⇄U and/or *R*⇄*S* stereochemical inversion. The enantiomeric inversion of the sterically unconstrained **1**, **2a**, and **3** occurs directly with a retention of the sickle or U conformation, whereas congested sickle-**2b**—**d** racemize via the short-lived U conformers.

Experimental

Instruments. Infrared (IR) spectra were recorded on a Shimadzu FTIR-8000 spectrometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were measured on a JEOL GX270 (270 MHz) or a JEOL ALPHA400 (400 MHz) instrument. The chemical shifts are expressed in parts per million (ppm) downfield from tetramethylsilane, and signal patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. The carbon nuclear magnetic resonance spectra (^{13}C NMR) were recorded on a JEOL ALPHA400 instrument (100 MHz), and the chemical shifts are reported in ppm relative to chroloform-*d* (77.0 ppm) as an internal standard.

Materials. The enamides **1**—**3** were obtained by *N*-acylation of 6,7-dimethoxy-1-methyl-3,4-dihydroisoquinoline[6] and 1-(3,4-dimethoxyphenylmethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline[7] under the reported conditions.[1c] The IR, UV, and NMR data were described in Ref. 1c. 1-Formylpiperidine and 1-acetylpiperidine were purchased from Tokyo Kasei. 1-*p*-Bromobenzoylpiperidine and 1-pivaloylpiperidine were prepared from piperidine and the corresponding acid chloride (dichloromethane, 0 °C, 30 min). All of the deuterated solvents were purchased and used without further purification. A signal assignment for compounds **1** and **2** was made by a combination of the 2D nuclear Overhouser enhancement and exchange spectroscopy (NOESY), C–H correlation spectroscopy, and correlation spectroscopy via long-range couplings (COLOC) in chloroform-*d* at 20—27 °C. A 2D incredible natural-abundance double quantum transfer experimental (2D INADEQUATE) was carried out for discriminating between the C(1) and C(4a) signals of **2a** and **2c**. Those two carbon signals for **2d** could not be assigned. The ^{1}H and ^{13}C NMR data of **1** and **2** with assignment are as follows, where only assignable proton signals of U isomer are listed:

Sickle-1a: ^{1}H NMR (400 MHz, 24 °C) δ = 2.84 (t, 2, J = 5.9 Hz, C(4)H$_2$), 3.88 (s, 3, C(6)OCH$_3$), 3.89 (t, 2, J = 5.9 Hz, C(3)H$_2$), 3.91 (s, 3, C(7)OCH$_3$), 4.82 (d, 1, J = 1.5 Hz, *cis*-CONC=CH), 5.19 (d, 1, J = 1.5 Hz, *trans*-CONC=CH), 6.59 (s, 1, C(5)H), 7.11 (s, 1, C(8)H), 8.64 (s, 1, CHO); ^{13}C NMR (100 MHz, 24 °C) δ = 28.70 (C(4)), 38.60 (C(3)), 55.80 (C(6)O*C*H$_3$), 55.94 (C(7)O*C*H$_3$), 94.65 (C(1)=*C*), 106.53 (C(8)), 110.96 (C(5)), 121.88 (C(8a)), 127.29 (C(4a)), 140.70 (C(1)), 147.91 (C(7)), 149.92 (C(6)), 160.44 (CHO).

U-1a: ^{1}H NMR (400 MHz, 24 °C) δ = 2.89 (t, 2, J = 5.9 Hz, C(4)H$_2$), 3.70 (t, 2, J = 5.9 Hz, C(3)H$_2$), 5.62 (br s, 1, C=C*H*H), 5.95 (br s, 1, C=CH*H*), 6.57 (s, 1), 7.13 (s, 1), 8.38 (s, 1, CHO).

1b: ^{1}H NMR (400 MHz, 24 °C) δ = 2.23 (s, 3, NCOCH$_3$), 2.83 (t, 2, J = 6.0 Hz, C(4)H$_2$), 3.88 (s, 3, C(6)OCH$_3$), 3.92 (s, 3, C(7)OCH$_3$), 3.98 (t, 2, J = 6.0 Hz, C(3)H$_2$), 4.97 (br s, 1, *cis*-CONC=CH), 5.61 (br s, 1, *trans*-CONC=CH), 6.60 (s, 1, C(5)-H), 7.09 (s, 1, C(8)H); ^{13}C NMR (100 MHz, 25 °C) δ = 22.21 (NCO*C*H$_3$), 28.33 (C(4)), 41.43 (C(3)), 55.67 (OCH$_3$), 55.81 (OCH$_3$), 104.01 (C(1)=*C*), 106.52 (C(8)), 111.04 (C(5)), 123.46 (C(8a)), 127.78 (C(4a)), 142.98 (C(1)), 147.50 (C(7)), 149.61 (C(6)), 169.07 (N*C*OCH$_3$).

Sickle-1b: ^{1}H NMR (400 MHz, −50 °C) δ = 2.23 (s, 3, NCOCH$_3$), 2.83 (t, 2, J = 5.9 Hz, C(4)H$_2$), 3.89 (s, 3, C(6)OCH$_3$), 3.93 (s, 3, C(7)OCH$_3$), 3.98 (t, 2, J = 5.9 Hz, C(3)H$_2$), 4.94 (d, 1, J = 1.5 Hz, *cis*-CONC=CH), 5.63 (s, 1, *trans*-CONC=CH), 6.60 (s, 1, C(5)H), 7.04 (s, 1, C(8)H).

U-1b: ^{1}H NMR (400 MHz, −50 °C) δ = 2.30 (s, 3, NCOCH$_3$), 2.90 (t, 2, J = 5.9 Hz, C(4)H$_2$), 3.81 (t, 2, J = 5.9 Hz, C(3)H$_2$), 5.37 (s, 1, C=C*H*H), 5.80 (s, 1, C=CH*H*), 6.58 (s, 1), 7.10 (s, 1).

2a: ^{1}H NMR (400 MHz, 26 °C) δ = 2.88 (t, 2, J = 5.9 Hz, C(4)-H$_2$), 3.86 (s, 3, C(3′)OCH$_3$ or C(4′)OCH$_3$), 3.87 (s, 3, C(3′)OCH$_3$ or C(4′)OCH$_3$), 3.89 (s, 3, C(6)OCH$_3$), 3.95 (s, 3, C(7)OCH$_3$), 3.99 (t, 2, J = 5.9 Hz, C(3)H$_2$), 6.61 (s, 1, C(5)H), 6.75 (s, 1, C(1)=CH), 6.83 (d, 1, J = 8.3 Hz, C(5′)H), 6.93 (d, 1, J = 2.0 Hz, C(2′)H), 6.97 (dd, 1, J = 8.3 and 2.0 Hz, C(6′)H), 7.20 (s, 1, C(8)H), 8.16 (s, 1, CHO); ^{13}C NMR (100 MHz, 26 °C) δ = 28.58 (C(4)), 38.24 (C(3)), 55.67 (2 OCH$_3$), 55.73 (OCH$_3$), 55.96 (OCH$_3$), 105.49 (C(8)), 111.36 (C(5′)), 111.45 (C(5)), 111.58 (C(2′)), 113.31 (C(1)=*C*), 121.54 (C(6′)), 123.45 (C(8a)), 127.22 (C(4a)), 127.69 (C(1′)), 132.44 (C-(1)), 147.83 (C(7)), 148.02 (C(4′)), 148.89 (C(3′)), 149.45 (C(6)), 162.66 (CHO).

2b: ^{1}H NMR (400 MHz, 21 °C) δ = 1.81 (s, 3, NCOCH$_3$), 2.64—2.76 (m, 1, C(4)*H*H), 3.10—3.23 (m, 2, C(3)*H*H and C(4)-H*H*), 3.88 (s, 3, OCH$_3$), 3.89 (s, 6, 2 OCH$_3$), 3.98 (s, 3, C(7)-OCH$_3$), 4.97—5.11 (m, 1, C(3)H*H*), 6.63 (s, 1, C(5)H), 6.72 (s, 1, C(1)=CH), 6.86 (d, 1, J = 9.3 Hz, C(5′)H), 7.06 (s, 1, C(2′)), 7.07 (d, 1, J = 9.3 Hz, C(6′)), 7.14 (s, 1, C(8)H); ^{13}C NMR (100 MHz, 22 °C) δ = 21.50 (NCO*C*H$_3$), 27.99 (C(4)), 41.41 (C(3)), 55.60 (OCH$_3$), 55.64 (OCH$_3$), 55.74 (OCH$_3$), 55.97 (OCH$_3$), 105.82 (C(8)), 110.57 (C(2′) or C(6′)), 111.14 (C(5′)), 111.55 (C(5)), 118.65 (C(1)=*C*), 121.26 (C(2′) or C(6′)), 125.51 (C(8a)), 127.67 (C(4a)), 128.05 (C-(1′)), 134.90 (C(1)), 147.49 (C(7)), 148.45 (C(4′)), 148.77 (C(3′)), 149.27 (C(6)), 169.77 (N*C*OCH$_3$).

2c: ^{1}H NMR (400 MHz, 26 °C) δ = 2.88 (dd, 1, J = 16.0 and 3.4 Hz, C(4)*H*H), 3.25 (ddd, 1, J = 16.0, 13.2, and 5.4 Hz, C(4)H*H*), 3.37 (ddd, 1, J = 13.2, 12.1, and 3.4 Hz, C(3)*H*H), 3.79 (s, 3, C(3′)-OCH$_3$), 3.89 (s, 3, C(4′)OCH$_3$), 3.93 (s, 3, C(6)OCH$_3$), 3.97 (s, 3, C(7)OCH$_3$), 5.12 (dd, 1, J = 12.1 and 5.4 Hz, C(3)H*H*), 6.33 (d, 1, J = 1.5 Hz, C(2′)H), 6.35 (s, 1, C(1)=CH), 6.60 (dd, 1, J = 8.3 and 1.5 Hz, C(6′)H), 6.70 (s, 1, C(5)H), 6.73 (d, 2, J = 8.3 Hz, *p*-BrC$_6$*H*$_2$H$_2$), 6.76 (d, 1, J = 8.3 Hz, C(5′)H), 7.06 (s, 1, C(8)H), 7.16 (d, 2, J = 8.3 Hz, *p*-BrC$_6$H$_2$*H*$_2$); ^{13}C NMR (100 MHz, 27 °C) δ = 29.06 (C(4)), 42.14 (C(3)), 55.70 (OCH$_3$), 55.89 (OCH$_3$), 55.94 (OCH$_3$), 56.20 (OCH$_3$), 105.74 (C(8)), 110.91 (C(2′)), 111.11 (C(5′)), 111.77 (C-(5)), 118.18 (C(1)=*C*), 120.90 (C(6′)), 123.80 (NCO*C* or *C*Br), 124.91 (C(8a)), 127.51 (C(4a)), 127.96 (C(1′)), 128.91 (2 NCO*C*C or 2 *C*CBr), 130.01 (2 NCOC*C* or 2 *C*CBr), 134.59 (NCO*C* or *C*Br), 135.00 (C(1)), 148.07 (C(7) and C(4′)), 148.88 (C(3′)), 149.68 (C-(6)), 168.39 (NCO).

2d: ^{1}H NMR (400 MHz, 25 °C) δ = 0.99 (br s, 9, COC(CH$_3$)$_3$), 2.55—2.75 (br s, 1, C(4)*H*H), 3.05—3.30 (br s, 2, C(3)*H*H and C(4)-H*H*), 3.88 (s, 3, OCH$_3$), 3.89 (s, 6, 2 OCH$_3$), 3.97 (s, 3, OCH$_3$), 5.03—5.20 (br s, 1, C(3)H*H*), 6.55 (s, 1, C(1)=CH), 6.61 (s, 1, C(5)-H), 6.85 (d, 1, J = 8.3 Hz, C(5′)H), 7.03 (s, 1, C(2′)H), 7.06 (dd, 1, J = 8.3 and 1.5 Hz, C(6′)H), 7.13 (s, 1, C(8)H); ^{13}C NMR (100 MHz, 22 °C) δ = 28.00 (C(4)), 28.54 (COC(*C*H$_3$)$_3$), 41.11 (CO*C*(CH$_3$)$_3$), 45.95 (C(3)), 55.71 (OCH$_3$), 55.75 (OCH$_3$), 55.79 (OCH$_3$), 56.09 (OCH$_3$), 106.25 (C(2′)), 110.90 (C(5′)), 111.27 (C(8)), 111.55 (C-(5)), 121.91 (C(1)=*C*), 122.10 (C(6′)), 127.33 (C(1) or C(4a)), 128.29 (C(1′)), 128.73 (C(8a)), 136.94 (C(1) or C(4a)), 147.57 (*C*OCH$_3$), 148.60 (*C*OCH$_3$), 148.65 (*C*OCH$_3$), 148.98 (*C*OCH$_3$) 178.08 (NCO).

Sickle-3a: ^{1}H NMR (400 MHz, 20 °C) δ = 2.90 (t, 2, J = 6.4 Hz, C(4)H$_2$), 3.40 (s, 3, CH$_3$O), 3.78 (s, 3, CH$_3$O), 3.83 (t, 2, J = 6.4 Hz, C(3)H$_2$), 3.88 (s, 6, 2 CH$_3$O), 6.37 (s, 1, C(1)=CH), 6.65 (s, 1, C(5)H), 6.79—6.90 (m, 4, aromatic), 8.71 (s, 1, CHO); ^{13}C NMR (100 MHz, 21 °C) δ = 28.48 (C(4)), 39.88 (C(3)), 55.30 (CH$_3$O),

55.78 (CH_3O), 55.82 (CH_3O), 55.90 (CH_3O), 110.54 (C(5)), 110.71 (C(8), C(2′), C(5′) or C(6′)), 111.14 (C(8), C(2′), C(5′) or C(6′)), 111.98 (C(8), C(2′), C(5′) or C(6′)), 116.20 (C(1)=*C*), 121.81 (C(8), C(2′), C(5′) or C(6′)), 123.09 (C(1), C(4a), C(8a) or C(1′)), 128.72 (C(1), C(4a), C(8a) or C(1′)), 129.27 (C(1), C(4a), C(8a) or C(1′)), 133.94 (C(1), C(4a), C(8a) or C(1′)), 146.57 (*C*$COCH_3$), 148.21 (*C*$COCH_3$), 148.80 (*C*$COCH_3$), 149.15 (*C*$COCH_3$), 160.86 (CHO).

U-3a: ^{1}H NMR (400 MHz, 20 °C) δ = 2.96 (t, 2, J = 5.9 Hz, C(4)H_2), 8.39 (s, 1, CHO).

Solid-State Structural Analysis. Colorless needle-like crystals of **2a** were obtained upon standing a solution in a 1 : 5 mixture of dichloromethane and ethanol (10 g/120 mL) at 0 °C for 24 h. An ORTEP drawing with a numbering scheme, crystallographic data, table of atomic parameters, anisotropic temperature factors, and a complete listing of the bond angles and distances for **2a** are deposited as Document No. 69030 at the Office of the Editor of Bull. Chem. Soc. Jpn. The crystal structures of **2c** and **2d**, along with complete listings of the atomic parameters, anisotropic temperature factors, bond distances, and bond angles were given in the Supplementary Material of Ref. 1a.

Ab Initio Calculation of 4. The calculations of molecular energies of **4** were performed on Silicon Graphics Indigo^2 at the restricted Hartree–Fock level using the 6-31G* basis set of Gaussian 92,[8] deducing the molecular energies of sickle-**4** and U-**4** to be −399.605717403 Hartree and −399.601285164 Hartree, respectively.

Determination of Energy Barrier of Interconversion between Enatiomers of 2c. A sample of **2c** (5.6 mg) was dissolved in dimethyl-d_6 sulfoxide (0.9 mL) in a 5-mm NMR tube, sealed, and subjected to a 400-MHz ^{1}H NMR analysis. The signals of the two protons at the C(4) position appeared at δ = 2.88 and 3.09 as multiplets, respectively, at 24 °C (297 K). When the spectra were taken at temperatures from 24 to 149 °C, the two signals merged into one broad signal at 100 °C (373 K). The rate constant of inversion (k_{inv}) was calculated using the Gutowsky–Holm equation (1), where $\delta\nu$ is the half width of a given coalescence signal,

$$k_{inv} = \frac{\pi\delta\nu}{\sqrt{2}}. \quad (1)$$

Substitution of $\delta\nu$=61 Hz afforded $k_{inv} = 1.4\times10^2$ s^{-1}. With the Eyring's method, the energy barrier for the enantiomer interconversion was calculated to be 74 kJ mol^{-1}. The reliability of these values was confirmed as follows. The ABXY four-spin system consisting of C(4)H, C(4)H′, C(3)H, and C(3)H′ was simulated by a lineshape analysis program, DNMR-SIM,[9] with the following fixed parameters at 297 K: $J_{C(4)H-C(3)H}$=3.9 Hz, $J_{C(4)H-C(3)H'}$=0.0 Hz, $J_{C(4)H'-C(3)H}$=12.3 Hz, $J_{C(4)H'-C(3)H'}$=5.4 Hz, $J_{C(4)H-C(4)H'}$=16.8 Hz, and $J_{C(3)H-C(3)H'}$=12.3 Hz; δ=2.88 (C(4)H), δ=3.10 (C(4)H′) δ=3.33 (C(3)H), δ=4.89 (C(3)H′); T_2=0.5 s. The spectrum generated by varying the k_{inv} value well fitted the experimental one with k_{inv}=8.0 s^{-1}, showing $\Delta G^{\ddagger}$=68 kJ mol^{-1}. The observed spectra at temperatures below 343 K were in good accordance with a simulation performed on the assumption that the coupling constants and T_2 values are temperature-independent, while some deviation occurred above 343 K, probably due to the T_2 effect. Thus, the rate constant and the activation-free energy at 373 K were roughly estimated to be 6.6×10 s^{-1} and 79 kJ mol^{-1}, respectively, on the basis of the activation parameters, $\Delta H^{\ddagger}$=23 kJ mol^{-1} and $\Delta S^{\ddagger}$=−150 J mol^{-1} K^{-1}, which were obtained by an Eyring plot using reliable k_{inv} values: 8.0 s^{-1} at 297 K, 14 s^{-1} at 313 K, 19 s^{-1} at 323 K, 23 s^{-1} at 333 K, and 30 s^{-1} at 343 K.

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References

1) a) R. Noyori, M. Ohta, Yi Hsiao, M. Kitamura, T. Ohta, and H. Takaya, *J. Am. Chem. Soc.*, **108**, 7117 (1986); b) M. Kitamura, Yi Hsiao, R. Noyori, and H. Takaya, *Tetrahedron Lett.*, **28**, 4829 (1987); c) M. Kitamura, Yi Hsiao, M. Ohta, M. Tsukamoto, T. Ohta, H. Takaya, and R. Noyori, *J. Org. Chem.*, **51**, 297 (1994). BINAP=2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.

2) a) R. Noyori and M. Kitamura, "Modern Synthetic Methods," ed by R. Scheffold, Springer-Verlag, Berlin (1989), p. 115; b) R. Noyori, *Chem. Soc. Rev.*, **18**, 187 (1989); c) R. Noyori, *Science*, **248**, 1194 (1990); d) R. Noyori and H. Takaya, *Acc. Chem. Res.*, **23**, 345 (1990); e) R. Noyori, *CHEMTECH*, **22**, 360 (1992).

3) Notable exceptions: a) A. Jössang, M. Lebœuf, A. Cavé, M. Damak, and C. Riche, *C. R. Acad. Sc. Paris, Série C*, **1977**, 467; b) T. Nozaka, I. Morimoto, M. Ishino, T. Okitsu, H. Kondoh, K. Kyogoku, Y. Sugawara, and H. Iwasaki, *Chem. Pharm. Bull.*, **35**, 2844 (1987).

4) For structural studies of the amide linkage in crystalline state or solution, see: C. J. Brown, *Acta Crystallogr.*, **21**, 442 (1966); B. F. Pedersen, *Acta Chem. Scand.*, **21**, 1415 (1967); G. V. Garner, O. Meth-Cohn, and H. Suschitzky, *J. Chem. Soc. C*, **1971**, 1234; T. Kojima, T. Kido, H. Itoh, T. Yamane, and T. Ashida, *Acta Crystallogr., Sect. B*, **B36**, 326 (1980); E. Subramanian and R. Parthasarathy, *Int. J. Pept. Protein Res.*, **33**, 345 (1989); A. Itai, Y. Toriumi, N. Tomioka, H. Kagechika, I. Azumaya, and K. Shudo, *Tetrahedron Lett.*, **30**, 6177 (1989); Q.-P. Wang, A. J. Bennet, R. S. Brown, and B. D. Santarsiero, *J. Am. Chem. Soc.*, **113**, 5757 (1991); A. Itai, Y. Toriumi, S. Saito, H. Kagechika, and K. Shudo, *J. Am. Chem. Soc.*, **114**, 10649 (1992); A. Greenberg and C. A. Venanzi, *J. Am. Chem. Soc.*, **115**, 6951 (1993). For theoretical studies, see: S. Tsuzuki and K. Tanabe, *J. Chem. Soc., Perkin Trans. 2*, **1991**, 1255; K. B. Wiberg and C. M. Breneman, *J. Am. Chem. Soc.*, **114**, 831 (1992); S. Saito, Y. Toriumi, N. Tomioka, and A. Itai, *J. Org. Chem.*, **60**, 4715 (1995). Reviews: L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca (1948); J. Zabicky, "The Chemistry of Amides," Interscience Publishers, London (1970).

5) M. Ōki, "Applications of Dynamic NMR Spectroscopy to Organic Chemistry," in "Methods in Stereochemical Analysis," ed by A. P. Marchand, Verlag-Chemie, Weinheim (1985), Vol. 4. For the original paper, see: H. Eyring, *Chem. Rev.*, **17**, 65 (1935).

6) A. Brossi, L. A. Dolan, and S. Teitel, *Org. Synth.*, **56**, 3 (1977).

7) J. S. Buck, R. D. Haworth, and W. H. Perkin, *J. Chem. Soc.*, **125**, 2176 (1924).

8) M. J. Frisch, G. W. Trucks, M. Head-Gordon, P. M. W. Gill, M. W. Wong, J. B. Foresman, B. G. Johnson, H. B. Schlegel, M. A. Robb, E. S. Replogle, R. Gomperts, J. L. Andres, K. Raghavachari, J. S. Binkley, C. Gonzalez, R. L. Martin, D. J. Fox, D. J. Defrees, J. Baker, J. J. P. Stewart, and J. A. Pople, "Gaussian-92," Gaussian Inc., Pittsburgh, PA (1992).

9) R. Fuhler, T. Lenzen, and G. Hägele, *Comput. Chem.*, **19**, 277 (1995).