Theoretical calculations of minimum energy structures and thermodynamics for the formation of cyclic amidines and imidates by intramolecular nucleophilic addition/elimination reactions

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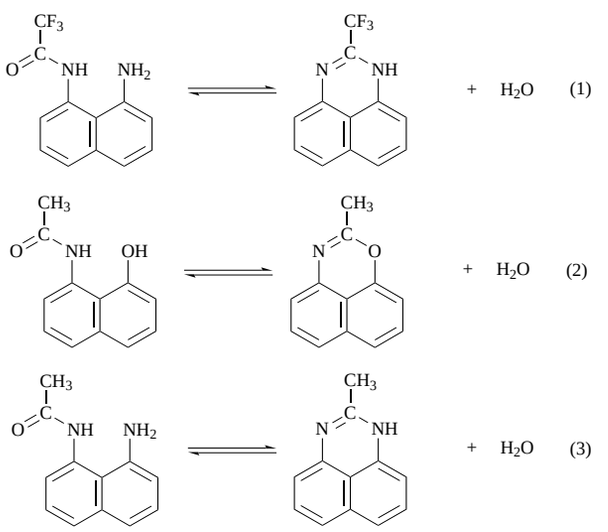
Theoretical calculations of minimum energy structures and thermodynamic terms using SCF theory with thermodynamic and solvation corrections have been made of the cyclisation of 1-amino-8-(acetylamino)naphthalene to give 2-methylperimidine with the liberation of water and of the related reaction of 1-hydroxy-8-(acetylamino)naphthalene to 2-methylnaphtho[1,8-*d*,*e*][1,3]oxazine. The calculations predict that in the gas phase the former reaction is strongly thermodynamically favourable ($\Delta G = -37.9$ kJ mol^{-1}, $\Delta H = -0.6$ kJ mol^{-1} and $T\Delta S = +37.3$ kJ mol^{-1} at 298.2 K) whereas the latter is much less favourable ($\Delta G = -2.0$ kJ mol^{-1}, $\Delta H = +31.1$ kJ mol^{-1} and $T\Delta S = +33.1$ kJ mol^{-1} at 298.2 K). The results are in qualitative agreement with experimental observations for the reactions in solution. Reasons for the different behaviour of the two reactions are discussed.

Introduction

It has been observed[1] that in 70% (v/v) Me_2SO–H_2O, 1-amino-8-(trifluoroacetylamino)naphthalene undergoes an intramolecular addition reaction with elimination of water to form 2-(trifluoromethyl)perimidine, reaction (1). In contrast 2-methylnaphtho[1,8-*d*,*e*][1,3]oxazine was found[2] to undergo a thermodynamically favourable hydration and ring-opening in aqueous solution to give 1-hydroxy-8-(acetylamino)naphthalene, as in the reverse of reaction (2). Both reactions were found to occur to completion in these directions. In order to understand the factors which account for this differing behaviour, theoretical calculations of the minimum energy structures of the reactants and products and the thermodynamic terms for reactions (2) and (3) have been carried out.



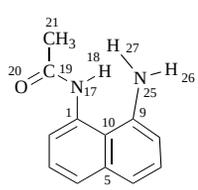
Computational procedures

We have used GAUSSIAN94[3] to perform *ab initio* restricted Hartree–Fock (RHF) calculations of the fully optimised structures and thermochemical properties of each of the compounds **1** to **4**, using a 6-31G* basis set augmented by a set of p-type gaussians with exponent 1.1 on each hydrogen directly bonded to nitrogen or oxygen. Initial geometries were obtained from a preliminary RAM1 optimisation in each case. Direct self-consistent field (SCF) calculations were performed and all vibrational frequencies were calculated analytically. Solvation effects were incorporated by means of the self-consistent reaction field (SCRF) procedure using the recommended cavity radii and a relative permittivity of 80. The computations were performed on a Cray J932/32, a Convex C3870, a Fujitsu VPX240/10 and a six-processor DEC AXP system.

Results and discussion

Calculations with 1-amino-8-(acetylamino)naphthalene and 2-methylperimidine

The important bonds lengths and bond angles in the calculated minimum energy structures for 1-amino-8-(acetylamino)-naphthalene (**1**) and 2-methylperimidine (**2**) are given in Table



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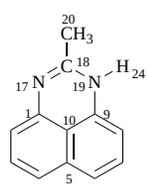

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1. In 1-amino-8-(acetylamino)naphthalene the naphthalene ring is slightly distorted from planarity with a dihedral angle of −1.9° between C(4)C(3) and C(2)C(1) and an angle of −2.2° between C(9)C(8) and C(7)C(6). The CH_3CONH group is non-planar with a dihedral angle of −175.9° between C(21)C(19) and N(17)C(1) and an angle of 2.9° between O(20)C(19) and N(17)C(1). There is also a substantial twist of the amide group out of the plane of the naphthalene ring with dihedral angles between H(18)N(17) and C(1)C(10) of 16.8° and between C(19)N(17) and C(1)C(10) of −164.6°. In addition the amino group is displaced from the plane of the naphthalene ring, there being a dihedral angle of 184.3° between N(25)C(9) and C(10)C(5). The hydrogen atoms of the amino group are located above and below the plane of the naphthalene ring though not to the same extent, with dihedral angles of 65.3 and −174.0° respectively between H(26)N(25) and C(9)C(10) and between H(27)N(25) and C(9)C(10). The structure adopted by 1-amino-8-acetylaminonaphthalene reduces the unfavourable interactions between the amide and amine groups. Distortions such

Table 1 Important bond lengths and bond angles in the fully optimised structures

Bond lengths/pm		Bond angles/°	
1-Amino-8-(acetylamino)naphthalene (**1**)			
C(1)N(17)	140.9	C(10)C(1)N(17)	118.8
N(17)C(19)	136.1	C(1)N(17)C(19)	128.7
N(17)H(18)	99.4	C(1)N(17)H(18)	114.8
C(19)O(20)	119.9	N(17)C(19)O(20)	125.3
C(19)C(21)	151.7	N(17)C(19)C(21)	113.7
N(25)H(26)	100.1	C(9)N(25)H(26)	111.5
N(25)H(27)	99.8	C(9)N(25)H(27)	110.8
C(9)N(25)	142.2	C(10)C(9)N(25)	121.0
2-Methylperimidine (**2**)			
C(1)N(17)	139.8	C(10)C(1)N(17)	120.6
N(17)C(18)	126.7	C(1)N(17)C(18)	118.5
C(18)N(19)	136.8	N(17)C(18)N(19)	124.3
C(18)C(20)	150.2	N(17)C(18)C(20)	120.4
N(19)H(24)	99.3	C(18)N(19)H(24)	119.1
		C(9)N(19)H(24)	118.9
		C(9)N(19)C(18)	122.1
C(9)N(19)	139.0	C(10)C(9)N(19)	115.5
1-Hydroxy-8-(acetylamino)naphthalene (**3**)			
C(1)N(17)	140.5	C(10)C(1)N(17)	119.2
N(17)C(19)	136.4	C(1)N(17)C(19)	129.2
N(17)H(18)	99.1	C(1)N(17)H(18)	115.3
C(19)O(20)	119.8	N(17)C(19)O(20)	125.6
C(19)C(21)	151.7	N(17)C(19)C(21)	113.0
O(25)H(26)	94.3	C(9)O(25)H(26)	110.6
C(9)O(25)	136.2	C(10)C(9)O(25)	118.7
2-Methylnaphtho[1,8-*d*,*e*][1,3]oxazine (**4**)			
C(1)N(17)	140.2	C(10)C(1)N(17)	119.0
N(17)C(18)	125.5	C(1)N(17)C(18)	118.8
C(18)O(19)	135.0	N(17)C(18)O(19)	126.1
C(18)C(20)	149.4	N(17)C(18)C(20)	122.9
		C(9)O(19)C(18)	119.6
C(9)O(19)	136.6	C(10)C(9)O(19)	118.0

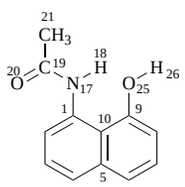
as this are often found in naphthalene derivatives with substituents at the 1 and 8 positions.

The minimum energy structure calculated for 2-methylperimidine (**2**) is almost precisely planar except for the hydrogen atoms of the methyl group. The naphthalene ring is planar with all dihedral angles of 0.00 or 180.00°. The hydrogen atom attached to N(19) is very slightly displaced from the plane of the molecule with a dihedral angle of 179.95° between H(24)N(19) and C(9)C(10).

The energies, enthalpies, entropies and Gibbs energies calculated for the minimum energy structures of **1** and **2** and for H_2O are given in Table 2 together with the changes in these quantities accompanying cyclisation, reaction (3). Values are calculated for cyclisation in the gas phase and in solution in a solvent of relative permittivity 80, the value for water. The corrections from the gas phase to solution are estimated in GAUSSIAN94 by a SCRF calculation using the Onsager reaction field model. Although this is a crude procedure the size of the solvation correction is small and the major conclusions are unlikely to be changed by using a more accurate procedure. The calculation does not take into account specific hydrogen-bond interactions which may be important for these molecules. The results in Table 2 show that cyclisation and elimination of water from 1-amino-8-(acetylamino)naphthalene in the gas phase is almost thermoneutral ($\Delta H = -0.6$ kJ mol^{-1}). However the cyclisation is driven strongly in the forward direction of reaction (3) by a large favourable entropy change ($T\Delta S = +37.3$ kJ mol^{-1}) giving an overall Gibbs energy change $\Delta G = -37.9$ kJ mol^{-1}. The favourable entropy change will be made up of a negative term due to the loss of internal degrees of freedom on cyclisation and a larger positive contribution accompanying the liberation of an additional product molecule (water). In solution the reaction is calculated to occur with a favourable enthalpy change ($\Delta H_{solv} = -7.0$ kJ mol^{-1}), with a very strongly favourable entropy change ($T\Delta S_{solv} = +36.6$ kJ mol^{-1}) and overall with a favourable Gibbs energy change ($\Delta G_{solv} = -43.6$ kJ mol^{-1}). Thus the calculations are compatible with the experimental observation[1] that the cyclisation of 1-amino-8-(trifluoroacetylamino)naphthalene to give 2-(trifluoromethyl)perimidine in 70% (v/v) Me_2SO–H_2O occurs to completion.

Calculations with 1-hydroxy-8-(acetylamino)naphthalene and 2-methylnaphtho[1,8-*d*,*e*][1,3]oxazine

The important bond lengths and bond angles in the optimised structures of 1-hydroxy-8-(acetylamino)naphthalene (**3**) and



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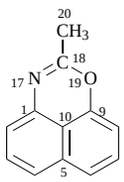

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2-methylnaphtho[1,8-*d*,*e*][1,3]oxazine (**4**) are given in Table 1. In **3** the naphthalene ring is close to planarity with all dihedral angles of 0.0 or 180.0° and in **4** the naphthalene ring is effectively planar with all dihedral angles of 0.00 or 180.00°. In 1-hydroxy-8-(acetylamino)naphthalene the hydroxy group is in the plane of the naphthalene ring with the hydrogen atom pointing away from the amide group. The amide group is almost exactly planar with a dihedral angle of −178.5° between N(17)C(1) and C(21)C(19) and an angle of 0.6° between N(17)C(1) and C(20)C(19). It also lies almost exactly in the plane of the naphthalene ring with a dihedral angle of 0.4° between H(18)N(17) and C(1)C(10). Hence the hydroxy and amide groups in **3** can be accommodated at the 1 and 8 positions with relatively little strain. This is in contrast to the distortion found in the structure of 1-amino-8-(acetylamino)-naphthalene. In 2-methylnaphtho[1,8-*d*,*e*][1,3]oxazine (**4**) the oxazine heterocycle is planar with all dihedral angles of 0.00 or 180.00° and the N=C–O atoms lie in the same plane as the naphthalene ring.

The calculated energies and the enthalpy, entropy and Gibbs energy changes for the cyclisation of 1-hydroxy-8-(acetylamino)naphthalene to give 2-methylnaphtho[1,8-*d*,*e*][1,3]-oxazine with the liberation of water, reaction (2), are given in Table 2. The energy and enthalpy changes accompanying the cyclisation are strongly unfavourable but a large and favourable entropy change results in a calculated Gibbs energy change which predicts that the cyclisation is very slightly thermodynamically favourable in the gas phase and in solution with $\Delta G = -2.0$ kJ mol^{-1} and $\Delta G_{solv} = -2.8$ kJ mol^{-1} respectively. Spectrophotometric measurements of the equilibrium between 1-hydroxy-8-(acetylamino)naphthalene and 2-methylnaphtho-[1,8-*d*,*e*][1,3]oxazine in aqueous solution at 298.2 K show that ring opening of 2-methylnaphtho[1,8-*d*,*e*][1,3]oxazine to 1-hydroxy-8-(acetylamino)naphthalene occurs to completion. The difference between this experimental result and the value $\Delta G_{solv} = -2.8$ kJ mol^{-1} calculated in the present work may arise because in the calculation, the effect of solvation does not include specific hydrogen-bond interactions. These could be particularly important in stabilising 1-hydroxy-8-(acetylamino)-naphthalene and the calculated value of ΔG_{solv} in the direction of cyclisation without these terms would then be lower than the experimental value.

Comparison of calculations for the cyclisation of 1-amino-8-(acetylamino)naphthalene and 1-hydroxy-8-(acetylamino)-naphthalene

The calculated Gibbs energy changes for reactions (2) and (3)

Table 2 Energies for optimised structures **1** to **4** and for H_2O and thermodynamic terms for the cyclisation of 1-amino-8-(acetylamino)naphthalene and 1-hydroxy-8-(acetylamino)naphthalene at 298.2 K. The values refer to the gas phase except those shown with a subscript 'solv' which refer to solution in a solvent of dielectric constant 80.

	1	**2**	**3**	**4**	H_2O
$-E$/hartree[a]	645.203 503	569.175 324	665.033 288	588.993 423	76.023 615
$-E_{solv}$/hartree[a]	645.205 930	569.176 767	665.036 816	588.993 623	76.026 998
$-H$/hartree[a]	644.954 161	568.957 733	664.797 877	588.789 392	75.996 640
$-H_{solv}$/hartree[a]	644.956 643	568.959 245	664.801 462	588.789 654	76.000 071
$+TS$/hartree[a]	0.052 674	0.045 536	0.053 767	0.045 022	0.021 361
$+TS_{solv}$/hartree[a]	0.052 891	0.045 464	0.053 568	0.045 021	0.021 368
$-G$/hartree[a]	645.006 835	569.003 269	664.851 644	588.834 414	76.018 001
$-G_{solv}$/hartree[a]	645.009 534	569.004 709	664.855 030	588.834 675	76.021 439
a_o/Å	4.87	4.74	4.74	4.47	2.53
Basis set size	258	233	253	228	25

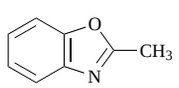
	Cyclisation of 1-amino-8-(acetylamino)naphthalene	Cyclisation of 1-hydroxy-8-(acetylamino)naphthalene
ΔE/kJ mol^{-1}	12.0	42.7
ΔE_{solv}/kJ mol^{-1}	5.7	42.5
ΔH/kJ mol^{-1}	−0.6	31.1
ΔH_{solv}/kJ mol^{-1}	−7.0	30.8
ΔS/J K^{-1} mol^{-1}	125.1	111.0
ΔS_{solv}/J K^{-1} mol^{-1}	122.8	112.7
$T\Delta S$/kJ mol^{-1}	37.3	33.1
$T\Delta S_{solv}$/kJ mol^{-1}	36.6	33.6
ΔG/kJ mol^{-1}	−37.9	−2.0
ΔG_{solv}/kJ mol^{-1}	−43.6	−2.8

[a] 1 hartree = 2625 kJ mol^{-1}.

lead to the conclusion that in the gas phase, the cyclisation of 1-amino-8-(acetylamino)naphthalene is thermodynamically much more favourable than the cyclisation of 1-hydroxy-8-(acetylamino)naphthalene. This is in qualitative agreement with the results of experimental measurements for the two reactions in solution.[1,2] The calculations show that both reactions are almost equally favoured entropically with gas phase values of $T\Delta S = +33.1$ and $= +37.3$ kJ mol^{-1} respectively for reactions (2) and (3). Although there will be some loss of internal degrees of freedom accompanying the formation of a cyclic species and this will differ somewhat for the two reactions, the predominant contribution to the entropy change is made by the liberation of a water molecule accompanying the reaction. The difference in thermodynamic feasibility of the two reactions is determined by the difference in the enthalpy changes. The enthalpy change accompanying the gas-phase cyclisation of 1-hydroxy-8-(acetylamino)naphthalene, reaction (2), is very strongly unfavourable with $\Delta H = +31.1$ kJ mol^{-1} whereas for 1-amino-8-(acetylamino)naphthalene the reaction is almost thermoneutral with $\Delta H = -0.6$ kJ mol^{-1}. Contributions to this difference may arise from differences in strain energy for the two cyclic species and the two open species as well as from the differences in the individual bonds which are being made and broken in the two reactions. Because of the out-of-plane distortions in **1**, the calculations suggest that 1-amino-8-(acetylamino)naphthalene is more strained than 1-hydroxy-8-(acetylamino)naphthalene and the relief of this strain would make cyclisation of 1-amino-8-(acetylamino)naphthalene more favourable. However the nature of the bonds being broken and formed in the cyclisations is likely to be a more important factor. There are two differences in the bond making and breaking processes between the two reactions. The cyclisation of 1-hydroxy-8-(acetylamino)naphthalene involves the formation of a carbon–oxygen bond and the breakage of an oxygen–hydrogen bond whereas the cyclisation of 1-amino-8-(acetylamino)naphthalene involves the formation of a carbon–nitrogen bond and the breakage of a nitrogen–hydrogen bond. Using average values of enthalpies of dissociation for these bonds leads to the prediction that the enthalpy of cyclisation of 1-amino-8-(acetylamino)naphthalene will be *ca.* 20 kJ mol^{-1} more favourable than the enthalpy of cyclisation of 1-hydroxy-8-(acetylamino)naphthalene as a result of the different bonds which are made and broken. The calculated difference in enthalpies of cyclisation for the two processes in the gas phase is *ca.* 31.7 kJ mol^{-1}.

Comparison with other reactions

The formation of amidines and imidates from the intermolecular reactions of amides with amines or alcohols respectively is usually a thermodynamically strongly unfavourable reaction. If amidines and imidates are introduced into an aqueous medium, hydrolysis of the amidine to the amide and amine and the imidate to the amide and alcohol (or ester and amine) occurs.[4] The formation of cyclic imidates from the corresponding intramolecular reactions are also found to be unfavourable. Thus for 2-methylbenzoxazole[5] (**5**), 2-methyl-4*H*-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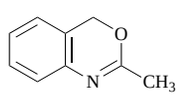
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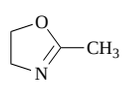
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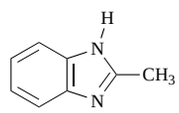
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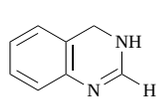
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3,1-benzoxazine[6] (**6**) and 2-methyl-4,5-dihydrooxazole[7] (**7**) and for 2-methylnaphtho[1,8-*d*,*e*][1,3]oxazine, the subject of the present work, equilibrium lies strongly towards the open species. The formation of cyclic amidines can be more favourable but the equilibrium position depends on such factors as the ring size and nature of the reacting groups. In the case of 2-methylbenzo[*d*]imidazole[8] (**8**) and 2-(trifluoromethyl)perimidine,[1] the equilibrium lies strongly towards the cyclic species. However for 3,4-dihydroquinazoline (**9**) it is observed that ring opening occurs in aqueous solution to give 2-amino-*N*-formylbenzylamine.[9] In general we conclude that the formation of cyclic amidines may be a thermodynamically favourable process because favourable entropy changes may dominate over less favourable enthalpy changes. In the formation of cyclic

imidates the favourable entropy of cyclisation is insufficient to overcome the strongly unfavourable enthalpy changes involved in the cyclisation.

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