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On the Structure of "5-Nitrosotropolone"

Ai Ito, Hideaki Muratake, and Koichi Shudo*

Research Foundation Itsuu Laboratory, 2-28-10 Tamagawa, Setagaya-ku, Tokyo 158-0094, Japan

kshudo@itsuu.or.jp

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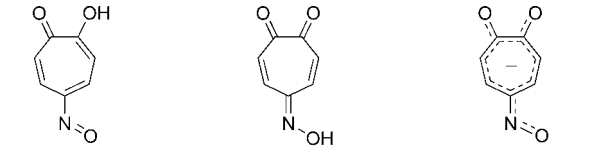


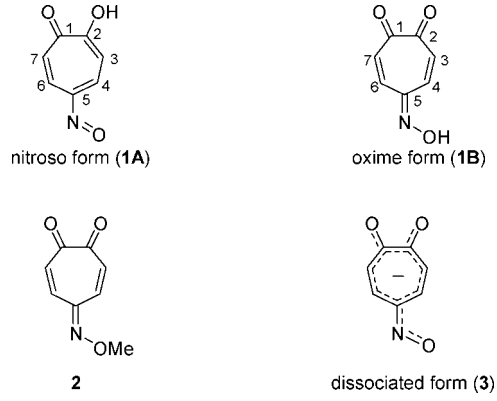
It has long been discussed whether "5-nitrosotropolone" **1** takes the nitroso structure **1A** or the tautomeric oxime structure **1B**. Analysis of NMR and UV spectra data in this study indicates that the tropoquinone-5-monoxime **1B** is preferred. The UV absorption shift to longer wavelength at dilute solutions is attributable to the dissociated form **3**.

Introduction

Tropolone (2-hydroxy-2,4,6-cycloheptatrien-1-one) is a non-benzenoid aromatic compound having a flat seven-membered ring that shows cycloheptatrienylium ion character. The chemical properties of tropolone are well documented.[1] Its behavior is intermediate between those of phenol, β-diketones, and benzoic acid: it is readily halogenated and reacts with a diazonium ion like phenol, but does not react readily with most electrophilic reagents used in the Friedel−Crafts, Gattermann, and Kolbe−Schmidt reactions, and it can be regarded as a vinylogous carboxylic acid.[2]

Nitrosation of tropolone with sodium nitrite in acetic acid proceeds smoothly, and "5-nitrosotropolone" **1** is obtained in good yield.[1,3] This is a key compound that can be derivatized to various 5-substituted tropolones,[3,4] such as 5-amino, 5-halo, and 5-carboxyl and further to 5-aryl and 5-heterocyclic substituted compounds. Whether the compound exists as the nitroso structure **1A** or its tautomeric oxime structure **1B** has long been discussed (Scheme 1). Nozoe et al. supported the nitroso structure **1A** based on the UV spectra, though "5-nitrosotropolone" undergoes reactions characteristic of **1B**.[1,5] Ikegami and Asao also reported that the nitroso structure **1A** is dominant, based on ESR and NMR studies.[6]

SCHEME 1



In this paper, we carefully investigated the structure of "5-nitrosotropolone" by means of NMR and UV spectral methods, and concluded that it exists in the form of tropoquinone-5-monoxime **1B**, rather than 5-nitrosotropolone **1A**.

Results and Discussion

NMR Spectra of "5-Nitrosotropolone" 1. The ^{1}H NMR spectrum of "5-nitrosotropolone" **1** in DMSO-d_6 (Figure 1, spectrum A) was compared with that in CD_3OD (Figure 2,

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(4) (a) Nozoe, T.; Mukai, T.; Kunori, M.; Muroi, T.; Matsui, K. *Sci. Rep. Tohoku Univ., First Ser.: Chem.* **1951**, *35*, 242–259. (b) Nozoe, T.; Seto, S.; Ito, S.; Sato, M. *Proc. Jpn Acad.* **1951**, *27*, 426–429. (c) Cook, J. W.; Loudon, J. D.; Steel, D. K. V. *J. Chem. Soc.* **1954**, 530–535.

(5) Nozoe, T.; Sato, M.; Matsuda, T. *Sci. Rep. Tohoku Univ., First Ser.: Chem.* **1954**, *37*, 407–421.

(6) Ikegami, Y.; Asao, T. *Chem. Lett.* **1974**, 805–808.

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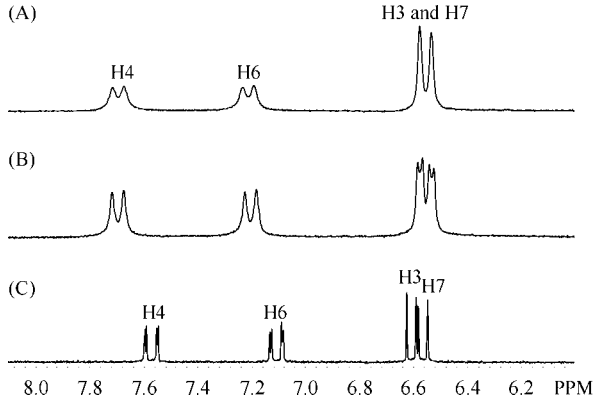


FIGURE 1. ^{1}H NMR spectra of **1** and **2** in DMSO-d_6: (A) **1**; (B) **1** with CF_3COOD (3 equiv); and (C) **2**. Proton numberings are shown in Scheme 1.

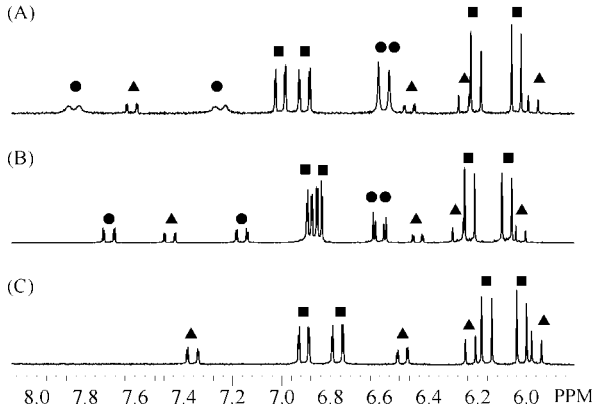


FIGURE 2. ^{1}H NMR comparison of "5-nitrosotropolone" **1** (A), methyl oxime **2** (B), and a mixture of dimethyl ketal **6a** and **6b** (C) in CD_3OD. Circles show tropoquinone oxime species, triangles and squares show respectively *E* (**4a**, **5a**, **6a**) and *Z* (**4b**, **5b**, **6b**) conformational ketal species, which are formed spontaneously in CD_3OD.

spectrum A). The spectrum in DMSO-d_6 could be interpreted in terms of structure **1A** with restricted rotation between the carbon and the N═O group or the oxime structure **1B**. However, the spectrum in CD_3OD could not be simply explained by **1A** or **1B**, but indicated the existence of other species.

Synthesis and NMR Spectra of Methyl Oxime 2. Nozoe et al. reported that treatment of **1** with diazomethane failed to give a methylated compound, yielding only a resinous product.[1,3e] In this experiment, methylation of **1** in acetonitrile with methyl iodide in the presence of potassium carbonate gave only the methylated compound **2** (Scheme 1), though the isolated yield was poor (20−26%). It was necessary to stop the reaction even though some starting material remained, because **2** was unstable under the reaction conditions. We could not crystallize **1**, obtaining only pseudocrystals, but **2** crystallized as prisms, and X-ray crystallographic analysis revealed the tropoquinone-5-methyl oxime structure **2** (see the Supporting Information).

Signals of the ^{1}H NMR spectrum of methyl oxime **2** in DMSO-d_6 (Figure 1, spectrum C) were easily assigned, with the aid of ^{1}H/^{13}C correlation experiments, including C−H long-range couplings (see the Supporting Information). The H4 and H6 proton signals were found at δ 7.56 and 7.10 ppm, respectively. The proton at the *syn* site to the OMe substitute

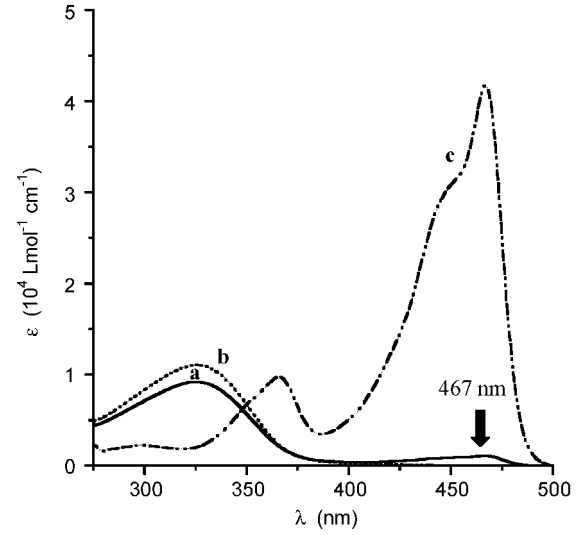


FIGURE 3. UV spectra of **1** at 6.6×10^{-5} M in acetonitrile: (a) **1** in acetonitrile; (b) **1** in 0.1 M trifluoroacetic acid/acetonitrile; and (c) **1** in 0.1 M DABCO/acetonitrile. In spectrum b, the weak, longer wavelength absorption (>400 nm) disappeared.

was found at lower field, as in the case of 1,4-benzoquinone 4-oxime methyl ether.[7]

The ^{1}H NMR spectra of **1** in various aprotic solvents, DMSO-d_6, DMF-d_7, and CD_3CN, are quite similar to those of the methyl oxime **2** (see the Experimental Section). It is quite reasonable that "5-nitrosotropolone" **1** takes the oxime structure **1B** in aprotic solvents. The ^{1}H NMR signals are somewhat broadened, but the addition of a trace of trifluoroacetic acid sharpened the peaks without significantly changing their positions (e.g., Figure 1, spectrum B).

UV Spectrum of 1 in Aprotic Solvent. The UV spectrum of **1** in an aprotic solvent, acetonitrile, was analyzed at the concentration of 6.6×10^{-5} M (Figure 3).[8] The bold curve (spectrum a) is the UV spectrum in neat acetonitrile: the maximum absorption was observed at 325 nm ($\epsilon = 9200$), and a weak but distinct maximum was found at 467 nm ($\epsilon = 1100$) with a shoulder at 450 nm, which coincides with the maximum absorption at 467 nm ($\epsilon = 41\,700$) of **1** under basic conditions [in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO)] (spectrum c). This absorption maximum of **1** in basic solution can be assigned to the ionic or dissociated form (**3**) of "5-nitrosotropolone" **1** (Scheme 1). The absorption at 325 nm is close to the absorption at 338 nm ($\epsilon = 16\,000$) in the acetonitrile solution of the methyl oxime **2** (see the Supporting Information, Table S1 and Figure S1). In the spectrum of **1** under acidic conditions with trifluoroacetic acid (spectrum b), the weak, longer wavelength absorption disappeared.

The ratio of the dissociated form **3** to the neutral form was concentration-dependent (Figure 4a) and also water-content-dependent (Figure 4b). In very dilute solutions, "5-nitrosotropolone" partially dissociated to the ion **3**. Generally, the degree of dissociation of weak acids depends on concentration, i.e., as the concentration of a weak acid decreases, the degree of dissociation increases.[9] The increase of the absorption at 467

(7) Norris, R. K.; Sternhell, S. *Aust. J. Chem.* **1966**, *19*, 841–860.
(8) All operations for sample preparation for UV spectrometry in acetonitrile were carried out in a drybox, under argon gas flow. Acetonitrile dehydrate (01837-25, 99.5%, Kanto Chemical Co., Inc.) was used as the solvent.
(9) Kuhn, H.; Försterling, H.-D. *Principles of Physical Chemistry*; John Wiley & Sons: Chichester, England, 2000; pp 579−584.

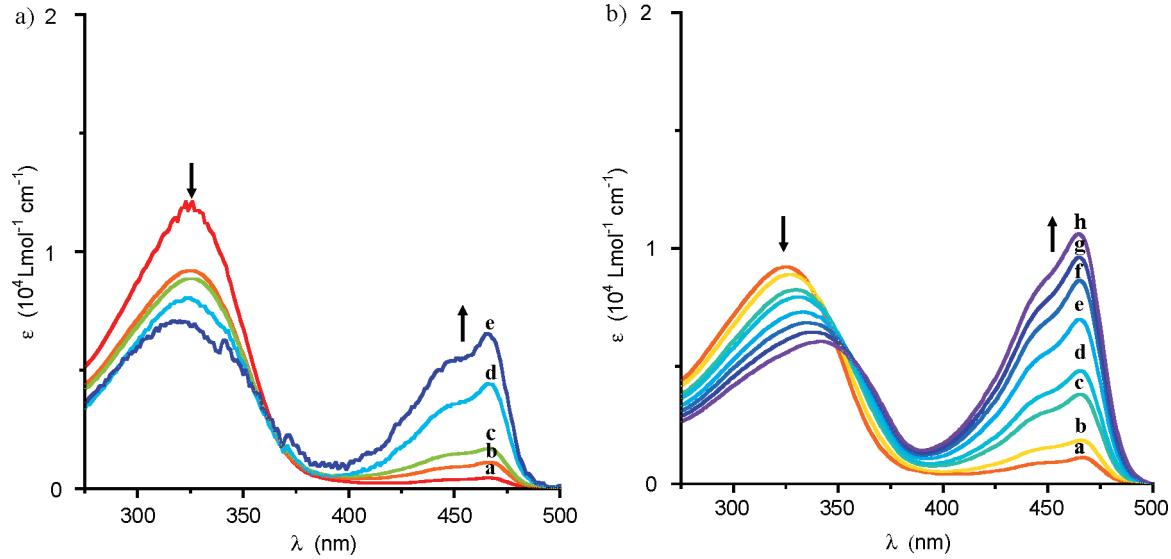
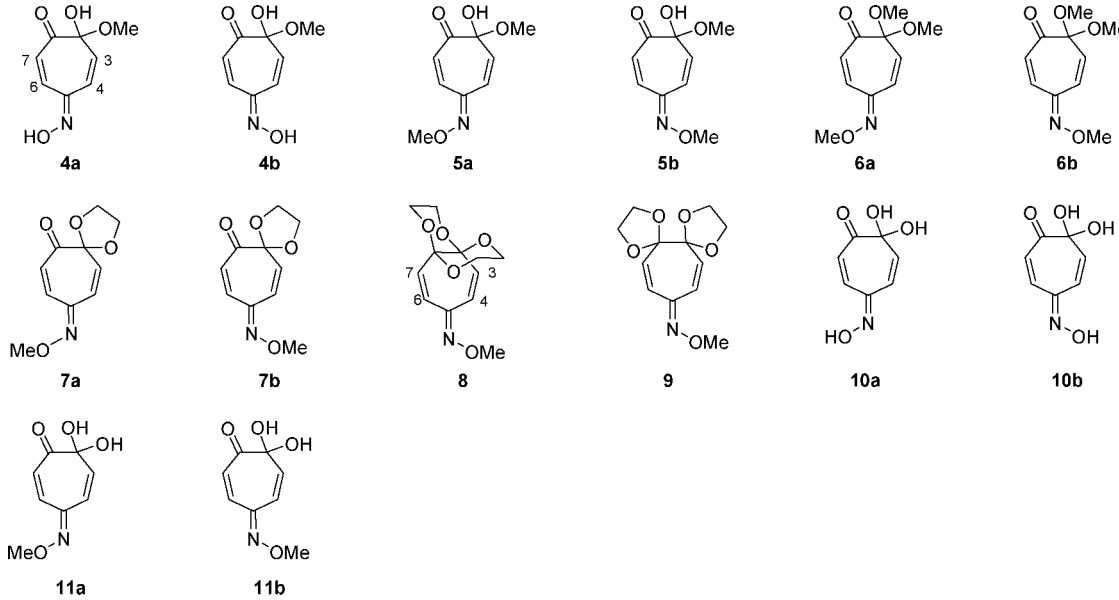


FIGURE 4. (a) UV spectra of **1** in acetonitrile at various concentration: (a) 3.3×10^{-4} M, (b) 6.6×10^{-5} M, (c) 3.3×10^{-5} M, (d) 6.6×10^{-6} M, and (e) 6.6×10^{-7} M). (b) UV spectra of **1** in acetonitrile (6.6×10^{-5} M) containing water: (a) 0%, (b) 1%, (c) 2%, (d) 3%, (e) 4%, (f) 5%, (g) 7%, and (h) 9%.

SCHEME 2



nm reflects higher dissociation to the ionic form. Addition of a small amount of water (Figure 4b) caused an increase of the dissociated form owing to increase of the polarity of the solvent, which more efficiently solvates and stabilizes the more polar dissociated form **3**.

Thus, the broadening of the ^{1}H NMR signals of **1** in DMSO-d_6 can be attributed to the presence of a small amount of the dissociated form (**3**). In the presence of trifluoroacetic acid, the equilibrium is shifted essentially to one species, **1B** (Figure 1, spectrum B).

NMR Spectra in Protic Solvents. The ^{1}H NMR spectrum of **1** in CD_3OD (Figure 2, spectrum A) showed, in addition to the oxime species **1B**, the signals of at least two other species, **4a** and **4b** (Scheme 2). However, when CD_3OD was removed by evaporation, and the residue was redissolved in DMSO-d_6, the signals of these two species **4a** and **4b** disappeared. The ^{1}H NMR spectrum of **2** in CD_3OD (Figure 2, spectrum B) also showed the presence of two species **5a** and **5b** corresponding to **4a** and **4b**. These results suggest that these species are hemiketal or dimethyl ketal compounds.

To support these structures, the methyl oxime **2** was treated with orthoformic acid trimethyl ester and *p*-toluenesulfonic acid in methylene chloride at room temperature to give two isomeric dimethyl ketals **6a** and **6b**. In the ^{1}H NMR spectrum of a mixture of **6a** and **6b** in CD_3OD (Figure 2, spectrum C), the H6 (δ 7.36) of **6a** was shifted to lower field than H6 (δ 6.77) of **6b** owing to greater conjugation of the carbonyl group and the anisotropic effect of the oxime oxygen, whereas H4 (δ 6.51) of **6a** was shifted to higher field than that of the H4 (δ 6.91) of **6b**. These assignments were confirmed by ^{1}H/^{13}C correlation experiments (see the Supporting Information). ^{1}H NMR spectra of **5a** and **5b** in CD_3OD were slightly different from those of **6a** and **6b** in CD_3OD (Figure 2, spectra B and C). These results indicated that **5a** and**5b** are hemiketals, which is consistent with the fact that the compounds could not be isolated from the NMR solution.

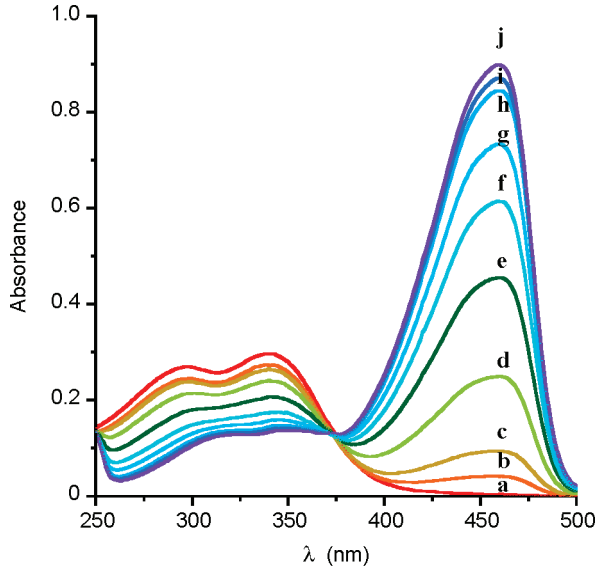


FIGURE 5. pH dependence of UV spectra of **1** in aqueous solution: (a) pH 3.10, (b) pH 4.70, (c) pH 5.02, (d) pH 5.58, (e) pH 5.77, (f) pH 6.06, (g) pH 6.38, (h) pH 6.50, (i) pH 7.15, and (j) pH 8.87.

Ketalization of the methyl oxime **2** with 1.1 equiv of ethylene glycol gave a mixture of the monoethylene ketals **7a** and **7b** and a trace amount of bisketal **8**, with some recovery of **2**. Treatment of the monoethylene ketal **7** with 2-ethyl-2-methyl-1,3-dioxolane gave another bisketal **9** together with bisketal **8**. However, when **2** was treated with excess 2-ethyl-2-methyl-1,3-dioxolane or ethylene glycol, only bisketal **8** was formed. The structure of bisketal **8** was established by X-ray crystallography (see the Supporting Information).

Thus, we can conclude that the NMR solution of **1** in CD_3OD consists of oxime **1B**, and hemiketal isomers **4a** and **4b**. In the ^1H NMR spectrum of **1** and **2** in D_2O, signals of the hydrates **10** and **11** were observed, respectively. A similar reaction was reported for cyclohepta-3,6-diene-1,2,5-trione, which forms a hydrate and hemiketal reversibly at room temperature in water and primary alcohols.[10]

UV Spectra in Protic Solvents. An aqueous solution of "5-nitrosotropolone" **1** were titrated over the pH range of 3.10−8.87 (Figure 5). The spectra showed three peaks at 299, 342, and 460 nm. The absorption at 460 nm was enhanced by alkali and quenched with acid. It can be attributed to the dissociated form **3**. On the other hand, the two absorptions at 299 and 342 nm were enhanced by acid and diminished by alkali. The UV spectra in methanol were essentially the same as those in Nozoe's report.[1,5]

The UV spectrum of an acid solution (at pH 3.10, spectrum a) showed two absorptions at 299 and 342 nm, which are close to the absorptions at 306 and 349 nm of the methyl oxime **2** in aqueous solution (see the Supporting Information, Table S1 and Figure S1). The absorption at 306 nm observed in an aqueous solution of **2** can be assigned to the hydrate **10**, because it is similar to the 305 nm band of dimethyl ketal **6** in aqueous solution (see the Supporting Information, Table S1 and Figure S1). The absorption at 342 nm of **1** is close to the absorption observed in a methanol solution of the methyl oxime **2**. Thus, the absorptions in neutral solution should be assigned to the hemiketal **10** (299 nm), oxime form **1B** (342 nm), and the dissociated form **3** (460 nm). These conclusions are consistent with the NMR measurements, which indicated that **1** and **2** partly form hydrates **10** and **11**, respectively, in D_2O.

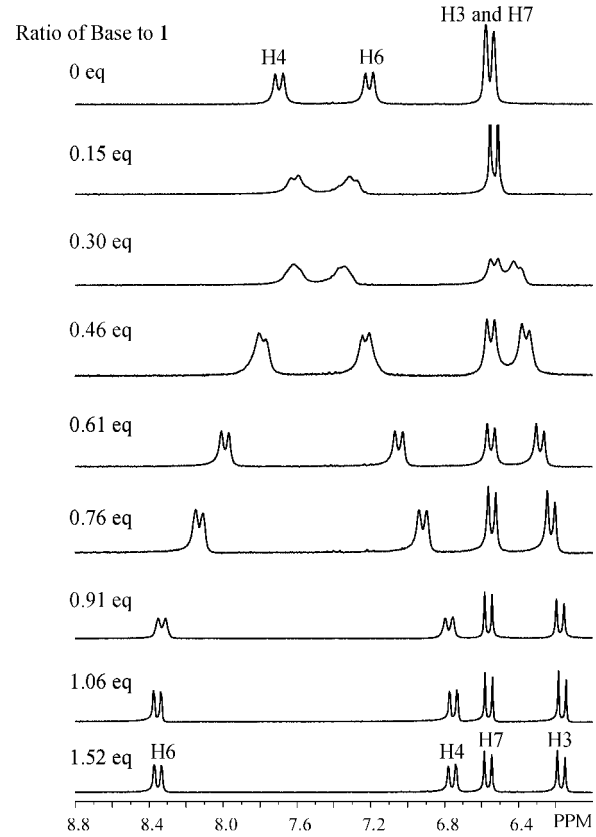


FIGURE 6. ^1H NMR spectra of **1** with NaOD/D_2O in DMSO-d_6.

The pK_a value[11] of **1** was calculated to be 5.86 at room temperature by plotting the absorbance at 460 nm against the pH (see the Supporting Information, Figure S2); an isosbestic point was observed at 378 nm. This means that there is no intermediate species between the acidic forms showing the shorter wavelength absorptions (a mixture of **1** and its hydrates, **10a**,**b**) and the dissociated form (**3**). The pK_a value of **1** is plausibly the dissociation constant of **1B**, since the conversion between **1B** and the hydrate **10** is fast, the equilibrium is not much affected by the acidity, and the acidity of the hydrate is far lower.

It can be concluded that the pH- and concentration-dependent changes in the spectrum of **1** in protic solvents are not based on the structure change of nitroso-oxime isomerization, but principally reflect the ratio of dissociation.

^1H NMR Spectrum of the Dissociated Form 3. The ^1H NMR spectrum of **1** in DMSO was followed during titration with NaOH/D_2O (Figure 6). As discussed above, the addition of NaOH/D_2O increased the ratio of the dissociated form **3**, resulting in broadening of the signals. As more alkali was added, the chemical shifts in particular of H4 and H6 changed significantly and the signals sharpened. These shifts suggest large anisotropic effects of the partial negative charge on the oxygen atom and restricted rotation of the carbon−nitrogen partial double bond. The structure of the dissociated form **3** is thus found to be unsymmetrical, at least at the NMR level.

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(11) Imafuku, K.; Takata, Y.; Matsumura, H. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 2913.

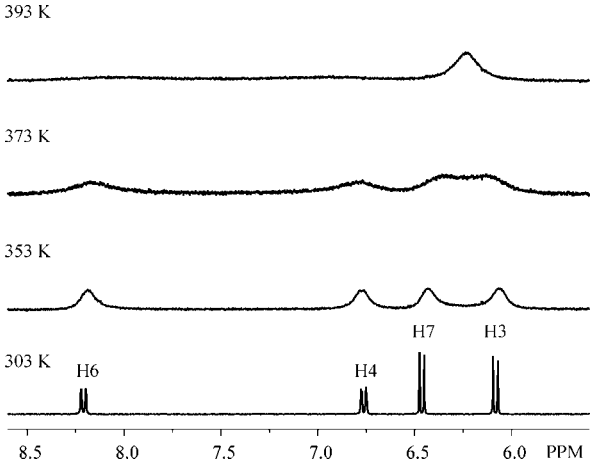

FIGURE 7. ^{1}H NMR spectra of "5-nitrosotropolone" potassium salt in DMSO-d_6 at various temperatures.

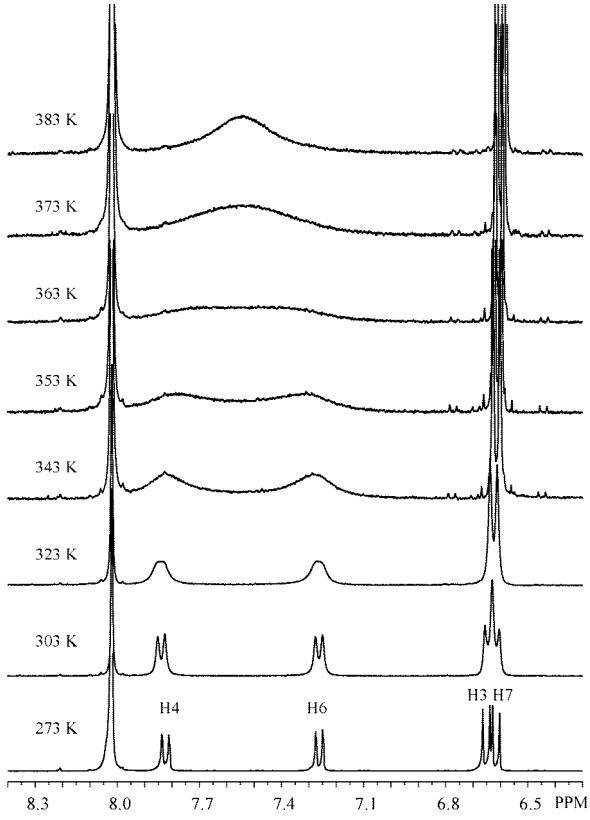

FIGURE 8. ^{1}H NMR spectra of "5-nitrosotropolone" in DMF-d_7 at various temperatures.

The temperature dependence of the ^{1}H NMR spectrum of the potassium salt of "5-nitrosotropolone" **1** in DMSO-d_6 was examined (Figure 7). Coalescence of the H3 and H7 proton signals was observed at around 373−393 K, which indicates that the rotation barrier of the carbon−nitrogen partial double bond is about 17.5−18.5 Kcal mol^{-1}.

The temperature dependence of ^{1}H NMR spectrum of "5-nitrosotropolone" in DMF-d_7 was also examined (Figure 8). At 303 K, the signals were somewhat broadened, but became sharper when the temperature was lowered to 273 K. On the other hand, coalescence of the H4 and H6 signals was observed at around 353−363 K (indicating a rotation barrier of about 16.2−16.7 Kcal mol^{-1}). Generally, the degree of dissociation of weak acids depends on temperature. As the temperature increases, the degree of dissociation becomes greater, and this also affects the coalescence point. Thus, the sharp signals at 273 K correspond to the "frozen" spectrum of **1B**. The signal coalescence is not attributable to the rapid exchange of restricted rotation positions around the nitroso C−N bond as suggested by Asao et al.,[6] but to the rapid exchange of two oxime syn-anti structures of **1B** via the dissociated form **3**.

Conclusions

Careful analysis of NMR and UV spectra demonstrated that the solution structure of "5-nitrosotropolone" **1** is the oxime form **1B**. In a nucleophilic protic solution, such as methanol or water, **1B** is in equilibrium with the hemiketal **4** and hydrate **10**. It is important to note that the NMR and UV spectra are highly concentration-dependent. The canonical structure of "5-nitrosotropolone" **1** should be the oxime structure **1B**.

Experimental Section

"5-Nitrosotropolone" 1.[3b−d] Tropolone (0.20 mol, 24.4 g) was dissolved in acetic acid (64 mL) and H_2O (21 mL) and stirred at 0 °C. A solution of sodium nitrite (0.29 mol, 20.0 g) in H_2O (48 mL) was added dropwise to the above solution at 0 °C, and the mixture was stirred for 1 h. A yellow precipitate was collected by filtration and rinsed with H_2O (20 mL) to give **1** (26.6 g, 88%). Mp around 180 °C dec. IR (KBr) (cm^{-1}) 1647, 1602, 1312, 1013. UV data: see the Supporting Information, Table S1. ^{1}H NMR spectra were determined in various deuterated solvents (DMSO-d_6, DMSO-d_6 + 5% NaOD, DMF-d_7, CD_3CN, CD_3OD, and D_2O) and ^{13}C NMR spectra in DMSO-d_6 and CD_3OD. ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.9 (br s, 1H, NOH),[7,12] 7.69 (br d, J = 12.6 Hz, 1H, H-4), 7.21 (br d, J = 12.6 Hz, 1H, H-6), 6.55 (br d, J = 12.6 Hz, 2H, H-3 and H-7). ^{1}H NMR [300 MHz, DMSO-d_6 + 5% NaOD (1.52 equiv), see Figure 6] δ 8.35 (dd, J = 12.0, 1.5 Hz, 1H, H-6), 6.76 (dd, J = 12.3, 1.5 Hz, 1H, H-4), 6.56 (d, J = 12.0 Hz, 1H, H-7), 6.11 (d, J = 12.3 Hz, 1H, H-3). ^{1}H NMR (500 MHz, DMF-d_7, at 303 K) δ 14.4 (br s, 1H, NOH), 7.84 (d, J = 13.0 Hz, 1H, H-4), 7.27 (d, J = 13.0 Hz, 1H, H-6), 6.67 (d, J = 13.0 Hz, 1H, H-3), 6.62 (d, J = 13.0 Hz, 1H, H-7). ^{1}H NMR (300 MHz, CD_3CN) δ 7.81−7.63 (m, 1H, H-4), 7.25−7.07 (m, 1H, H-6), 6.53 (d, J = 12.9 Hz, 2H, H-3 and H-7). ^{1}H NMR [300 MHz, CD_3OD, a mixture of **1** and hemiketal **4a** and **4b** in a ratio of ca. 1:0.3:1.6 (based on ^{1}H NMR integration)] for **1** δ 7.85 (br d, J = 12.0 Hz, 1H, H-4), 7.25 (br d, J = 12.0 Hz, 1H, H-6), 6.58 (d, J = 12.0, 2H, H-3 and H-7). ^{1}H NMR [300 MHz, CD_3OD, a mixture of **1** and hemiketal **4a** and **4b** in a ratio of ca. 1:0.3:1.6 (based on ^{1}H NMR integration)] for **4a** δ 7.61 (dd, J = 12.9, 1.5 Hz, 1H, H-6), 6.48 (dd, J = 12.0, 1.5 Hz, 1H, H-4), 6.26 (d, J = 12.9 Hz, 1H, H-7), 5.97 (d, J = 12.0 Hz, 1H, H-3). ^{1}H NMR [300 MHz, CD_3OD, a mixture of **1** and hemiketal **4a** and **4b** in a ratio of ca. 1:0.3:1.6 (based on ^{1}H NMR integration)] for**4b** δ 7.00 (dd, J = 12.0, 1.5 Hz, 1H, H-4), 6.91 (dd, J = 12.3, 1.5 Hz, 1H, H-6), 6.21 (d, J = 12.3 Hz, 1H, H-7), 6.04 (d, J = 12.0 Hz, 1H, H-3). ^{1}H NMR [300 MHz, D_2O, a mixture of **1** and hydrate **10a** and **10b** in a ratio of ca. 1:0.1:0.3 (based on ^{1}H NMR integration)] for **1** δ 7.86−7.63 (m, 1H, H-4), 7.30−7.02 (m, 1H, H6), 6.60 (d, J = 12.6 Hz, 2H, H-3 and H-7). ^{1}H NMR [300 MHz, D_2O, a mixture of **1** and hydrate **10a** and **10b** in a ratio of ca. 1:0.1:0.3 (based on ^{1}H NMR integration)] for **10a** δ 7.59 (br d, J = 12.9 Hz, 1H, H-6), 6.41 (br d, J = 11.7 Hz, 1H, H-4), 6.36 (d, J = 12.9 Hz, 1H, H-7), 6.18 (d, J = 11.7 Hz, 1H, H-3). ^{1}H NMR [300 MHz, D_2O, a mixture of **1** and hydrate **10a** and **10b** in a ratio of ca. 1:0.1:0.3 (based on ^{1}H NMR integration)] for **10b** δ 6.92 (dd, J = 12.3, 1.5 Hz, 1H, H-6),

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6.90 (dd, J = 12.0, 1.5 Hz, 1H, H-4), 6.29 (d, J = 12.3 Hz, 1H, H-7), 6.18 (d, J = 12.0 Hz, 1H, H-3). ^{13}C NMR (75 MHz, DMSO-d_6) δ 185.4, 183.8, 152.0, 139.3, 130.0, 127.8, 123.9. ^{13}C NMR [75 MHz, CD_3OD, a mixture of **1** and hemiketal **4a** and **4b**] only assignable signals for **4b** δ 193.8, 153.5, 140.2, 135.6, 126.0, 121.8, 99.5, ($O\underline{C}D_3$ peak overlapping with solvent peak). LR-MS m/z 151 (M^+, 48), 134 (8), 123 (22), 95 (14), 80 (30), 65 (100).

Potassium Salt of "5-Nitrosotropolone". To an ethanol solution of "5-nitrosotropolone" **1** was added 1 equiv of potassium hydroxide in ethanol and the mixture was evaporated at room temperature to give a brown precipitate. IR (KBr) (cm^{-1}) 1611, 1584, 1470, 1322. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.20 (dd, J = 12.0, 1.5 Hz, 1H, H-6), 6.76 (dd, J = 12.5, 1.5 Hz, 1H, H-4), 6.46 (d, J = 12.0 Hz, 1H, H-7), 6.07 (d, J = 12.5 Hz, 1H, H-3). ^{13}C NMR (75 MHz, DMSO-d_6) δ 184.5, 181.0, 164.1, 146.7, 119.0, 118.0, 117.5.

Cyclohepta-3,6-diene-1,2,5-trione-5-(*O*-methyloxime) (Tropoquinone-5-*O*-methyl oxime, 2). A solution of "5-nitrosotropolone" **1** (2.77 g, 18.3 mmol), potassium carbonate (K_2CO_3) (5.05 g, 36.6 mmol), 18-crown-6 (0.69 g, 1.84 mmol), and methyl iodide (5.7 mL, 91.5 mmol) in acetonitrile (MeCN) (80 mL) was heated at 60 °C for 5 h, then cooled to room temperature and filtered. The filtrate was concentrated in vacuo. The residue was flash-chromatographed [silica gel, ethyl acetate−hexane (1:3)] to give methyl oxime **2** (0.77 g, 26%). Mp 123−125 °C, yellow prisms (recryst from methylene chloride-hexane). IR (KBr) (cm^{-1}) 1662, 1643, 1619, 1314, 1037. UV data: see the Supporting Information, Table S1. ^{1}H NMR spectra were determined in various deuterated solvents (DMSO-d_6, DMF-d_7, CD_3CN, CD_3OD, and D_2O) and ^{13}C NMR spectra in DMSO-d_6 and CD_3OD. ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.56 (dd, J = 12.6, 1.0 Hz, 1H, H-4), 7.10 (d, J = 12.6, 1.0 Hz, 1H, H-6), 6.60 (d, J = 12.6 Hz, 1H, H-3), 6.57 (d, J = 12.6 Hz, 1H, H-7), 4.16 (s, 3H, NOMe). ^{1}H NMR (300 MHz, DMF-d_7) δ ca. 7.85−7.50 (m, 1H, H-4), ca. 7.30−7.05 (m, 1H, H-6), 6.68 (d, J = 12.6 Hz, 1H, H-3), 6.65 (d, J = 12.6 Hz, 1H, H-7), 4.23 (s, 3H, NOMe). ^{1}H NMR (300 MHz, CD_3CN) δ 7.63 (dd, J = 12.9, 2.1 Hz, 1H, H-4), 7.09 (dd, J = 12.9, 2.1 Hz, 1H, H-6), 6.55 (d, J = 12.9 Hz, 1H, H-7), 6.54 (d, J = 12.9 Hz, 1H, H-3), 4.17 (3H, s, NOMe). ^{1}H NMR [300 MHz, CD_3OD, a mixture of **2** and hemiketals **5a** and **5b** in a ratio of ca. 1:0.7:4 (based on ^{1}H NMR integration)] for **2** δ 7.70 (dd, J = 12.9, 1.5 Hz, 1H, H-4), 7.16 (dd, J = 12.9, 1.5 Hz, 1H, H-6), 6.60 (d, J = 12.9 Hz, 1H, H-7), 6.59 (d, J = 12.9 Hz, 1H, H-3), 4.21 (s, 3H, NOMe). ^{1}H NMR [300 MHz, CD_3OD, a mixture of **2** and hemiketals **5a** and **5b** in a ratio of ca. 1:0.7:4 (based on ^{1}H NMR integration)] for **5a** δ 7.46 (dd, J = 12.9, 1.5 Hz, 1H, H-6), 6.44 (dd, J = 12.0, 1.5 Hz, 1H, H-4), 6.28 (d, J = 12.9 Hz, 1H, H-7), 6.02 (d, J = 12.0 Hz, 1H, H-3), 4.06 (s, 3H, NOMe). ^{1}H NMR [300 MHz, CD_3OD, a mixture of **2** and hemiketals **5a** and **5b** in a ratio of ca. 1:0.7:4 (based on ^{1}H NMR integration)] for **5b** δ: 6.87 (dd, J = 12.0, 1.8 Hz, 1H, H-4), 6.85 (dd, J = 12.6, 1.8 Hz, 1H, H-6), 6.23 (d, J = 12.6 Hz, 1H, H-7), 6.08 (d, J = 12.0 Hz, 1H, H-3), 4.06 (s, 3H, NOMe). ^{1}H NMR [300 MHz, D_2O, a mixture of **2** and hydrate **11a** and **11b** in a ratio of ca. 1:0.2:0.5 (based on ^{1}H NMR integration)] for **2** δ: 7.68 (dd, J = 13.1, 1.8 Hz, 1H, H-4), 7.14 (dd, J = 12.9, 1.8 Hz, 1H, H-6), 6.60 (d, J = 12.9 Hz, 1H, H-7), 6.58 (d, J = 13.1 Hz, 1H, H-3), 4.13 (s, 3H, NOMe). ^{1}H NMR [300 MHz, D_2O, a mixture of **2** and hydrate **11a** and **11b** in a ratio of ca. 1:0.2:0.5 (based on ^{1}H NMR integration)] for **11a** δ 7.47 (dd, J = 12.9, 1.5 Hz, 1H, H-6), 6.38 (dd, J = 12.0, 1.5 Hz, 1H, H-4), 6.34 (d, J = 12.9 Hz, 1H, H-7), 6.11 (d, J = 12.0 Hz, 1H, H-3), 3.99 (s, 3H, NOMe). ^{1}H NMR [300 MHz, D_2O, a mixture of **2** and hydrate **11a** and **11b** in a ratio of ca. 1:0.2:0.5 (based on ^{1}H NMR integration)] for **11b** δ 6.87 (dd, J = 12.5, 1.5 Hz, 1H, H-6), 6.81 (dd, J = 12.2, 1.5 Hz, 1H, H-4), 6.29 (d, J = 12.5 Hz, 1H, H-7), 6.17 (d, J = 12.2 Hz 1H, H-3), 3.99 (s, 3H, NOMe). ^{13}C NMR (75 MHz, DMSO-d_6) δ 185.0, 183.5, 151.4, 137.5, 131.5, 129.1, 123.6, 64.3. ^{13}C NMR (75 MHz, CD_3OD, a mixture of **2** and hemiketal **5a** and **5b**) for **2** δ 186.6, 185.2, 152.8, 139.9, 131.9, 129.6, 125.5, 65.2. ^{13}C NMR (75 MHz, CD_3OD, a mixture of **2** and hemiketal **5a** and **5b**) for **5a** δ 194.4, 152.3, 134.0, 129.6, 129.4, 125.8, 99.5, 63.9 ($O\underline{C}D_3$ peak overlapping with solvent peak). ^{13}C NMR (75 MHz, CD_3OD, a mixture of **2** and hemiketal **5a** and **5b**) for **5b** δ 193.7, 153.8, 138.9, 127.1, 127.0, 121.8, 99.5, 64.0, ($O\underline{C}D_3$ peak overlapping with solvent peak). LR-MS m/z 150 (M^+ − Me, 42), 137 (13), 122 (15), 106 (12), 80 (80). Anal. Calcd for $C_8H_7NO_3$: C, 58.18; H, 4.27; N, 8.48. Found: C, 58.04; H, 4.48; N, 8.29.

Cyclohepta-3,6-diene-1,2,5-trione-5-*O*-methyloxime-2-dimethyl Ketal (6). A solution of **2** (47 mg, 0.285 mmol), orthoformic acid trimethyl ester (0.3 mL, 2.85 mmol), and a catalytic amount of *p*-toluenesulfonic acid (TsOH) in CH_2Cl_2 (3 mL) was stirred at room temperature for 16 h. The mixture was poured into saturated aqueous sodium hydrogen carbonate ($NaHCO_3$) and extracted with $CHCl_3$. The organic layer was washed with brine, dried over sodium sulfate (Na_2SO_4), and evaporated in vacuo. The residue was flash-chromatographed [silica gel, ethyl acetate−hexane (1:6)] to give a mixture of ketals **6a** and **6b** (48 mg, 80%, ca. 1:2.5, based on ^{1}H NMR integration). Mp 62−64 °C (a mixture of **6a** and **6b**). IR (KBr) (cm^{-1}) 1691, 1036. UV data: see the Supporting Information, Table S1. ^{1}H and ^{13}C NMR spectra were determined in $CDCl_3$ and CD_3OD. ^{1}H NMR (300 MHz, $CDCl_3$, a mixture of **6a** and **6b**) for **6a** δ 7.37 (dd, J = 12.9, 1.8 Hz, 1H, H-6), 6.49 (dd, J = 12.0, 1.8 Hz, 1H, H-4), 6.23 (d, J = 12.9 Hz, 1H, H-7), 5.97 (d, J = 12.0 Hz, 1H, H-3), 4.08 (s, 3H, NOMe), 3.30 (s, 6H, OMe × 2). ^{1}H NMR (300 MHz, $CDCl_3$, a mixture of **6a** and **6b**) for **6b** δ 6.88 (dd, J = 12.0, 1.5 Hz, 1H, H-4), 6.77 (dd, J = 12.3, 1.5 Hz, 1H, H-6), 6.19 (d, J = 12.3 Hz, 1H, H-7), 6.02 (d, J = 12.0 Hz, 1H, H-3), 4.08 (s, 3H, NOMe), 3.29 (s, 6H, OMe × 2). ^{1}H NMR (300 MHz, CD_3OD, a mixture of **6a** and **6b**) for **6a** δ 7.36 (dd, J = 12.9, 1.5 Hz, 1H, H-6), 6.51 (dd, J = 12.0, 1.5 Hz, 1H, H-4), 6.23 (d, J = 12.9 Hz, 1H, H-7), 5.96 (d, J = 12.0 Hz, 1H, H-3), 4.06 (s, 3H, NOMe), 3.24 (s, 6H, OMe × 2). ^{1}H NMR (300 MHz, CD_3OD, a mixture of **6a** and **6b**) for **6b** δ 6.91 (dd, J = 11.9, 1.5 Hz, 1H, H-4), 6.77 (dd, J = 12.5, 1.5 Hz, 1H, H-6), 6.16 (d, J = 12.5 Hz, 1H, H-7), 6.02 (d, J = 11.9 Hz, 1H, H-3), 4.06 (s, 3H, NOMe), 3.23 (s, 6H, OMe × 2). ^{13}C NMR (75 MHz, $CDCl_3$, a mixture of **6a** and **6b**) for **6a** δ 191.6, 151.1, 130.8, 129.5, 129.1, 123.7, 102.7, 63.4, 50.3. ^{13}C NMR (75 MHz, $CDCl_3$, a mixture of **6a** and **6b**) for **6b** δ 191.1, 152.6, 136.0, 133.2, 126.8, 122.0, 102.6, 63.6, 50.3. ^{13}C NMR (75 MHz, CD_3OD, a mixture of **6a** and **6b**) for **6a** δ 193.1, 152.4, 131.9, 130.6, 130.4, 124.6, 104.0, 63.9, 50.5. ^{13}C NMR (75 MHz, CD_3OD, a mixture of **6a** and **6b**) for **6b** δ 192.7, 153.9, 137.2, 134.4, 127.9, 123.1, 104.0, 64.0, 50.5. LR-MS m/z 196 (M^+ − Me, 42), 180 (100), 152 (33), 132 (40), 120 (27), 106 (18). HRMS Calcd for $C_{10}H_{13}NO_4$ 211.0844, found 211.0855.

Ketalization of the Methyl Oxime 2 to Form Monoethylene Ketal 7. A solution of **2** (121 mg, 0.73 mmol), ethylene glycol (44 μL, 0.80 mmol), and a catalytic amount of TsOH in $CHCl_3$ (5 mL) was heated at reflux for 3 h. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was flash-chromatographed [silica gel, ethyl acetate−hexane (1:4)] to give a mixture of **7a** and **7b** (67 mg, 44%, ca. 1:5, based on ^{1}H NMR integration). Mp 70−72 °C [a mixture of **7a** and **7b**, yellow prisms (recryst from ether−hexane)]. IR (KBr) (cm^{-1}) 1675, 1036, 1009. ^{1}H NMR (300 MHz, $CDCl_3$, a mixture of **7a** and **7b**) for **7a** δ 7.46 (dd, J = 12.6, 1.8 Hz, 1H, H-6), 6.49 (dd, J = 12.3, 1.5 Hz, 1H, H-4), 6.29 (d, J = 12.6 Hz, 1H, H-7), 6.14 (d, J = 12.3 Hz, 1H, H-3), ca. 4.10−3.92 (m, 8H), 4.08 (s, 3H, NOMe). ^{1}H NMR (300 MHz, $CDCl_3$, a mixture of **7a** and **7b**) for **7b** δ 6.94 (dd, J = 12.3, 1.5 Hz, 1H, H-4), 6.86 (dd, J = 12.6, 1.8 Hz, 1H, H-6), 6.26 (d, J = 12.6 Hz, 1H, H-7), 6.23 (d, J = 12.3 Hz, 1H, H-3), ca. 4.10−3.92 (m, 8H), 4.08 (s, 3H, NOMe). ^{13}C NMR (75 MHz, $CDCl_3$, a mixture of **7a** and **7b**) for **7a** δ 190.4, 152.1, 137.0, 133.3, 127.0, 121.0, 106.5, 65.6, 63.6. ^{13}C NMR (75 MHz, $CDCl_3$, a mixture of **7a** and **7b**) for **7b** δ 191.2, 150.7, 130.0, 129.7, 129.2, 124.1, 106.5, 65.6, 63.5. LR-MS m/z 209 (M^+, 5), 194 (60), 178 (100), 150 (26), 134 (83), 106 (43), 98 (36), 80 (73), 52 (37). HRMS Calcd for $C_{10}H_{11}NO_4$: 209.0687, found 209.0714.

Ketalization of Monoethylene Ketal 7 to Form Bisketal 8 and 9. A solution of **7** (20 mg, 0.1 mmol), 2-ethyl-2-methyl-1,3-dioxolane (0.4 mL), and a catalytic amount of TsOH in CH_2Cl_2 (2 mL) was stirred at room temperature for 3 days, poured into saturated aqueous $NaHCO_3$, and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was purified by PTLC [ethyl acetate−hexane (1:4)] to give **8** (3 mg, 12%) and **9** (4 mg, 16%). **8**: Mp 98−100 °C, colorless prisms (recryst from ether−hexane). IR (KBr) (cm^{-1}) 1089, 1047. UV data: see the Supporting Information, Table S1). ^1H NMR (300 MHz, $CDCl_3$) δ 6.99 (dd, J = 12.9, 1.8 Hz, 1H, H-4), 6.41 (dd, J = 12.9, 1.8 Hz, 1H, H-6), 5.93 (d, J = 12.9 Hz, 1H, H-7), 5.74 (d, J = 12.9 Hz, 1H, H-3), ca. 4.20−4.05 (m, 4H), 3.99 (s, 3H, NOMe), ca. 3.85−3.68 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 134.9, 131.5, 129.7, 121.1, 94.1, 93.7, 62.8, 61.4. LR-MS m/z 222 (M^+ − OMe, 2), 193 (8), 178 (7), 165 (30), 137 (99), 121 (100). Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.78; H, 5.86; N, 5.47. **9**: Mp 94−96 °C, colorless prisms (recryst from ether–hexane). IR (KBr) (cm^{-1}) 1054, 1029. UV data: see the Supporting Information, Table S1. ^1H NMR (300 MHz, $CDCl_3$) δ 6.82 (dd, J = 12.6, 1.5 Hz, 1H, H-4), 6.24 (dd, J = 12.6, 1.5 Hz, 1H, H-6), 6.13 (d, J = 12.6 Hz, 1H, H-7), 5.95 (d, J = 12.6 Hz, 1H, H-3), ca. 4.18−3.90 (m, 8H), 3.98 (s, 3H, NOMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 136.7, 132.4, 126.8, 118.1, 108.3, 107.9, 66.5, 62.7. LR-MS (m/z) 253 (M^+, 3), 222 (96), 194 (20), 178 (20), 166 (33), 150 (34), 122 (23), 106 (71), 80 (100). Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.62; H, 5.83; N, 5.60.

Direct Ketalization of 2 to Form 8 with Ethylene Glycol. A solution of **2** (15 mg, 0.09 mmol), ethylene glycol (0.5 mL), and a catalytic amount of TsOH in $CHCl_3$ (3 mL) was heated at reflux for 1.5 h. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was flash-chromatographed (silica gel, ethyl acetate–hexane (1:2) to give **8** (16.5 mg, 73%).

Direct Ketalization of 2 to form 8 with 2-Ethyl-2-methyl-1,3-dioxolane. A solution of **2** (100 mg, 0.61 mmol), 2-ethyl-2-methyl-1,3-dioxolane (0.75 mL, 6.1 mmol), and a catalytic amount of TsOH in CH_2Cl_2 (10 mL) was stirred at room temperature for 2 h. The mixture was poured into saturated aqueous $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated in vacuo. The residue was recrystallized from ether−hexane to give **8** (148 mg, 96%).

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Supporting Information Available: General experimental procedures, ^1H NMR spectra of for **1**, **2**, **6**, **7**, **8**, and **9**, X-ray crystallographic data for **2** and **8** in CIF format, table of UV absorption data for **1**, **2**, **6**, **8**, and **9** in various solvents (acetonitrile, water, and methanol), UV absorption comparison of **2** and **6**, and plot of the absorption at 460 nm of **1** against pH. This material is available free of charge via the Internet at http://pubs.acs.org.

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