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SOLVENT EFFECTS ON RELATIVE STABILITY OF MERIDINE AND ITS TAUTOMER:
MO CALCULATIONS

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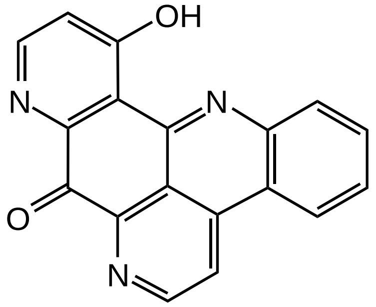
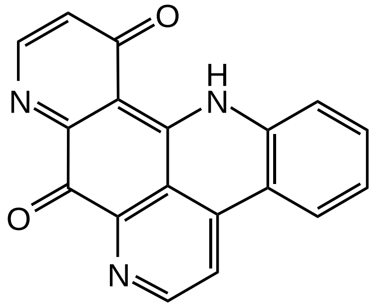
Abstract—The solvent effect on the ground-state energy difference of meridine (enol form) and meridin-12(13*H*)-one (keto form) is examined by use of AM1 and COSMO methods. The results show that solvents stabilize the keto form more than the enol form. In apolar solvents, the enol form is the predominant species, whereas in polar solvents, the enol and keto forms are present in an almost equal amount.

INTRODUCTION

Meridine (**1**) is a biologically active pentacyclic aromatic alkaloid, isolated from ascidian by Schmitz and co-workers.[1] This molecule exhibits cytotoxic and antifungal activities.[1,2] The isolation of meridine and its biological activities have stimulated synthetic organic chemists' interest in preparing meridine. Two groups have succeeded in synthesizing meridine.[3] An X-Ray structural analysis of the molecule has been made and the molecule has been identified as 12-hydoxybenzo[*b*]pyrido[4,3,2-*de*][1,7]phenanthrolin-8(8*H*)-one.[1] The molecule is characterized by having a proton donor (-OH) group and a proton acceptor (-N=) site. The intramolecular proton transfer from the acidic center to the



Meridine (**1**)



Meridin-12(13*H*)-one (**2**)

We dedicate this paper to Professor Shô Ito on the occasion of his 77th birthday.

basic group gives a tautomer of meridine, meridin-12(13*H*)-one (**2**). Schmitz *et al.* have also reported the isolation of **2** and the transformation from **2** to **1** in $CDCl_3$: After **2** had been stored in $CDCl_3$ for 1-2 days, the ^1H NMR spectrum of the sample was indistinguishable from that of meridine.[1] This led us to investigate the effect of solvent on the energetical stability of **1**, **2**, and the transition state (**3**) between the two forms. In this paper, we examine the relative stability of **1**, **2**, and **3** in solution by using AM1 and COSMO methods.

CALCULATION METHOD

Computations were carried out with the use of MOPAC93 Program.[4] Full geometry optimizations were performed by using AM1 method.[5] All structural parameters were optimized. The ground-state structure was minimized until a gradient norm of less than 0.01 kcal $mol^{-1}A^{-1}$ was achieved. The effect of solvent on the stability of the ground-state structure was examined by using COSMO method.[6] All calculations in this work were carried out with the use of the Silicon graphics(SGI), IRIS INDIGO/ELAN, and IBM, RS/6000 model 590.

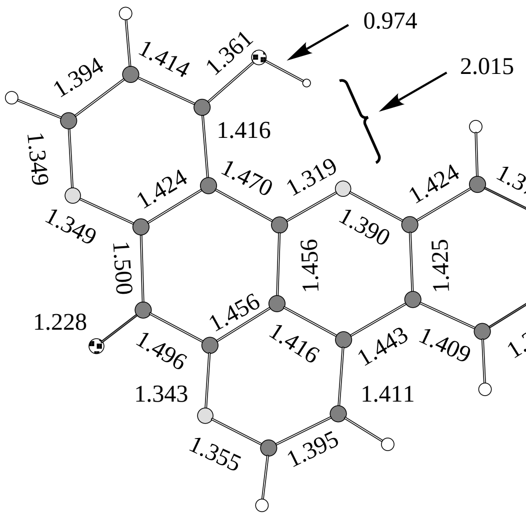
RESULTS AND DISCUSSION

We begin with the optimization of the gas-phase structures of meridine (enol form) (**1**), its keto form (**2**), and the transition state (**3**) between these forms. The optimized structures of **1**, **2**, and **3** are shown in Figure 1. The calculated dipole moment is 6.1 for **1**, 7.9 for **2**, and 7.8 Debye for **3**. From the viewpoint of polarity, **3** is closer to **2** than to **1**. The calculated heats of formation of **1** – **3** (ΔH_f(**1**), ΔH_f(**2**), and ΔH_f(**3**)) as well as the energy differences (ΔH_f(**2**) – ΔH_f(**1**), ΔH_f(**3**) – ΔH_f(**1**), and ΔH_f(**3**) – ΔH_f(**2**)) are summarized in Table 1. In the gas phase, the enol form (**1**) is more stable in energy than the

Table 1 Calculated Heats of Formation (kcal mol^{-1}) of Meridine (**1**), Meridin-12(13*H*)-one (**2**), and Transition State (**3**)

Solvent (ε)[a)]	ΔH_f(**1**)	ΔH_f(**2**)	ΔH_f(**3**)	ΔH_f(**2**)-ΔH_f(**1**)	ΔH_f(**3**)-ΔH_f(**1**)	ΔH_f(**3**)-ΔH_f(**2**)
Non	57.48	80.43	64.44	6.96	22.95	15.99
$CHCl_3$ (4.8)	43.00	63.17	45.74	2.74	20.17	17.43
CH_2Cl_2 (10.335)	39.31	58.80	40.61	1.30	19.49	18.19
2-Propanol (19.92)	37.54	56.68	38.03	0.49	19.14	18.65
EtOH (24.55)	37.16	56.23	37.50	0.34	19.07	18.73
MeCN (36.0)	36.63	55.59	36.74	0.11	18.96	18.85
DMSO (45.0)	36.39	55.27	36.40	0.01	18.88	18.87
H_2O (78.3)	36.02	54.82	35.82	-0.20	18.80	19.00

a) ε denotes the relative dielectric constant.



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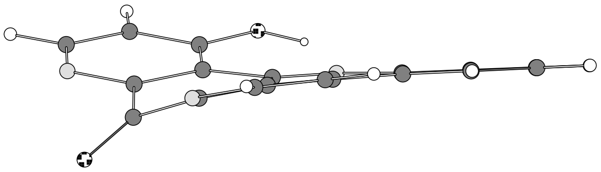
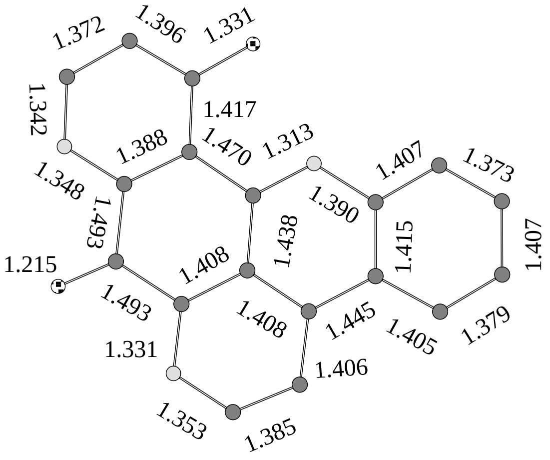


Side View



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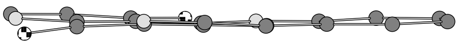
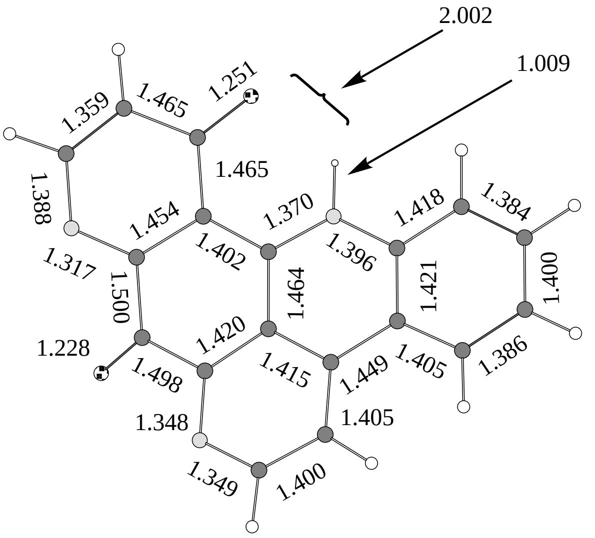


Side View

Figure 1. Optimized geometrical structures of meridine (**1**), meridin-12(13*H*)-one (**2**), and the transition state (**3**) as well as observed geometrical structure (**1'**) of meridine (Ref. 1). Distances in Å.



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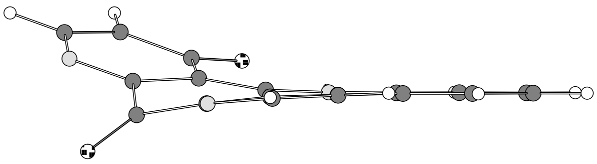
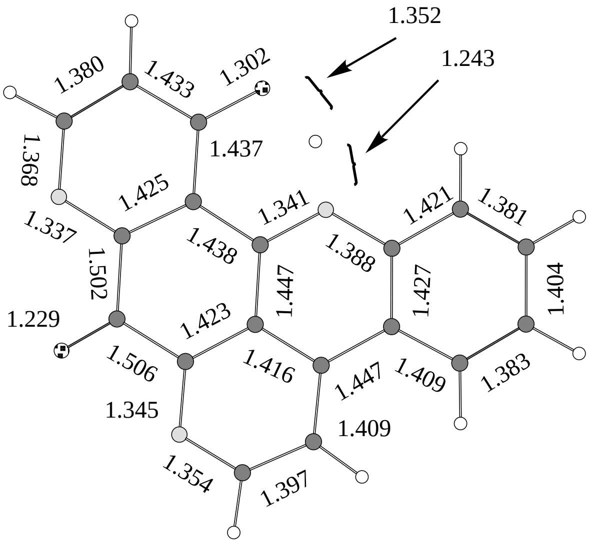


Side View



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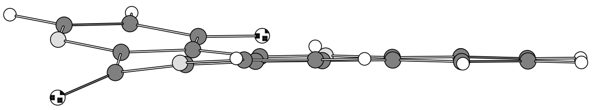

Side View

Figure 1 (Continued). Optimized geometrical structures of meridine (**1**), meridin-12(13*H*)-one (**2**), and the transition state (**3**) as well as observed geometrical structure (**1'**) of meridine (Ref. 1). Distances in Å.

keto form (**2**).

We next investigated the solvent effect on the energetical stability of **1** – **3** by using COSMO method. Calculations were performed in $CHCl_3$, CH_2Cl_2, 2-propanol, EtOH, MeCN, DMSO, and H_2O. The calculated heats of formation of the solvated species are summarized also in Table 1.

Table 1 reveals the solvent effect on the the energy difference, $\Delta H_f(\mathbf{2}) - \Delta H_f(\mathbf{1})$. In an apolar solvent such as $CHCl_3$, the enol form (**1**) is favorable. However, the energy difference, $\Delta H_f(\mathbf{2}) - \Delta H_f(\mathbf{1})$, in solution is smaller than in the gas phase. This means that the solvent more stabilizes **2** than **1**. This is probably because **1** is less polar than **2**; the calculated dipole moment of **1** is 6.1 whereas that of **2** is 7.9 Debye. In the polar solvents the keto form (**2**) is as stable as the enol form (**1**). For example, DMSO gives the energy difference of only 0.01 kcal mol^{-1}. In the most polar solvent, H_2O, the keto form (**2**) is slightly more stable than the enol form (**1**).

Table 1 also shows that the difference, $\Delta H_f(\mathbf{3}) - \Delta H_f(\mathbf{1})$, decreases with the increase in the polarity of solvents. This calculated results predict that polar solvents transform the enol (**1**) into the keto form (**2**) more readily than apolar solvents.

In contrast, the energy difference, $\Delta H_f(\mathbf{3}) - \Delta H_f(\mathbf{2})$, increases with the increase in the polarity of solvents. This implies that polar solvents give a large barrier for the transformation of the keto (**2**) into the enol form (**1**) and hence predict that **2** can be isolated. This prediction agrees with the experimental finding that **2** was isolated, its NMR spectrum being obtained.[1] The keto form (**2**) is sufficiently stable to show its biological activities.[1]

The relative ratio of different tautomers depends on the energy differences between two tautomeric species. Using the values of $\Delta H_f(\mathbf{2}) - \Delta H_f(\mathbf{1})$, we calculated the relative ratio of the enol (**1**) and the keto form (**2**) in the gas phase as well as in solutions at 298 K. The results are listed in Table 2. As shown in Table 2, **1** is the only species in the gas phase. In $CHCl_3$, **1** still predominates over **2**. This is in agreement with the available experimental finding, which indicates that after the keto form, meridin-12(13*H*)-one (**2**), had been stored in $CDCl_3$ for 1-2 days, the ^1H NMR spectrum of the sample

Table 2. Ratio of Meridine (**1**) and Meridin-12(13*H*)-one (**2**)

Solvent	**1**	**2**
Non	99.99 %	0.01 %
$CHCl_3$	99	1
CH_2Cl_2	90	10
2-Propanol	69	31
EtOH	64	36
MeCN	54	46
DMSO	50	50
H_2O	42	58

was indistinguishable from that of the enol form, meridine (**1**).[1] Table 2 also predicts an almost equal mixture of **1** and **2** in polar solvents. This suggests that both **1** and **2** are present in aqueous solutions. If polar or aqueous solutions or media are used in the study of the biological activities of the two forms, the solutions or the media include both **1** and **2**. The biological activities of **1** and **2** have been reported by Schmitz,[1] McCarthy,[2a] Longley and co-workers.[2b] The observed activity of meridine (**1**) might originate from the keto form (**2**) and *vice versa*. The origin of the biological activity of meridine seems to be unclear and deserves further study.

CONCLUSION

The calculated results show that solvents play an important role in the relative stability of meridine and its tautomer, meridin-12(13*H*)-one. The enol form, meridine, is the only species in apolar solvents. Polar solvents stabilize preferentially the keto form, meridin-12(13*H*)-one. Both the enol and keto forms can be present in polar solvents.

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