# Dynamic Behavior of Cyclic Hemiacetals of 2-Hydroxy-2-(2-hydroxyphenyl)-1,3-indandione Derivatives

Suzumi Hashimoto, Natsumi Sakuma, Hidetsugu Wakabayashi, Hiroshi Miyamae, and Keiji Kobayashi*
*Department of Chemistry, Graduate School of Material Science, Josai University, Sakado 350-0295*

(Received April 7, 2008; CL-080357; E-mail: kobayak@josai.ac.jp)

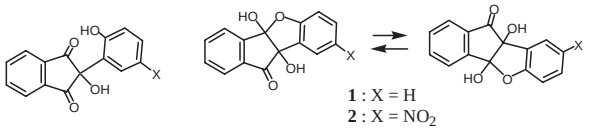
Dynamic interconversion between the two enantiomeric hemiacetal structures in acetonitrile was revealed from the variable-temperature $^1$H NMR spectra for the compounds obtained by the reaction of ninhydrin with phenol and *p*-nitrophenol.

Intramolecular cyclic hemiacetals generally equilibrate to their ring-opened carbonyl–alcohol tautomer in solution. Both ring-closed and ring-opened forms coexist regardless of their relative population. Glucose is a typical example, which is in equilibrium between anomeric $\alpha$- and $\beta$-hemiacetals through a trace amount of the ring-opened form. The equilibration is slow and kinetically led to a static equilibrium composition. In contrast, the dynamic equilibrium between ring-opened and ring-closed tautomers is rarely encountered for intramolecular hemiacetal structures.

The Friedel–Crafts reaction of ninhydrin with phenols preferentially undergoes ortho-selective reactions to form 2-hydroxy-2-(2-hydroxypheny)-1,3-indandiones. According to the literature, these products exist exclusively in cyclic hemiacetal structures as a result of static equilibrium.[1] In this study, we demonstrate the existence of a novel dynamic equilibrium between an enantiomeric pair of the intramolecular hemiacetals via the ring-opened form. Such behavior was observed in the reaction products of ninhydrin with phenol and *p*-nitrophenol, referred to as **1** and **2**, respectively (Scheme 1). It is rather surprising that this dynamic nature of **1** has been overlooked so far despite of the extensive investigation of this compound.[1]

The crystalline product obtained by the reaction of ninhydrin with phenol has been confirmed by X-ray analysis to be benz[*b*]indeno[2,1-*d*]furan-10-one derivative **1**,[2] which corresponds to an intramolecular hemiacetal of 2-hydroxy-2-(2-hydroxyphenyl)-1,3-indandione (Figure 1). However, the $^1$H NMR spectrum of **1** was not able to be exactly attributed to a cyclic hemiacetal structure; a hemiacetal structure should display four nonequivalent signals for the protons of the 1,3-indandione moiety, whereas only two broad signals were observed for those at ambient temperature in acetonitrile. A decrease in temperature resulted in the splitting of the two broad signals into four signals at about $-45\,^\circ$C (Figure 2a). The signals due to hydroxy protons at 5.3 ppm also underwent splitting into two broad signals at a temperature as low as $-40\,^\circ$C (Figure 3).

These results are interpreted in terms of the involvement of a dynamic internal conversion between the enantiomeric pairs of




**Scheme 1.**

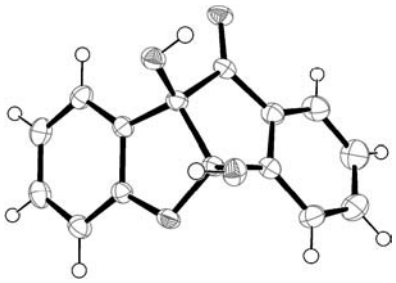


**Figure 1.** X-ray structure of **1**.

the ring-closed form of **1** in solution, resulting in a time-averaged structure of $C_s$ symmetry. Alternatively, the dynamic behavior is attributed to a conformational interconversion of the ring-opened form by exchanging intramolecular hydrogen-bonding sites without forming a covalent bond. The time averaging of this motion would also give rise to observable temperature-dependent behavior. However, the chemical shifts of the hydroxy protons at 5–6 ppm are consistent with those of non-hydrogen-bonded hydroxy protons. Thus, the molecular motion observed here is not attributed to an exchange of the hydrogen-bonding sites in the ring-opened form but to the interconversion of the cyclization sites. The ring-opened form was not observed in a whole range of temperature. The activation free energy ($\Delta G^\ddagger$) was roughly estimated to be 52 kJ·mol$^{-1}$ at $-10\,^\circ$C by the coalescence temperature ($T_c$) method based on the chemical shift difference between the two signals ($\Delta\nu = 113$ Hz) in the indan moiety.[3] The spectrum reverted to the original state upon warming.

Another example showing the dynamic nature of intramolecular hemiacetal structures was found in the reaction product of ninhydrin with *p*-nitrophenol, benz[*b*]indeno[2,1-*d*]furan-10-one derivative **2**. The $^1$H NMR spectrum of **2** in $CDCl_3$ indicates that the ring-closed hemiacetal structure and the ring-opened tautomer coexist in a ratio of 10:3 and the former is not in dynamic equilibrium between its enantiomeric structures.[4] However, in $CD_3CN$, only the ring-closed form under interconversion was observed. Thus, the remarkably broad signals from 7.5 to 8.0 ppm, which are assignable to the protons of the indan subunit, varied to two doublet and two triplet peaks at approximately $-30\,^\circ$C (Figure 2b), indicating the involvement of dynamic behavior in the ring-closed form of **2**.

Among the variety of alkyl-substituted derivatives prepared in our study,[5] no compounds exhibited the dynamic phenomenon except for **1** and **2**. Why did **1** and **2** exhibit dynamic nature? To answer this question is difficult at this stage. At least for the nitro compound **2**, which contains a hydroxy group of high acidity, consequently, of low nucleophilicity, the energy of the ring-closed form relative to that of the ring-opened form would

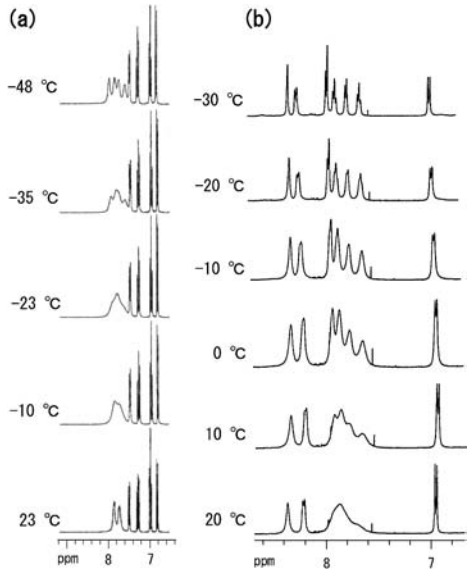



**Figure 2.** (a) Temperature-dependent $^1$H NMR spectra of **1** in $CD_3CN$. (b) Temperature-dependent $^1$H NMR spectra of **2** in $CD_3CN$.

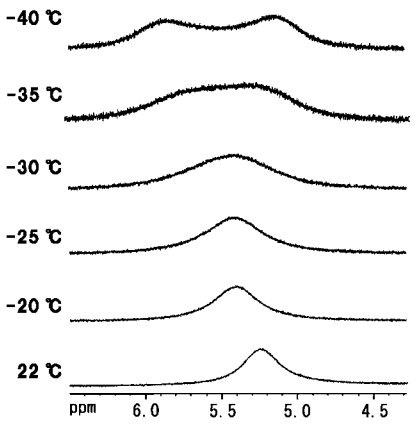



**Figure 3.** Temperature dependence of the $^1$H NMR signals of the OH protons of **1** in $CD_3CN$.

be raised, thus making the barrier for cyclization lower.

It should be noted that the equilibrium is sensitive to the solvent used. This might be a reason for overlooking the dynamic nature of **1**. When DMSO was used as a solvent at ambient temperature, a significant change in the NMR spectrum of **1** was observed: the two broad signals due to the indan subunit changed to two well-separated doublet and triplet sets, indicating that the interconversion had frozen. Furthermore, signals ascribable to the ring-opened form of **1** occurred with relative integral intensities of 32%. The involvement of the ring-opened form is evident from the broad singlet signal due to the four aromatic protons of the 1,3-indandione moiety.[6] The coexistence of the ring-opened form and the fixation of the hemiacetal structure in DMSO can be interpreted as being due to the strong hydrogen-bonding ability of DMSO which may stabilize the ground state of the hemiacetal tautomers, particularly, those of the ring-opened form, because of the intervention of its phenolic hydroxy group. When the NMR spectrum was measured at 120 °C in DMSO-$d_6$, the signals broadened appreciably but did not result in coalescence, indicating that even at 120 °C the dynamic equilibrium is suppressed in DMSO. At 120 °C the population of the ring-opened form is slightly increased to 39%, indicating that the energy ($\Delta H$) difference between the ring-opened and ring-closed forms is not significant in DMSO. The same interpretation is thought to hold for the behavior of **2** observed when the solvent was changed from chloroform to acetonitrile.

In summary, compounds **1** and **2** were in dynamic interconversion between their enantiomeric hemiacetal structures in acetonitrile at room temperature. In DMSO for **1** and in chloroform for **2**, the ring-opened structures occurred in appreciable quantities along with the ring-closed form, whereas the latter was not in dynamic motion.

## References and Notes

1 a) J.-P. Poupelin, G.-S. Ruf, J.-C. Perche, J.-C. Roussey, B. Laude, G. Narcisse, F. B.-Logeais, F. Hubert, *Eur. J. Med. Chem.* **1980**, *15*, 253. b) J.-P. Poupelin, G.-S. Ruf, J.-C. Perche, R. Lacroix, G. U-Ernouf, G. Narisse, F. Hubert, *Eur. J. Med. Chem.* **1979**, *14*, 171. c) H. N. Song, H. J. Lee, H. R. Kim, E. K. Ryu, J. N. Kim, *Synth. Commun.* **1999**, *29*, 3303. d) H. N. Song, M. R. Seong, H. J. Lee, J. N. Kim, *Synth. Commun.* **1999**, *29*, 2759. e) J. L. Bullington, J. H. Dodd, *J. Org. Chem.* **1993**, *58*, 4833. f) S. Das, R. Frohlich, A. A. Pramanik, *Org. Lett.* **2006**, *8*, 4263. g) J. E. Na, K. Y. Lee, J. Seo, J. N. Kim, *Tetrahedron Lett.* **2005**, *46*, 4505.

2 Crystal data of **1**: $C_{15}H_{10}O_4$, triclinic, space group $P\bar{1}$(#2), $a = 7.7910(2)$, $b = 9.0677(2)$, $c = 9.1110(3)$ Å, $\alpha = 70.857(3)^\circ$, $\beta = 84.833(4)^\circ$, $\gamma = 81.713(3)^\circ$, $Z = 2$, $V = 601.09(3)$ Å$^3$, $D_{calc} = 1.405$ g/cm$^3$, $R_1$ ($I > 3.00\sigma(I)$) 0.044, $wR_2$ ($I > 3.00\sigma(I)$) 0.065. CCDC 679076.

3 This value is a rough estimation, because the coalescence method based on the interconversion between two equivalent sites is applicable to two signals without spin-coupling. The OH signals shown in Figure 3 cannot be used for estimation of $\Delta G^{\ddagger}$ because the frozen spectrum is not available at −40 °C owing to proton-exchangeability.

4 For the ring-closed form of **2**: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.92 (d, $J = 9$ Hz, 1H), 7.62 (t, $J = 9$ Hz, 1H), 7.83 (d, $J = 9$ Hz, 1H), 7.84 (t, $J = 9$ Hz, 1H), 7.96 (d, $J = 9$ Hz, 1H), 8.24 (dd, $J = 9$ Hz, 2 Hz, 1H), 8.46 (d, $J = 2$ Hz, 1H). For the ring-opened form of **2**: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.07 (d, $J = 9$ Hz, 1H), 7.95 (d, $J = 3$ Hz, 1H), 7.96 and 8.08 (AA′BB′, 4H), 8.16 (dd, $J = 9$ Hz, 3 Hz, 1H).

5 The reactions of ninhydrin with phenols such as 3-*tert*-butylphenol, 4-*tert*-butylphenol, 3-isopropylphenol, 5-methylresorcinol, and 4-phenylphenol were carried out and their hemiacetal products showed no dynamic behavior.

6 For the ring-closed form of **1**: $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 6.70 (s, 1H, OH), 6.81 (d, $J = 8$ Hz, 1H), 6.94 (t, $J = 9$ Hz, 1H), 7.25 (t, $J = 8$ Hz, 1H), 7.42 (d, $J = 8$ Hz, 1H), 7.62 (t, $J = 8$ Hz, 1H), 7.72 (d, $J = 8$ Hz, 1H), 7.89 (t, $J = 8$ Hz, 1H), 7.97 (d, $J = 8$ Hz, 1H), 8.05 (s, 1H, OH). For the ring-opened form of **1**: $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 6.60 (d, $J = 8$ Hz, 1H), 6.92 (t, $J = 8$ Hz, 1H), 7.10 (s, 1H, OH), 7.15 (t, $J = 8$ Hz, 1H), 7.64 (d, $J = 8$ Hz, 1H), 8.0–8.03 (broad s, 4H).

Published on the web (Advance View) May 31, 2008; doi:10.1246/cl.2008.696