Cyclic Allylamine–Enamine Systems. Part 7.[1] A Theoretical Study of the Relative Energies of Isomeric Cyclic Allylamine–Enamine Systems

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The relative energies of a series of isomeric cyclic allylamine–enamine systems have been calculated by MINDO/3 and *ab initio* MO methods including complete geometry optimisation. The MINDO/3 results are shown to be reliable by comparison with experiment and with the *ab initio* results. Thus, for a particular pair of *N*-methyltetrahydropyridine-4-carbaldehyde isomers (**12**) and (**13**), both *ab initio* and MINDO/3 methods give similar optimised geometries and predict the enamine to be more stable than the allylamine by 1.5 and 1.3 kJ mol^{-1} respectively. This energy difference is predicted to be increased by up to 3 kJ mol^{-1} in water.

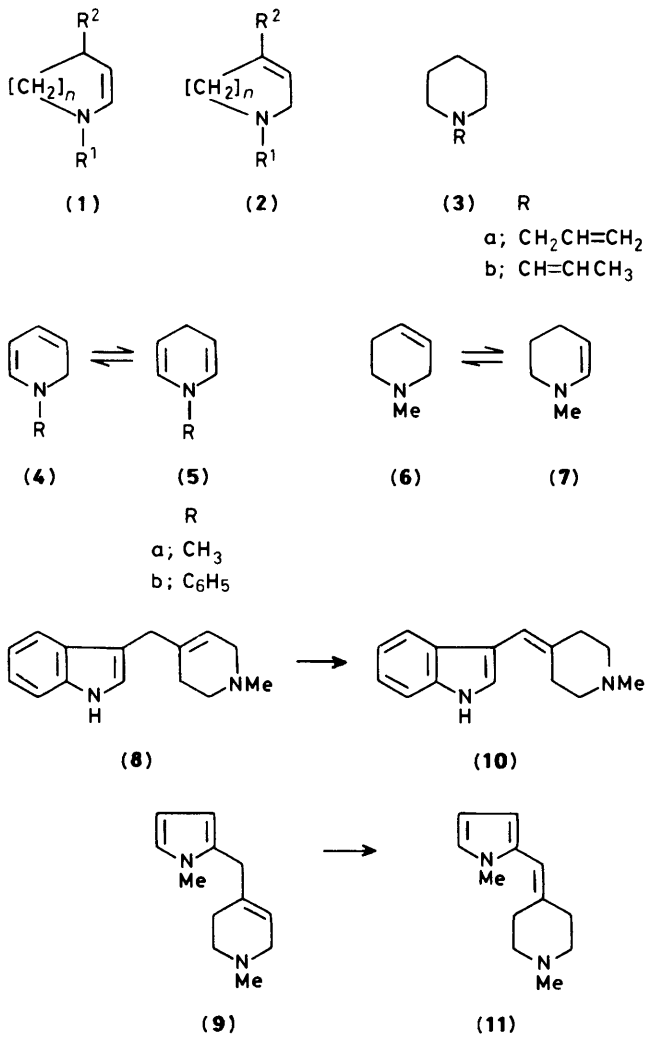
Cyclic enamines (**1**) are extremely useful intermediates for the construction[2] of the polycyclic ring systems of alkaloids. Their synthesis can be achieved in several ways. The approach we have adopted[1] is based on the efficient synthetic pathways available for the preparation of the isomeric cyclic allylamines (**2**), by way of borohydride reduction of pyridinium salts giving (**2**; n = 2), and metal–acid reduction of pyrroles giving (**2**; n = 1). This approach requires a method for subsequent isomerisation of the allylamine isomer (**2**) into the enamine (**1**).

The strong base-catalysed isomerisation of non-cyclic† allylamines into the corresponding enamines has been recognised as a preparatively useful process for some time.[3] The conjugation between the nitrogen lone pair and the double bond is invoked to explain the preference for the enamine isomer. One estimate,[4] arrived at by comparing heats of hydrogenation of (**3a**) and (**3b**), gave a figure of 10.5 ± 2 kJ mol^{-1} for this conjugation energy.

With both nitrogen and a double bond in a six-membered cyclic framework, measurements of the enamine conjugation energy are now available[5–7] from comparisons within the pairs (**4a**)/(**5a**), (**4b**)/(**5b**), and (**6**)/(**7**). Values of 9.6, 3.8, and 16.7 kJ mol^{-1}, respectively, resulted from equilibration studies in KOBu^t–Me_2SO at 90 °C. Interestingly, when the allylamines (**8**)[1] and (**9**)[8] were comparably treated, isomeric substances (**10**) and (**11**) were formed in which the double bond had moved into conjugation with the aromatic rings rather than into the enamine position.

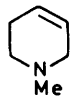
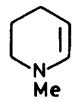
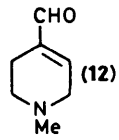
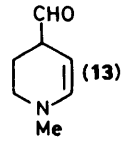
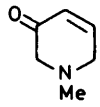
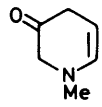
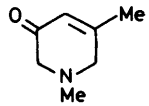
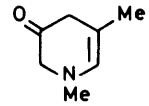
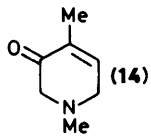
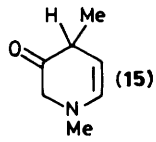
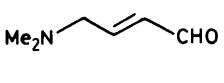
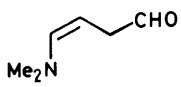
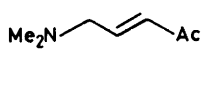
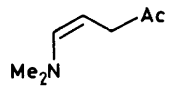
The need for such a strong base to effect isomerisation stems from the low acidity of the allylic protons in (**2**), but although these conditions place restrictions on the character of groups elsewhere in the molecule, the strong base-catalysed isomerisation of cyclic allylamines can nonetheless be synthetically useful in simple cases.[3,8,9]

The attachment of a carbonyl group to a cyclic allylamine (**2**; R^2 = COR^3) acidifies the allylic protons, making a weaker, milder base sufficient to allow equilibration between allylamine and enamine isomers. However, it also introduces the complication that double bond/carbonyl group conjugation must be sacrificed for the desired isomerisation to take place. It was therefore of relevance to enquire, in the light of the above estimates which showed a relatively small energy gain on enamine conjugation, whether the loss of C=C/C=O conjugation would be sufficient to prevent the isomerisation of (**2**; R^2 = COR^3) being synthetically useful. We have demonstrated experimentally[3,10] that conjugated ketones *can* be isomerised to the corresponding enamines using NaOMe–MeOH. Further, we have utilised species of the form (**2**; n = 2, R^2 = COR^3) for



† 'Non-cyclic' implies in this context compounds in which the double bond and the nitrogen are *not* in the same ring.

Table 1. Heats of formation (ΔH_f/kJ mol^{-1}) given by MINDO/3 method

Allylamine	Enamine	ΔH_f allylamine	ΔH_f enamine	$\Delta(\Delta H_f)$
		99.9	70.9	29.0
		139.7	115.2	24.5
 (12)	 (13)	−31.6	−32.9	1.3
		−28.5	−53.5	25.0
		−51.2	−78.7	27.5
 (14)	 (15)	−52.9	−52.2	−0.7
		−6.9	−22.0	15.1
		−50.8	−57.9	7.1

the construction of alkaloid skeletons, using both mild base- and mild acid-catalysed processes.[10–12]

In this paper, we report theoretical investigations of the relative stabilities of a series of allylamines and enamines, using both semiempirical and *ab initio* molecular orbital (MO) methods. These calculations are designed to assess the usefulness of these MO methods to predict the quite small energy differences which are indicated to exist between these isomers.

Computational Methods and Results

The prediction of the relative energies of the allylamine–enamine systems requires a knowledge of the molecular geometries of the isomers. In the absence of a range of experimental structural data such geometries must be obtained theoretically. The use of *ab initio* MO calculations, incorporating analytic energy gradients, to obtain accurate molecular structures is now well established.[13] The use of a split-valence (3-21G) basis[14] is needed to give both geometries and relative energies to an acceptable degree of accuracy. For example, previous studies of lactam–lactim tautomerism have given relative energetics accurate to *ca.* 10 kJ mol^{-1}.[15] Since such calculations are extremely time-consuming the use of the more rapid semiempirical methods (for example MNDO, MINDO/3) has obvious attractions.[16] However, for a series of lactam–lactim and amine–imine tautomers, the semiempirical MINDO/3 method was shown to have serious deficiencies.[17]

We here investigate the use of both *ab initio* and MINDO/3 methods to study a series of allylamine–enamine systems. The theoretical heats of formation of a series of allylamines and enamines, calculated by the MINDO/3 method including full geometry optimisation, are shown in Table 1. For those systems where the allylamine isomer lacked conjugation, the enamine was, as expected, found to be the more stable isomer by more than 20 kJ mol^{-1}. The additional stabilisation of the allylamine arising from conjugation with a carbonyl group reduces the energy difference between the isomers, particularly when the exocyclic carbonyl group has some conformational freedom. Thus, in the case of the isomers (**12**) and (**13**) this energy difference is only *ca.* 1 kJ mol^{-1}. However, in only one case [(**14**) and (**15**)] is the allylamine predicted to be the more stable, and then only by < 1 kJ mol^{-1}.

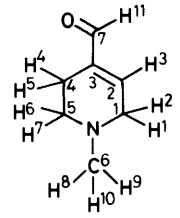
In view of the small energy differences found for some of the carbonyl compounds, and the possible unreliability of the MINDO/3 method, *ab initio* calculations were carried out to estimate the relative stabilities of the isomers (**12**) and (**13**). Full

Table 2. Optimised molecular geometry[a] of the allylamine (**12**)

Atom[b]	X[c]	Y	Z
N	3.144 964	−0.161 880	−0.508 250
	3.322 991	−0.087 178	−0.111 083
C-1	2.250 149	2.361 997	0.188 493
	2.226 979	2.372 796	0.126 197
C-2	−0.590 556	2.511 487	0.158 582
	−0.586 163	2.443 289	0.091 669
C-3	−2.055 096	0.503 213	−0.020 770
	−2.182 285	0.428 338	0.045 029
C-4	−1.014 315	−2.144 113	−0.186 791
	−0.969 517	−2.165 180	0.017 192
C-5	1.728 889	−2.200 547	0.738 079
	1.881 160	−2.345 211	0.335 032
C-6	5.892 952	−0.405 175	−0.338 319
	5.995 453	−0.258 797	−0.294 526
C-7	−4.820 041	0.799 004	−0.059 786
	−4.975 639	0.750 162	−0.000 265
O	−6.294 925	−0.948 226	−0.178 773
	−6.577 986	−0.818 633	−0.249 229
H-1	3.012 362	3.715 681	−1.149 539
	2.945 919	3.674 550	−1.406 586
H-2	2.912 449	2.922 903	2.067 842
	2.881 660	3.412 265	1.880 883
H-3	−1.400 960	4.371 132	0.305 920
	−1.348 344	4.399 581	0.107 180
H-4	−1.083 738	−2.775 146	−2.134 815
	−1.538 596	−3.164 717	−1.763 659
H-5	−2.184 004	−3.401 642	0.925 838
	−1.857 248	−3.374 150	1.510 762
H-6	2.594 945	−3.982 674	0.233 411
	2.620 549	−3.918 240	−0.896 999
H-7	1.784 226	−2.020 586	2.792 734
	2.283 739	−3.134 126	2.284 953
H-8	6.599 011	−0.224 036	1.593 049
	7.051 811	0.248 473	1.476 638
H-9	6.457 720	−2.230 356	−1.069 326
	6.688 964	−2.187 064	−0.807 241
H-10	6.775 737	1.043 434	−1.485 014
	6.804 367	1.029 735	−1.769 224
H-11	−5.474 988	2.745 064	0.030 898
	−5.509 797	2.820 617	0.232 731

[a] Co-ordinates given for the optimised *ab initio* 3-21G geometry, followed by those for the MINDO/3 geometry. [b] Atom numbering show in (A).

(A)



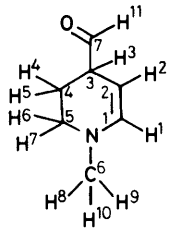
[c] Co-ordinates in a.u.

Table 3. Optimised molecular geometry[a] for enamine (**13**)

Atom[b]	X[c]	Y	Z
N	3.298 177	−0.088 110	−0.302 202
	3.365 377	−0.178 026	0.052 832
C-1	1.880 093	−2.271 778	−0.071 689
	1.901 530	−2.337 452	−0.128 190
C-2	−0.575 463	−2.345 916	0.415 865
	−0.636 281	−2.329 413	−0.408 583
C-3	−2.135 149	0.034 009	0.733 433
	−2.196 514	0.051 850	−0.610 772
C-4	−0.668 840	2.300 050	−0.399 179
	−0.625 961	2.426 356	−0.000 461
C-5	2.101 710	2.275 334	0.468 888
	2.224 686	2.261 955	−0.334 531
C-6	6.046 515	−0.207 606	−0.177 850
	6.021 015	−0.292 920	0.440 397
C-7	−4.575 939	−0.261 534	−0.720 182
	−4.660 627	−0.108 117	0.818 906
O	−6.676 175	0.016 981	0.132 660
	−6.765 513	−0.174 734	0.007 933
H-1	2.922 240	−3.990 770	−0.340 398
	2.947 129	−4.161 728	0.001 370
H-2	−1.506 657	−4.136 569	0.583 734
	−1.641 629	−4.151 179	−0.550 296
H-3	−2.609 002	0.389 868	2.693 074
	−2.705 240	0.223 993	−2.679 437
H-4	−0.694 398	2.162 912	−2.443 801
	−1.027 065	3.063 756	1.981 032
H-5	−1.555 104	4.062 514	0.146 708
	−1.327 053	4.061 489	−1.141 637
H-6	3.113 523	3.830 831	−0.394 152
	3.147 992	3.717 864	0.920 294
H-7	2.187 703	2.508 496	2.512 441
	2.727 495	3.020 010	−2.272 307
H-8	6.698 400	−1.950 796	−1.027 757
	6.738 904	−2.251 385	0.772 267
H-9	6.848 172	1.353 300	−1.231 348
	6.682 582	0.825 638	2.113 211
H-10	6.752 725	−0.121 073	1.753 122
	7.167 600	0.445 191	−1.182 616
H-11	−4.273 004	−0.763 146	−2.693 205
	−4.311 339	−0.183 144	2.944 228

[a] Co-ordinates given for the optimised *ab initio* 3-21G geometry, followed by those for the MINDO/3 geometry. [b] Atom numbering shown in (B).

(B)



[c] Co-ordinates in a.u.

geometry optimisations of the allylamine (**12**) and enamine (**13**) were carried out in a split-valence 3-21G basis, using the program GAMESS[18] which employs analytic first derivatives of the energy to locate stationary points on the energy surface. In Tables 2 and 3 we show the co-ordinates of the optimised structures obtained by the MINDO/3 and *ab initio* methods for these two molecules. We find that for all bond lengths, the two methods give values which differ by less than 0.005 Å.

The relative energies obtained by the two methods are shown in Table 4. In common with the MINDO/3 method, the *ab initio* calculation predicts the enamine isomer to be the more stable by an amount (1.5 kJ mol^{-1}) very close to the semi-empirical result. It has been suggested that *ab initio* calculations using molecular geometries optimised at the MINDO level may be used to obtain tautomeric energy differences, thus avoiding the time-consuming geometry optimisation at the *ab initio* level.[19] For this reason we show in Table 4 the energies of the two isomers calculated in both an STO-3G and a 3-21G basis using the optimised molecular geometries obtained from the MINDO/3 method. It can be seen that for both basis sets this approach severely overestimates the relative stability of the

Table 4. Total energies (a.u.) for the allylamine (**12**) and the enamine (**13**) from *ab initio* calculations

	3-21G//3-21G	3-21G//MINDO/3[a]	STO-3G//MINDO/3
Allylamine (**12**)	−398.5231	−398.4883	−395.7562
Enamine (**13**)	−398.5236	−398.4955	−395.7620
ΔE/kJ mol^{-1}	1.5	18.7	15.4

[a] This notation indicates a calculation at the optimised MINDO/3 geometry using a 3-21G basis.

enamine isomer, as judged by comparison with the fully optimised 3-21G results.

In view of the quite small energy difference between the two isomers predicted by both *ab initio* and MINDO/3 methods, the role of solvent effects on their relative stability has been briefly examined. In protic solvents the explicit inclusion of hydrogen bonding would need to be considered in a complete study. However, we here use the reaction field continuum model [20] to estimate the stabilisation of each isomer in water. In this method the solvent–solute interaction (F) is given by equation (1), where μ is the molecular dipole moment and α the

$$F = -f\mu^2/2(1 - f\alpha) \quad (1)$$

molecular polarisability, and f is given by equation (2), where ε

$$f = (2\varepsilon - 2)/(2\varepsilon + 1)a_s^3 \quad (2)$$

is the solvent dielectric constant and a_s the radius of the spherical cavity containing the solute molecule. The dipole moments for the isomers (**12**) and (**13**) were obtained from the *ab initio* 3-21G calculation at the optimised geometries (3-21G//3-21G) yielding values of 1.55 and 1.84 D, respectively. The polarisabilities (α) were obtained by the method of Miller and Savchik.[21] In view of the larger dipole moment for the enamine (**13**) than for the allylamine (**12**), the reaction field continuum model predicts greater solvent–solute interaction for the enamine isomer. This additional stabilisation ranges from 2.8 kJ mol^{-1} for a cavity of radius 2.9 Å to 0.6 kJ mol^{-1} for one of radius 3.9 Å.

Conclusions

As judged by comparison with experiment, and with *ab initio* calculations, the MINDO/3 method is successful in accurately predicting the relative energetics of a series of isomeric allylamines and enamines. For the pair of isomers (**12**) and (**13**) both *ab initio* and MINDO/3 methods give very similar optimised geometries, and predict (**13**) to be slightly more stable than (**12**). This energy difference is increased by up to 3 kJ mol^{-1} in water owing to solvent–solute interaction.

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