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RELATIVE STABILITY OF CRYPTOLEPINONE AND HYDROXYCRYPTOLEPINE

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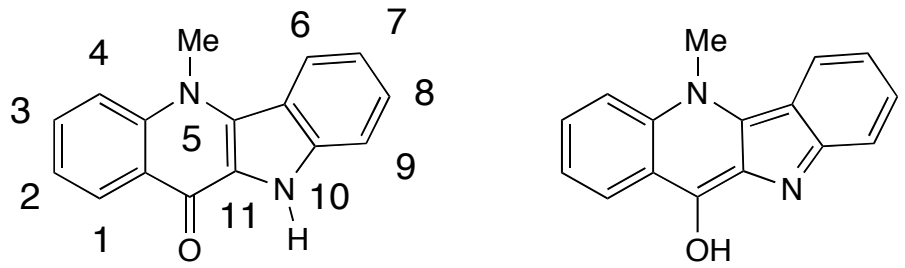
Abstract – The relative stability between cryptolepinone and 11-hydroxycryptolepine in solvents has been investigated by use of semiempirical molecular orbital and hybrid-density functional methods. The results have predicted that only cryptolepinone exists in all solvents examined (pyridine, acetone, MeOH, MeCN and DMSO), disagreeing with the experimental findings in which in MeOH and MeCN both cryptolepinone and 11-hydroxycryptolep are present. This disagreement suggests that MeOH and MeCN solutions include chemical species other than 11-hydroxycryptolepin.

Cryptolepinone (**1**) is one of the indoloquinoline alkaloids isolated from the roots of *Cryptolepis sanguinolenta* (Lindl.) Schlechter (*Asclepiadaceae* or *Pepiplocaceae*) used in West Africa for the treatment of various fevers including hepatitis, of malaria and of rheumatism.[1, 2] This alkaloid has received great attention because of an open question about its molecular structure.[2] The alkaloid may exist as two forms, cryptolepinone (**1**) (the keto form) and 11-hydroxycryptolepine (**2**) (the enol form). Which is stable ? It remains unclear.[2c, 2e] The molecule has been described as both **1** and **2** by independent research groups.[2] Houghton and co-workers have first isolated this alkaloid and identified it as **2**.[2a] Cooper et al. have synthesized cryptolepinone, and by comparing NMR and IR data, they have concluded that the natural product hydroxycryptolepine is properly represented as **1**.[2b] Martin and co-workers have also isolated the alkaloid and investigated its structure, using various NMR methods,[2d,2e] and have confirmed the structure of this molecule as cryptolepinone (**1**).[2e] Fort et al. have pointed out

that the structure of cryptolepinone should be considered as either the keto (**1**) or the enol (**2**) tautomer, depending on solvents:[2c] in MeOH and MeCN both the keto and the enol form exist while in less polar pyridine and acetone and in more polar DMSO only the keto form exists. These experimental results have led us to investigate the solvent dependence of the relative stability of cryptolepinone (**1**) and 11-hydroxycryptolepine (**2**) by use of AM1, PM3 and COSMO methods as well as hybrid-density functional (DFT) methods with the self-consistent reaction field (SCRF) techniques.



1 **2**

Chart 1 Cryptolepinone (**1**) and 11-hydroxycryptolepine (**2**)

To address the question of which is more stable the keto (**1**) or the enol form (**2**), we have examined the relative stability of the two forms with and without the presence of solvents, using AM1 and PM3 calculational methods.[3, 4] Solvent effects are considered by use of COSMO method.[5] Semiempirical computations were carried out by use of MOPAC 93 program.[6] All structural parameters were optimized. The ground-state structure was minimized until a gradient norm of less than 0.01 kcal/mol Å was achieved.

The relative energies both in the gas phase and in solvents obtained by AM1 and PM3 calculations together with COSMO method are summarized in Table 1. Solvents examined in the present study are pyridine, acetone, MeOH, MeCN and DMSO, which have been used by Bierer and co-workers.[2c] Table 1 shows that in the gas phase, the keto form (**1**) is 18.9 kcal/mol lower in energy at AM1 level and 23.1 kcal/mol at PM3 level. The presence of solvents lowers the relative energy. The more polar solvent results in the smaller relative energy. In the most polar solvent used here, DMSO, the calculated relative energies are 16.9 kcal/mol (AM1) and 17.8 kcal/mol (PM3). The enol form (**2**) is thus predicted to be more energetically stabilized than the keto form (**1**) in polar solvents.

Table 1. Relative energies (ΔE) of cryptolepinone (**1**) and 11-hydroxycryptolepine (**2**)

Solvent (ε)[a]	ΔE [kcal/mol]	
	AM1	PM3
none	18.94 [b]	23.12
pyridine (12.3)	17.10	18.63
acetone (20.70)	16.95	18.21
MeOH (32.63)	16.87	17.95
MeCN (36.0)	16.86	17.92
DMSO (45.0)	16.85	17.84

[a] ε denotes the relative dielectric constant.
[b] Positive values indicate that **1** is energetically more stable than **2**.

As shown in Table 1, however, AM1 and PM3 calculations reveal that the keto form (**1**) is still much more stable than the enol form (**2**) in all the solvents. These results are in agreement with the experimental findings for pyridine-*d*5, acetone-*d6* and DMSO-*d6*, in which only the keto form was observed.[2c] In contrast, Fort et al. reported that the keto and enol forms were present in a 4:1 ratio for MeCN-*d3* and in a 9:1 ratio for MeOH-*d4*.[2c] These experimental results disagree with the results of AM1 and PM3 calculations, which still gives the rather large relative-energies in MeOH (16.9 kcal/mol (AM1) and 18.0 kcal/mol (PM3)) and in MeCN (16.9 kcal/mol (AM1) and 17.9 kcal/mol (PM3)). At AM1 and PM3 levels, the presence of only the keto form in MeOH and MeCN is expected.

To obtain more detailed information on the relative stability of the keto (**1**) and enol (**2**) forms in solvents, we have focussed on MeCN and DMSO and made hybrid-density functional (DFT) calculations,[7] using Gaussian 98 program.[8] The geometrical structures of the two forms have been fully optimized with the use of the DFT method (the B3LYP functional[9] with the 6-31G(d,p) basis set) and of the Onsager SCRF model[10] (denoted as Onsager(solvent)-Method 1//Onsager(solvent)-Method 1; Method 1 indicates B3LYP/6-31(d,p)). The results obtained are summarized in Table 2.

These results agree with those of the AM1, PM3 and COSMO methods. Table 2 indicates that the solvents, MeCN and DMSO, reduce the relative energy: 15.0 kcal/mol in the gas phase, whereas 14.6 kcal/mol in MeCN and 14.6 kcal/mol in DMSO. Although these values are smaller than those of AM1 and PM3 calculations, the Onsager(solvent)-B3LYP/6-31(d,p) calculations show that the keto form (**1**) is

much more stable in energy than the enol form (**2**) in DMSO and even in MeCN. This predicts that in these solvents, only the keto form (**1**) is included.

Table 2. DFT calculations of relative energies (ΔE) of cryptolepinone (**1**) and 11-hydroxycryptolepine (**2**)

Method	ΔE [kcal/mol]
B3LYP/6-31G(d,p)// B3LYP/631G(d,p)	14.95[a)]
Onsager(MeCN)-Method 1//Onsager(MeCN)-Method 1[b)]	14.62
Onsager(DMSO)-Method 1//Onsager(DMSO)-Method 1	14.61
B3LYP/6-31++G(d,p)//B3LYP/6-31++G(d,p)	14.36
Onsager(MeCN)-Method 2//Onsager(MeCN)-Method 2[c)]	14.74
Onsager(DMSO)-Method 2//Onsager(DMSO)-Method 2	14.91
IPCM(MeCN)-Method 2//Onsager(MeCN)-Method 2	13.74
IPCM(DMSO)-Method 2//Onsager(DMSO)-Method 2	13.75

[a)] Positive values indicate that **1** is energetically more stable than **2**.

[b)] Method 1 indicates B3LYP/6-31G(d,p).

[c)] Method 2 indicates B3LYP/6-31++G(d,p).

For further examination of the solvent effect on the relative stability, we have then carried out the higher level of calculations, using B3LYP/6-31++(d,p) and the Onsager SCRF model. Full optimization has been done (Onsager(solvent)-Method 2//Onsager(solvent)-Method 2; Metod 2 indicates B3LYP/6-31++(d,p)). In Table 2 are summarized the results obtained. These calculations show that the keto form (**1**) is preferred to the enol form (**2**). However, in going from the gas phase to MeCN and DMSO, the relative energy is slightly increased. This is in contrast to the results of Onsager(solvent)-B3LYP/6-31(d,p) calculations. The difference between the results of the two methods is probably due to the difference in the estimated radius a_0 of a fixed spherical cavity for the Onsager model:[10] in the B3LYP/6-31++(d,p) method, the value for a_0 is 4.73 Å for **1** and 5.15 Å for **2** while that is 4.79 Å for **1** and 4.95 Å for **2** in the B3LYp/6-31(d,p) method. To confirm this, the isodensity polarized continuum (IPCM) SCRF model calculations[11] with B3LYP/6-31++(d,p) method were performed at the geometries optimized by the Onsager(solvent)-B3LYP/6-31++(d,p) model (IPCM(solvent)-Method 2//Onsager(solvent)-Method 2; Metod 2 indicates B3LYP/6-31++(d,p)). The results listed also in Table 2 show that the presence of the solvents, MeCN and DMSO, decreases the energy difference between the

two forms. This indicates that the results of the Onsager model calculations for the relative stability in MeCN and in DMSO depend on the calculational methods used: B3LYP/6-31(d,p) and B3LYP/6-31++(d,p).

As shown in Table 2, the highest level of calculation in this study, IPCM(solvent)-Method 2//Onsager(solvent)-Method 2 (Method 2: B3LYP/6-31++(d,p)), shows that the keto form (**1**) is preferred by 13.7 kcal/mol both in MeCN and in DMSO. This large value supports the prediction that in MeCN, only the keto form exists.

Table 3. Calculated dipole moments (in Debye) of cryptolepinone (**1**) and 11-hydroxycryptolepine (**2**) in the gas phase

Method	**1**	**2**
AM1//AM1	3.65	5.12
PM3//PM3	2.89	5.38
B3LYP/6-31G(d,p)// B3LYP/631G(d,p)	4.24	4.79
B3LYP/6-31++G(d,p)//B3LYP/6-31G(d,p)	4.72	5.14
B3LYP/6-31++G(d,p)//B3LYP/6-31++G(d,p)	4.79	5.12

Our calculations have shown that cryptolepinone (**1**) is much more stable than 11-hydroxycryptolepine (**2**) for all the solvents examined. This can be understood by inspecting the magnitudes of the dipole moments of **1** and **2** without solvents (or in the gas phase), which are summarized in Table 3. In all the methods, the calculated dipole moment of **1** is somewhat small as compared with that of **2**, although the difference between them is small. When the relative energy without solvents is sufficiently large, the small difference in dipole moment has a less effect on the relative energy in solvents.[10c-d] For the solvents investigated here, therefore, cryptolepinone (**1**) is still more stable than 11-hydroxycryptolepine (**2**).

The present calculational studies have shown that cryptolepinone (**1**) is more stable in energy than 11-hydroxycryptolepine (**2**) in pyridine, acetone, MeOH, MeCN and DMSO. This is independent of the calculational methods, semiempirical (AM1 and PM3) and DFT(B3LYP/6-31(d,p) and B3LYP/6-31++(d,p)) methods. The results obtained predict that only cryptolepinone (**1**) is present in the solvents examined here, even in MeCN. The calculated results for MeOH and MeCN are different from the experimental findings. This discrepancy suggests that MeOH and MeCN solutions involve different chemical species from 11-hydroxycryptolepine (**2**). It is difficult to predict them because of the

limited experimental information on their spectral data. Therefore, we have to limit ourselves to suggesting that cryptolepinone (**1**) suffers the specific coordination of MeCN-*d3* and of MeOH-*d4*. These molecules have common structural features: one Me group and one electronically-negative atom, that is, a nitrogen atom of a cyano group and an oxygen atom of a hydroxyl group. The lengths of the molecules are also similar. These molecules may coordinate at the same region of cryptolepinone (**1**). The potential formation of an adduct of cryptolepinone (**1**) when dissolved in MeCN-*d3* and in MeOH-*d4* may account for the observations in these solvents. The experimental reinvestigation of the chemical species in the MeOH-*d4* and MeCN-*d3* solutions is of great interest and it might disclose what they are.

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