  Bull. Chem. Soc. Jpn., 56, 1487—1489 (1983)

Conformations and Restricted Rotation about Amide C–N Bonds of 2,2-Dichloro-1′-formyl-3′,4′-dihydrospiro[cyclopropane-1,2′(1′*H*)-quinoline] and Related Compounds

Hiroko Suezawa (née Endo), Minoru Hirota,* Michiharu Sugiura,† and Yoshiki Hamada†

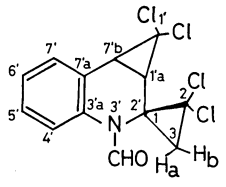
Department of Applied Chemistry, Faculty of Engineering, Yokohama National University, Hodogaya-ku, Yokohama 240

† *Faculty of Pharmacy, Meijo University, Tempaku-ku, Nagoya 468*

(Received November 5, 1982)

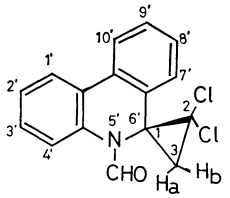
Conformational preference and rotational barriers of 1′,1′,2,2-tetrachloro-3′-formyl-1′a,7′b-dihydrospiro-[cyclopropane-1,2′(3′*H*)-cyclopropa[*c*]quinolines] (**1**) and related *N*-formyl heterocyclic compounds were determined by ^{1}H- and ^{13}C-NMR spectroscopy. The *sp*-conformer is usually more preferable in **1** and their rotational barriers about amide C–N bond are within a relatively narrow range from 70.7 to 72.8 kJ mol^{-1}. Infrared carbonyl absorptions of these compounds also support the preferred conformation from the NMR data. The results were discussed from the view point of N–C=O conjugation.

In the course of investigations on mono- and diazanaphthalenes and related heterocycles, a new synthesis of cyclopropa[*c*]quinolines,[1] 2,2-dichloro-1′-formylspiro-[cyclopropane-1,2′(1′*H*)-quinoline] and related heterocyclic amides[2,3] have been reported by the present authors. Steric effect on the conformations and dynamic behaviors of these amides are very interesting, since they have sterically hindered *N*-formyl groups. The rotational barriers of amides have been studied very extensively, and a great deal of investigations have been reported.[4] One of the present authors has also studied the effect of intramolecular hydrogen bonding on the rotational barrier of *N*,*N*-dimethylbenzamide.[5] In this connection, the conformational preference and rotational barriers of 1′,1′,2,2-tetrachloro-3′-formyl-1′a,7′b-dihydrospiro[cyclopropane-1,2′(3*H*)-cyclopropa[*c*]quinolines] (**1**), 2,2-dichloro-5′-formylspiro[cyclopropane-1,6′(5′*H*)-phenanthridine] (**2**), and related compounds were determined and discussed from the view of the ring-conformation and steric hindrance on the amide group in this paper.



1

a: Unsubstituted
b: 6′-CH_3 d: 7′-CH_3
c: 6′-C_2H_5O e: 7′b-CH_3



2

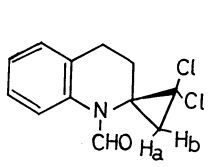
a: Unsubstituted
b: 3-CH_3

Experimental

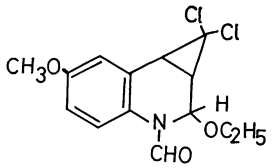
Preparation and identification of the materials were reported previously.[1-3,6] Commercially available spectro grade solvents were used without further purification. Temperature-dependent ^{1}H-NMR spectra were recorded on a JEOL JNM C-60H spectrometer. The exchange rates between the two sites (usually unequivalent) were evaluated by use of total line shape analysis program. NOE measurements were carried out with a JEOL JMN FX-90Q spectrometer. Infrared spectra were measured on carbon tetrachloride solutions using a Hitachi 225 infrared spectrophotometer.

Results and Discussion

Rotational Barriers about the C–N Bonds of N-*Formyl Groups and Conformational Preference.* In order to examine steric and electronic effects on the rotational barrier of **1**, ^{1}H dynamic NMR measurements were carried out on the following compounds in addition to **1** and **2**.

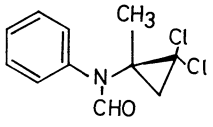


3

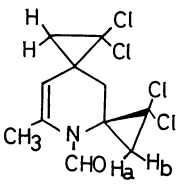


4

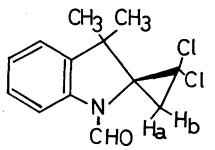
a: Unsubstituted
b: 3′-Br-4′-OCH_3



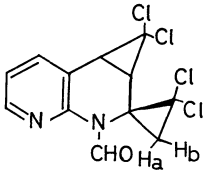
5



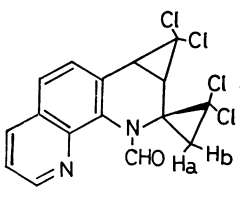
6



7



8



9

Table 1. ^{1}H-DNMR results (in $CDCl_3$) and infrared C=O absorptions (in CCl_4) of the heterocyclic amides **1**—**9**

Compd	CHO Chemical shift (Relative intensity)		T_c	ΔG^{*} [a]	$\nu_{C=O}$	
	sp	*ap*	K	kJ mol^{-1}	cm^{-1}	
1a	8.43(66)	8.30(34)	321.2	72.4	1709	1700 sh
1b	8.32(70)	8.21(30)	321	72.0	1708	1701 sh
1c	8.31(66)	8.23(34)	320	72.8	1706	1700 sh
1d	8.33(70)	**8.20**(30)	321	72.0	1709	1700 sh
1e	8.32(73)	8.20(27)	310	70.7	1709	1700 sh
2a	8.50(75)	8.45(25)	307.3	72.8	1702	1696 sh
2b	8.53(20)	8.41(80)	312.2	69.0	1697	1702 sh
3a	8.56(66)	8.45(34)	306	68.2	1696	1702 sh
3b	8.80(45)	**8.46**(55)	288.0	61.9	1708	1701 sh
4[b]	8.45(38)	8.65(62)[c]	363.2	80.8	1695	1701 sh
5	8.53(20)	8.44(80)	312	69.9	1700	1707 sh
6	**8.10**(35)[d]	**8.45**(65)[d]	324.8	70.7	1700	1707 sh
7	8.83(30)	**8.30**(70)	304.7	63.2	1687	1700 sh
8	9.05(100)[e]					
9	8.90(100)[e]					

a) ΔG^{*} values are always given with respect to the more stable conformer (at 298.2 K). b) In DMSO-d_6. c) Synperiplanar to ethoxyl group. d) With reference to vicinal CH_3 group. e) A sharp singlet at −60 °C.

The DNMR data including free energies of activation of these *N*-formyl azaheterocycles are given in Table 1, together with the chemical shift and intensity data at the temperatures below coalescence temperatures (T_c). Coalescence of the two formyl signals usually occurs near room temperature.

Since amide group has a tendency to take a planar conformation, the two different planar (or nearly planar) conformers ((A) and (B) in Fig. 1) are possible in these heterocyclic amide, each of which giving a separate formyl proton signal below T_c. With the compounds **1**—**6**, the signal at the lower field was assigned to the formyl proton *syn* to aromatic ring and the one at the higher field to the *anti* formyl proton. The assignment was ascertained by the nuclear Overhauser enhancement of *anti*-formyl proton by irradiation of 3-hydrogen atom (H_a) on the spirocyclopropane ring in some typical instances. Two formyl signals in **6** were assigned unambiguously by NOE

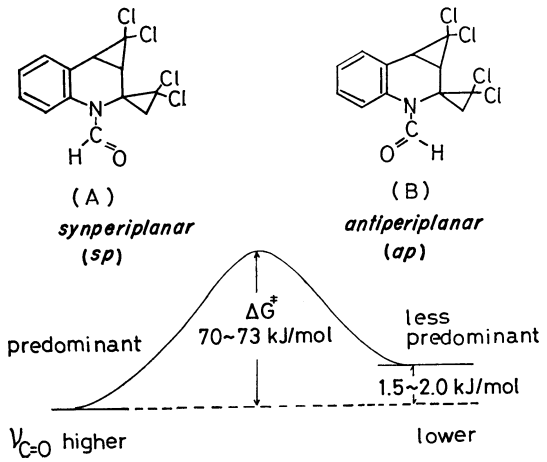


Fig. 1.

experiments irradiating both cyclopropyl methylene (H_a) and vicinal methyl groups (Chemical shifts given by bold letters in Table 1 were assigned by NOE.). The compound **1a** is expected to have a nearly planar and rather rigid tetrahydropyridine ring, because it has a fused cyclopropane ring on the 3 and 4 positions (1′a and 7′a positions of the new ring system). Thus the spirocyclopropane ring lies nearly perpendicular to the heterocyclic ring and facing to the formyl group. The *sp*-conformation is generally more stable than the *ap*-conformation in **1a**—**d**, the free energy difference between the two conformers being 1.5—2.0 kJ mol^{-1}. Since several evidence concerning the steric hindrance of *peri*(8)-hydrogen atom towards the planarity of 1-carbonyl group on the naphthalene nucleus have been reported,[8] the destabilizing effect due to *peri*-hydrogen might be the reason for the preference of *sp*-conformer in **1a**—**d**. Introduction of electron-donating substituent *para* to the formamide moiety on the aromatic ring is expected to lessen the resonance contribution by the aromatic ring and to increase the rotational barrier of the C–N bond. However, the ΔG^{*} values of **1b**—**d** agree with that of **1a**, showing no indication of substituent effect. Methyl substituent on 7′a-position in **1e** again does not affect the rotational barrier considerably. The ΔG^{*} and the conformational ratios of **2** are also very close to those of **1**. This can be another evidence for the nearly planar ring conformation of **1**.

^{13}C-NMR data of **1** and **2** are given in Table 2. These compounds have two separate signals in the carbonyl region. Since the formyl carbon atom is not expected to be displaced considerably by rotating the formyl group around the C–N bond, through-space field and anisotropy effect is assumed to be nearly identical on the carbonyl carbon atoms of the both conformers. Therefore, the difference in chemi-

Table 2. ^{13}C-Chemical shifts

Orientation of C=O group	*sp*-Conformer Towards dichloro-cyclopropropyl	*ap*-Conformer Towards aromatic ring
1b	164.5	160.9
1c	164.5	160.9
1e	164.9	160.9
2a	162.7	160.4
2b	162.4	160.4
3a	163.5	160.9
9	167.7	—

cal shifts should arise from the change in conjugation effect through C–N bond. This can be another evidence for the steric hindrance in different degrees to the planarity of conformers of **1** and **2**.

The rotational barriers of **3a**, **5**, and **6** (68.2, 69.2, and 70.7 kJ mol^{-1}, respectively) are almost similar to those of **1** and **2**, suggesting the similarity in conformations around the formyl groups of these compounds. Dispiro[cyclopropane-1,2′(1′*H*)-pyridine-4′,(3′*H*) 1″-cyclopropane] (**6**) is void of fused aromatic ring. However, it is reasonable that its ΔG^* value is almost identical with those of **1**, since the steric effect by *ortho*-methyl group is nearly equivalent to that of *peri*-hydrogen atom as evidenced by other experiments of the authors.[9] *N*-(2,2-Dichloro-1-methylcyclopropyl)formanilide also supposed to take a nearly planar conformation to keep the cross-conjugated amide system including cyclopropyl moiety. 1′-Formyl-3′,3′-dimethylspiro[cyclopropane-1,2′-indoline] (**7**) has a considerably low rotational barrier about the amide C–N bond. It is quite unexpected since the steric hindrance to the planarity seems less in this five-membered analog **7**. The rotational barrier about the similar bond of *N*-formylindoline has however been reported to be 64.8 kJ mol^{-1},[10] which is very close to the ΔG^* of **7**.

As a model for a formanilide in which aryl–nitrogen conjugation is forbidden perfectly by steric hindrance, the rotational barrier of *N*,2′,6′-trimethylformanilide (**10**) was determined to be 77.0 kJ mol^{-1}. The barrier is considerably high. This fact can be interpreted that the steric inhibition of Ar–N conjugation enhances the effect of N–C=O conjugation, resulting higher $C_{carbonyl}$–N bond order. The barriers of **1** and **2** are considerably lower than that of **10**. This implies the persistence of conjugative effect by aromatic system in **1** and other compounds of similar ΔG^* values, in spite of considerable deviation from the planarity and cross-conjugative effect by the carbonyl group.

The Infrared Carbonyl Frequency and Conjugative Effect. Frequencies (in cm^{-1}) of the carbonyl stretching absorption bands of **1**—**9** are given in Table 1. Carbonyl stretching frequency of amide is affected most remarkably by the amount of resonance contribution of mesomeric structure D. The contribution of D is suppressed both by the loss of the planarity of N–C=O system and the neighbor electronegative group repelling the negative charge on the carbonyl oxygen atom. In the case of the heterocyclic amide carrying spiro(dichlorocyclopropane)moiety (**1**, **3**, **5**, and **6**), the carbonyl group *syn* to the cyclopropane moiety absorbs at 1707—1709 cm^{-1}, considerably higher frequency than normal formanilide (for example, 1686 cm^{-1} for $C_6H_5NMeCHO$ (**11**)). The high frequency shift can be attributed to the neighbor electronegative group effect, in a through space manner, by the dichlorocyclopropane moiety. The carbonyl group opposing to *peri*-hydrogen atom generally absorbs at 1700—1701 cm^{-1}. The frequency is also considerably higher than that of **11**, suggesting the deviation from the planarity in this conformer. Intensities of the two carbonyl bands (in Table 1) agree qualitatively with the abundances of the two conformers which are estimated from the intensities of their ^{1}H signals at low temperatures (Table 1). Both carbonyl bands of the phenanthridine derivatives **2** shifts to *ca.* 5 cm^{-1} lower frequencies than the corresponding bands of **1**. Low frequency shifts are also observed with the carbonyl bands of **4** which is void of dichlorocyclopropane moiety. *N*-Formyltetrahydro-1,8-naphthyridine derivative **8** shows a single formyl signal at a very low field (9.05 ppm) in ^{1}H-NMR and also a symmetrical carbonyl band at 1712 cm^{-1}. This behavior is best explained by assuming that the *sp*-conformer is extremely stable, probably because of the electrostatic repulsive force between the lone pair electrons on heteroaromatic nitrogen and on carbonyl oxygen. Weak hydrogen bond-like attractive interaction between formyl hydrogen and lone pair electrons on heteroaromatic nitrogen is also possible.

The authors are grateful to Dr. Kazuhisa Abe for his kind advice and assistance throughout this work. This research was supported in part by the Grant-in-Aid for Special Project Research from the Ministry of Education, Science and Culture.

References

1) M. Sugiura, Y. Hamada, and M. Hirota, *Chem. Pharm. Bull.*, **27**, 1518 (1979).
2) Y. Hamada and M. Sugiura, *Yakugaku Zasshi*, **100**, 168 (1980).
3) Y. Hamada, M. Sugiura, and M. Hirota, *Tetrahedron Lett.*, **22**, 2893 (1981).
4) For review, see L. M. Jackman, "Dynamic Nuclear Magnetic Resonance Spectroscopy," ed by L. M. Jackman and F. A. Cotton, Academic Press, New York (1975), pp. 204—215.
5) M. Hirota and K. Todokoro, *Chem. Lett.*, **1974**, 777.
6) Y. Hamada and M. Sugiura, Preprint of the Tokai Regional Meeting of the Pharmaceutical Society of Japan, Nagoya, Oct. 1981, p. 108.
7) The conformations A and B (in Fig. 1) was named synperiplanar (*sp*) and antiperiplanar (*ap*), respectivily, with reference to the orientation of carbonyl oxygen to spirodichloropropane ring.
8) M. Ōki, M. Hirota, and S. Hirofuji, *Spectrochem. Acta*, **22**, 1537 (1966) and cited therein. On the steric effect of similar type in carbonium ions, see H. C. Brown, "Steric Effects in Conjugated System," ed by G. W. Gray Butterworths Publ. Ltd., London(1958), p. 103.
9) Y. Nagawa, M. Ono, M. Hirota, Y. Hamada, and I. Takeuchi, *Bull. Chem. Soc. Jpn.*, **49**, 1322 (1976); T. Kogane, R. Hirota, K. Abe, and M. Hirota, *J. Chem. Soc., Perkin Trans. 2*, **1981**, 652.
10) O. Buchardt, P. L. Kumler, and C. Lohse, *Acta Chem. Scand.*, **23**, 1155 (1969).