Calculated amide/enol of amide energy differences for several interesting amide systems†

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The calculated pK_{Enol} values for the enols of amides $Me_2CHCON(Me)Ph$ and $XCH_2CH(NH_2)CONHMe$ (X = H,OH) are lower by only 1.1–2.7 units than that of acetamide, and therefore these enols should not display unusual stability.

Although 'simple' enols (*i.e.* those lacking a β-electron-withdrawing substituent)[1] of aldehydes and ketones are much less stable than their aldehyde or ketone tautomers unless the enols are specially stabilised, they play an important role in several reactions.[2] Simple enols of carboxylic acid derivatives such as esters and amides are even much more unstable compared with the acid derivatives than the corresponding carbonyl/enol pair, owing to the stabilisation of the acid derivative by the alkoxy or amino substituent.[3] Recent calculations had shown that the equilibrium constant for the parent pair $MeCONH_2/CH_2{=}C(OH)NH_2$ expressed as pK_{Enol} (= $-\log K_{Enol}$; K_{Enol} = [Enol]/[Amide] at equilibrium) is 21.3 in the gas phase.[4] It is therefore not surprising that, from what we presently know, the role of enols of amides as reaction intermediates is limited.

A process in which enols of amides may play a role is peptide racemisation, since ketonisation of an intermediate planar enol of amide will give both *R* and *S* species of the amide. D-Serine and D-aspartate are observed in significant amount in mammalian tissues[5] and the enzyme responsible for serine isomerisation was recently isolated[5a] so that *in vivo* racemisation is possible.

Hegarty *et al.* reported recently experimental results which suggest that the enol 1-*N*-methylanilino-2-methylpropen-1-ol **2** of the amide *N*-methylanilino-2-methylpropionamide **1** exists in observable concentration in water-containing media and underwent tautomerisation to **1** at measurable rates.[6] Enols of amides as simple as **2** were not hitherto observed and, based on the shorter life times for related enols of acids,[7] they are not expected to have such a long lifetime. Since **2** resembles the intermediate enols expected in peptide racemisation we performed theoretical calculations for **1** and **2** as well as for two simple pairs of amides/enols of serine and alanine amides in order to find out if the enols are unusually thermodynamically stable, so that this may be reflected in their kinetic stability.

The relative stabilities of the amide **1** and the enol **2** as well as that of the other compounds in Table 1 were computationally determined by means of density functional theory at the B3LYP/6-31G** level.[8,9] This method has been extensively used in recent calculations of enols of carboxylic acid derivatives, and the calculated pK_{Enol} values were shown to be within *ca.* 2 pK_{Enol} units of the values measured in water.[4,10]

Several conformational isomers were examined for **1** and **2** and the most stable ones are shown in Fig. 1. with others given as ESI.† The phenyl ring of amide **1** is *anti* to the C=O bond and is perpendicular to the amide moiety, facing the isopropyl group. Another conformation with the phenyl ring coplanar to the amide moiety is not on a local minimum and converges to the structure shown in Fig. 1. The conformer with the carbonyl group and the phenyl ring *syn* to each other is 12.7 kJ mol^{-1} higher in energy than **1**. In enol **2**, the ethenol and the anilino moieties are twisted (O–C–N–Ph dihedral angle of 64°) and the enolic hydrogen is directed toward the Ph ring. Attempted optimisation of a planar conformation gave the twisted structure. Another conformer with the OH pointing away from the Ph ring is 4.0 kJ mol^{-1} less stable.

Table 1 Amide–enol isomerisation free energies ΔG (kJ mol^{-1}), electronic energies (ΔE) (kJ mol^{-1}) (in parentheses) and pK_{Enol} of amides calculated at the B3LYP/6-31G** level at 25 °C

Amide/enol	$\Delta G(\Delta E)$	pK_{Enol}
$Me_2CHCON(Me)Ph$ **(1)**/$Me_2C{=}C(OH)$-N(Me)Ph (**2**)	105.3 (103.2)	18.5
$MeCONH_2$ **(3)**/$CH_2{=}C(OH)NH_2$ **(6)**	121.2 (114.5)	21.3[4]
$HOCH_2CH(NH_2)CONHMe$ **(4)**/$HOCH_2C(NH_2){=}$C(OH)NHMe (**7**)	119.1 (123.7)	20.1
$MeCH(NH_2)CONHMe$ (**5**)/$MeC(NH_2){=}C(OH)NHMe$ (**8**)	112.7 (113.3)	19.8

The calculated energy difference between **1** and **2** is 103.2 kJ mol^{-1} in electronic energy and 105.3 kJ mol^{-1} in free energy, which corresponds to a pK_{Enol} value of 18.5 at 25 °C. This value is 2.8 pK_{Enol} units lower than that calculated for the parent acetamide system.[4] The pK_{Enol} value is much higher than those of enols of acids which were observed by flash photolysis, but had shorter lifetimes owing to a faster decomposition to the corresponding acids.[7] Clearly the unexpectedly long lifetime of enol **2**[6] does not reflect an unusual thermodynamic stability of the enol. The calculated gas phase K_{Enol} value for **1**, taking into account that the calculated solvent effects on pK_{Enol} values are small[4,11] suggests that **2** will not be observable in aqueous organic media at room temperature, based on data of pK_{Enol} values and the lifetimes of simple enols.[12] Indeed, the other observable simple enols of amides having two bulky β-Tip (Tip = 2,4,6-$Pr^i_3C_6H_2$) groups, *i.e.* $Tip_2C{=}C(OH)NR_2$[13] should have pK_{Enol} values of *ca.* 8, based on the calculated K_{Enol} of 9.3

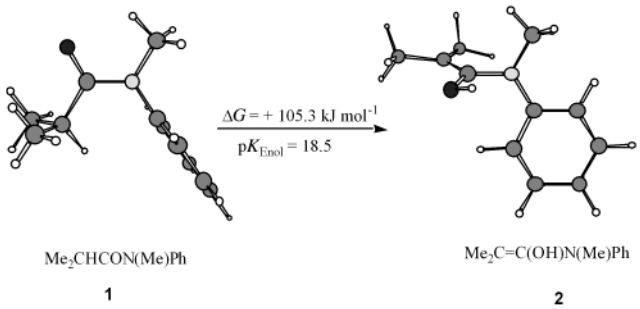

Fig. 1 Most stable conformational isomers for **1** and **2**.

† Electronic supplementary information (ESI) available: optimised structures of various conformers. See http://www.rsc.org/suppdata/cc/b0/b006216m/

for ditipylacetic acid[10] and the lower pK_{Enol} for acetamide than for AcOH.[4] The $t_{1/2}$ for the tautomerisation of diTip *N*,*N*-dimethylacetamide is *ca.* 20 min in 5:1 CD_3CN–THF-d_8 at 273 K.[13a]

Table 1 summarises the keto–enol isomerisation energies for the amide/enol pairs of the *N*-methyl amides of serine and alanine. Again, several conformations were found for each species (these are given in the ESI†) and the energy differences and the derived pK_{Enol} values in Table 1 are based on the most stable conformation of both species. For the two *N*-methylamides the pK_{Enol} values are *ca.* 1 unit lower than for the parent acetamide system but the 1,2-diaminoenols are still so unstable compared with the corresponding amide forms, that if a correlation between thermodynamic and kinetic stability exists in these cases, the isomerisation of peptides including serine and aspartic acid *via* the enol route is inferred to be very slow.[14]

Dissection of the overall effect of the C_β and nitrogen substituents to their individual effects on the amide and the enol is obtained by using the isodesmic reactions (1) and (2). All

$$XX'CHCONYY' + MeMe \rightleftharpoons XX'CHCH_2NYY' + MeCH{=}O \quad (1)$$

reaction free energies at 25 °C in kJ mol^{-1}

1: X=X′=Me, Y=Me, Y′=Ph	108.5
3: X=X′=Y = Y′=H	115.4
4: X=$HOCH_2$, X′=NH_2, Y=H, Y′=Me	129.5
5: X=Me, X′=NH_2, Y=H, Y′=Me	124.4

$$XX'C{=}C(OH)NYY' + MeMe \rightleftharpoons XX'CHCH_2NYY' + H_2C{=}CHOH \quad (2)$$

2: X=X′=Me, Y=Me, Y′=Ph	59.3
6: X=X′=Y=Y′=H	50.2
7: X=$HOCH_2$, X′ = NH_2, Y=H, Y′=Me	66.5
8: X=Me, X′=NH_2, Y=H, Y′=Me	67.7

reactions were found to be endothermic indicating that the interaction of the amino groups with either the carbonyl or the enol function stabilises the system and more so for the amide form. For the amino acid amides the amide forms (**4** and **5**) are more stabilised than acetamide by 9–14 kJ mol^{-1}, whereas the higher stabilisation of the enol forms (**7** and **8**) by *ca.* 17 kJ mol^{-1} result in lower pK_{Enol} values for the amino acid amides. The stabilisation of enol **2** is small, being only 9.1 kJ mol^{-1}, but the amide form **1** is less stabilised by 6.9 kJ mol^{-1} compared with acetamide and this destabilising interaction is responsible for the lower pK_{Enol} for **1**.

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Notes and references

1 H. Hart, *Chem. Rev.*, 1979, **79**, 515.
2 *The Chemistry of Enols*, ed. Z. Rappoport, Wiley, Chichester, 1990.
3 A. F. Hegarty and P. O'Neill in ref. 2, ch. 10, p. 639.
4 S. Sklenak, Y. Apeloig and Z. Rappoport, *J. Am. Chem. Soc.*, 1998, **120**, 10 359.
5 H. Wolosker, K. N. Sheth, M. Takahashi, J.-P. Mothet, R. O. Brady, Jr., C. D. Ferris and S. H. Snyder, *Proc. Natl. Acad. Sci. USA*, 1999, **96**, 721; H. Wolosker, S. Blackshaw and S. H. Snyder, *Proc. Natl. Acad. Sci. USA*, 1999, **96**, 13 409.
6 A. F. Hegarty, S. J. Eustance and C. Relihan, *7th European Symposium on Organic Reactivity (ESOR 7)*, Ulm, Germany, August 22–27, 1999, *Book of Abstracts*, A8, p. 68.
7 For a summary, see: A. J. Kresge, *Chem. Soc. Rev.*, 1996, **25**, 275.
8 A. D. Becke, *Phys. Rev. A*, 1988, **38**, 3098; C. Lee, W. Yang and R. G. Parr, *Phys. Rev. B*, 1988, **37**, 785.
9 All calculations were performed using the Gaussian 98 program: Gaussian 98, Revision A.6, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, Jr., R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 1998.
10 H. Yamataka and Z. Rappoport, *J. Am. Chem. Soc.*, 2000, **122**, in press.
11 J. Gao, *J. Mol. Struct. (THEOCHEM)*, 1996, **370**, 203.
12 J. Toullec, ch. 6 in ref. 2; J. R. Keeffe and A. J. Kresge, ch. 7 in ref. 2.
13 (*a*) J. Frey and Z. Rappoport, *J. Am. Chem. Soc.*, 1996, **118**, 3994; (*b*) Z. Rappoport, J. Frey, M. Sigalov and E. Rochlin, *Pure Appl. Chem.*, 1997, **69**, 1933.
14 Since the α-hydrogen to the amide function is acidic, ionization to a planar enolate ion is still a possible mechanistic route for racemisation of peptides.