Spectral Studies on Cyclic Enamino Ketones[1a]

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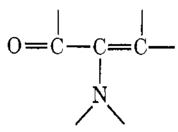
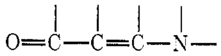
Vinyl proton chemical shifts in 3-amino-2-cycloalkenones parallel those of cyclic enamines in being inversely ordered relative to the following apparent order of increasing nitrogen lone-pair-electron delocalization: morpholino < dimethylamino < pyrrolidino and 1-cyclohexenylamines < 1-cyclopentenylamines. Similar effects are apparent in 2-amino-2-cycloalkenones, but the actual order of vinyl proton chemical shifts is reversed because of greater electron withdrawal from β positions in 2-cyclopentenones than from those in 2-cyclohexenone systems. Greater nitrogen lone-pair-electron delocalization into five- than six-membered rings is demonstrated by variable temperature nmr data which indicates ~2–3 kcal/mol larger $\Delta G^{\ddagger}$ for rotation about the C—N bond of the enamino ketone system in five- than in six-membered-ring 3-dimethylamino-2-cycloalkenones.

Monoenamines derived from 1,2- and 1,3-dicarbonyl compounds represent superimpositions of two important structural moieties: vinyl amines (enamines) and α,β-unsaturated carbonyl systems. 2-Amino-2-alkenones, **1** (derived from 1,2-dicarbonyl compounds), and 3-amino-2-alkenones, **2** (derived from 1,3-dicarbonyl compounds), may be viewed as either (a) α,β-unsaturated carbonyl systems with amino substituents at α and β positions, respectively, or (b) vinyl amines conjugated with carbonyl groups so as to place the carbonyl group α or β, respectively, to the amino substituent. Such a view suggests interesting possibilities regarding the distribution of electron density in these systems, especially in regard to sites of nucleophilic activity. Several reports related to alkylation, protonation, and other nucleophilic reactions of enamino ketones have appeared in the literature.[2-8] In considering the possibilities for electron density distribution in enamino ketones derived from cyclic 1,2 and 1,3 diketones it is helpful to note that the familiar canonical structures illustrating electron delocalization in α,β-unsaturated cyclic ketones, **3** and **4**, and enamines of cyclic ketones, **5** and **6**, may be combined to represent the principal contributing structures for resonance hybrids of 2-amino-2-cycloalkenones, **7–9**, and 3-amino-2-cycloalkenones, **10–13**.



$O{=}C{-}C(NR_2){=}C{-}$

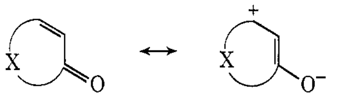
1



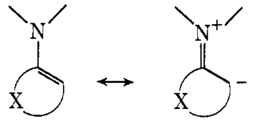
$O{=}C{-}C{=}C{-}N{-}$

2

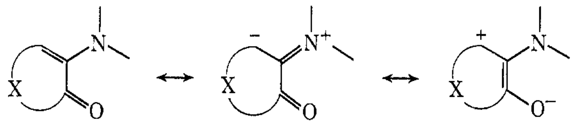
An interest in using monoenamines derived from diketones as synthetic intermediates led us to compare spectral data on a number of cyclic enamino ketones, related enamines, and α,β-unsaturated ketones. A summary of vinyl proton chemical shifts for these compounds is given in Table I. Ir and uv data for selected compounds also are included.



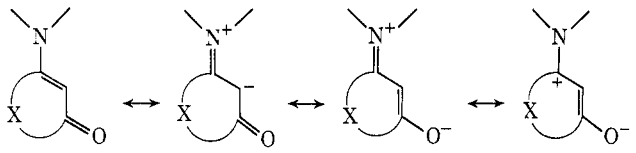
3 **4**



5 **6**



7 **8** **9**



10 **11** **12** **13**

Chemical shifts of vinyl protons have been interpreted previously as evidence for steric and electronic effects of delocalization of the nitrogen lone-pair electrons in simple enamines.[9,10] Increases of electron density at the carbon terminus of the enamine provide greater shielding of the vinyl proton and result in upfield shifts in the nmr absorptions of the vinyl proton. Inspection of the data for simple enamines, **14–21**, reveals several interesting facts regarding ring-size effects. The vinyl proton chemical shifts of five-membered-ring enamines are consistently smaller than those of the analogous six-membered-ring systems (**14** > **15**, **16** > **17**, **18** > **19**, **20** > **21**). This trend indicates that the nitrogen lone-pair electrons are more extensively delocalized into five- than six-membered rings, an observation consistent with previous reports.[9,10] The dependence of the vinyl proton shift on the structure of the amino group also is apparent. The pyrrolidino enamines, in which nitrogen is incorporated in a five-membered ring, provide greater shielding of the vinyl proton than either morpholino or piperidino enamines in which nitrogen is part of a six-membered ring. The dimethylamino derivatives exhibit intermediate levels of shielding for vinyl protons. The order of chemical

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[2] (a) G. H. Alt in "Enamines," A. G. Cook, Ed., Marcel Dekker, New York, N. Y., 1969, p 115; (b) G. H. Alt and A. J. Speziale, *J. Org. Chem.*, **29**, 794 (1964); (c) *ibid.*, **29**, 798 (1964); (d) *ibid.*, **30**, 1407 (1965).

[3] S. Danishefsky and R. Cavanavgh, *Chem. Ind.* (*London*), 2171 (1967).

[4] J. Goerdeler and U. Keuser, *Ber.*, **97**, 2209 (1964).

[5] C. A. Grob and H. J. Wilkens, *Helv. Chim. Acta*, **50**, 725 (1967).

[6] S. Hunig, E. Benzing, and E. Lucke, *Ber.*, **90**, 2833 (1957).

[7] N. J. Leonard and J. A. Adamick, *J. Amer. Chem. Soc.*, **81**, 595 (1959).

[8] A. I. Meyers, A. H. Reine, and R. Gault, *J. Org. Chem.*, **34**, 698 (1968).

[9] W. D. Gurowitz and M. A. Joseph, *ibid.*, **32**, 3289 (1967).

[10] K. Nagarajan and S. Rajappa, *Tetrahedron Lett.*, 2293 (1969).

shifts with respect to the amino group is as follows: morpholino > piperidino > dimethylamino pyrrolidino (*e.g.*, **16** > **20** > **18** > **14** and **17** > **21** > **19** > **15**).

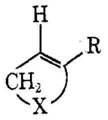
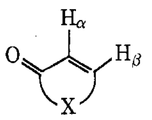
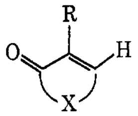
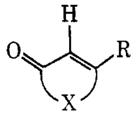
Enamino ketones may be considered as α,β-unsaturated ketones with an amino substituent at either the α or β position. The amino and keto groups, respectively electron releasing and electron withdrawing, exert opposing effects on the electron shielding of the enamine vinyl proton in both types of enamino ketones. Hence, the vinyl proton signals in the enamino ketones are observed at lower field than those of the simple enamines and at higher field than those of the corresponding α or β protons in the conjugated ketones. Structures **3** and **4** demonstrate that the conjugative electron withdrawal of the keto group is greater at the β position than the α position. The vinyl proton signals of the 2-amino-2-cycloalkenones, **24**–**27**, appear at lower field than those of the 3-amino-2-cycloalkenones, **28**–**34**, a comparison that is qualitatively similar to the relative chemical shifts of α and β protons in 2-cycloalkenones **22** and **23**. A greater electron density is indicated at the enamine carbon termini for the 3-amino-2-cycloalkenones than is the case for the 2-amino-2-cycloalkenones.

In the 3-amino-2-cycloalkenone systems the vinyl proton chemical shifts are smaller for five- than six-membered-ring derivatives (**30** < **28**, **32** < **31**, **34** < **33**), an indication that the generalization of greater nitrogen lone-pair-electron delocalization to the enamine carbon termini in five- *vs* six-membered rings observed in simple enamines also appears to apply to the 3-amino-2-cycloalkenones. However, the ir data indicate that the 3-pyrrolidino group is more effective in lowering the carbonyl stretching frequency in six- than in five-membered rings ($\Delta\nu$ for **28** *vs.* **22** = 96 cm^{-1} compared to $\Delta\nu$ for **30** *vs.* **23** = 74 cm^{-1}). The pyrrolidino group also produces a larger bathochromic shift in the uv for six- than for five-membered-ring derivatives ($\Delta\lambda$ for **28** *vs.* **22** = 77 nm compared to $\Delta\lambda$ for **29** *vs.* **23** = 62 nm). These observations suggest that in the 3-amino-2-cycloalkenone system electron density at carbon may be greater in five-membered-ring derivatives (structure **11** important) and electron density at oxygen may be greater in six-membered-ring derivatives (structure **12** important).

In the case of the 2-amino-2-cycloalkenones the larger shifts of vinyl protons in **25** and **27** compared to **24** and **26** appear to contradict the generalization that nitrogen lone-pair delocalization is greater into five- than six-membered rings. This point is clarified by the fact that the β proton in **23** is markedly less shielded than the β proton in **22** ($\Delta\nu$ = 0.76 ppm), an indication that a ring-size effect allows greater electron withdrawal from the β proton of α,β-unsaturated ketones in five- than in six-membered rings. It should be noted that the difference between the chemical shifts for the vinyl proton of **25** and the β proton of **23** (1.93 ppm) is greater than that between **24** and the β proton of **22** (1.45 ppm). Thus, greater delocalization of nitrogen lone-pair electrons into five- than six-membered rings also applies to the 2-amino-2-cycloalkenone systems, but the trend toward smaller chemical shifts for the five-membered-ring derivatives is reversed by the greater electron-withdrawal effect of the keto group in five- than in six-membered ring. Consequently, both structures **8** and **9** are more important in five- than in six-membered rings.

TABLE I

NMR CHEMICAL SHIFTS OF VINYL PROTONS AND OTHER SPECTRAL DATA OF ENAMINES AND ENAMINO KETONES

Compd[a]	Chemical shift of vinyl proton ppm	Ir (C=O, C=C), cm^{-1}	Uv, λ_{max} (log ϵ), nm
Enamines			
14 [R = Py; X = $(CH_2)_3$]	4.27		
15 [R = Py; X = $(CH_2)_2$]	4.00		
16[b] [R = Mp; X = $(CH_2)_3$]	4.57		
17 [R = Mp; X = $(CH_2)_2$]	4.37		
18 [R = Dm; X = $(CH_2)_3$]	4.46		
19 [R = Dm; X = $(CH_2)_2$]	4.16		
20[b] [R = Pp; X = $(CH_2)_3$]	4.53		
21[b] [R = Pp; X = $(CH_2)_2$]	4.25		
2-Cycloalkenones			
22[c] [X = $(CH_2)_3$]	5.93 (H_α) 6.99 (H_β)	1691 1621	225 (4.14)
23[c] X = $(CH_2)_2$]	6.10 (H_α) 7.75 (H_β)	1720 1593	217 (4.06)
2-Amino-2-cycloalkenones			
24 [R = Py; X = $(CH_2)_3$]	5.54	1674	217 (3.68)
25 [R = Py; X = $(CH_2)_2$]	5.82	1699 1606	
26 [R = Py; X = $CH(CH_3)CH_2$]	5.72	1700 1610	214 (3.78) 314 (3.48)
27 [R = Mp; X = $(CH_2)_2$]	6.32		
3-Amino-2-cycloalkenones			
28 [R = Py; X = $(CH_2)_3$]	5.06	1595 1546	302 (4.54)
29 [R = Py; X = $CH_2C(CH_3)_2CH_2$]	5.04	1598 1548	303 (4.53)
30 [R = Py; X = $(CH_2)_2$]	4.87	1646 1543	279 (4.40)
31 [R = Mp; X = $(CH_2)_3$]	5.24		
32 [R = Mp; X = $(CH_2)_2$]	5.05	1650 1550	281 (4.70)
33 [R = Dm; X = $CH_2C(CH_3)_2CH_2$]	5.14		305 (4.41)
34 [R = Dm; X = $(CH_2)_2$]	4.92	1635 1575	278 (4.12)

[a] Py = pyrrolidino, Mp = morpholino, Dm = dimethylamino, Pp = piperidino. [b] Data taken from ref 10. [c] E. S. Waight and H. N. A. Al-Jallo, *J. Chem. Soc. (B)*, 73 (1966).

Since the 3-amino-2-cycloalkenones may be considered to be vinylogous amides, it was apparent that the

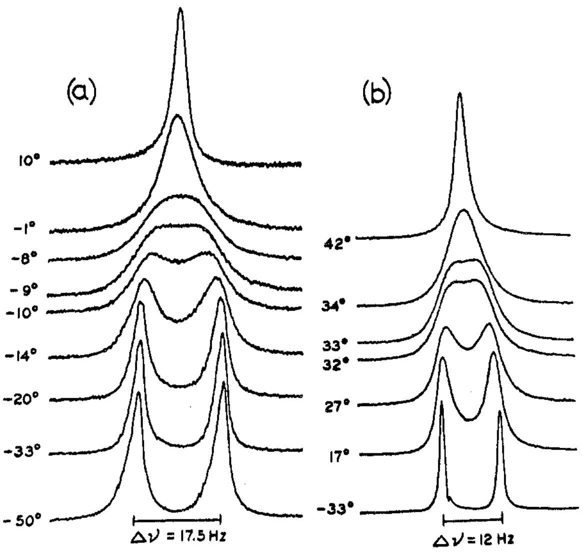
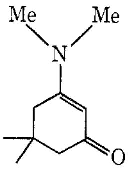
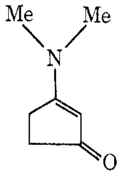


Figure 1.—The 100-MHz nmr spectra of methyl signals of (a) **33** and (b) **34** in $DCCl_3$ solution at various temperatures.

dnmr method of determining differences in rotational barriers about the C–N bond could be used for evaluating differences in the extent of nitrogen lone-pair-electron delocalization in these systems. An analogous nmr study of the C—N bond rotational barrier in the noncyclic vinylogous amide 3-dimethylaminoacrolein, $(CH_3)_2NCH{=}CHCHO$, reports the activation free energy for rotation at the coalescence temperature to be 15.8 kcal/mol.[11] In the present case the dimethylamino derivatives **33** and **34** were chosen for study because of the simplicity of the analysis. The nmr spectra for the *N*,*N*-dimethyl singlets of **33** and **34** over a temperature range including the coalescence point are shown in Figure 1. In the case of **33** the methyl signals are separated by a frequency difference of 17.5 Hz and coalesce at −9°. The separation of methyl signals in **34** is 12 Hz and coalescence occurs at 33°.



33



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Activation free energies for rotations were calculated by use of the Eyring equation[12] employing rotational rate constants calculated at coalescence temperatures.[13] The data and results of the calculations are summarized in Table II. Although the approximate methods employed may introduce considerable uncertainty regarding the absolute accuracy of the results,[14] comparison of the two results obtained by this method should be meaningful. The 2.4-kcal/mol greater activation free energy for **34** is a significant indication of a higher rotational barrier for the C—N bond in the five-membered-ring derivative compared to that in the six-membered analog. The higher rotational barrier in **34** indicates greater nitrogen lone-pair-electron delocalization in this system, a conclusion in agreement with previously presented data.

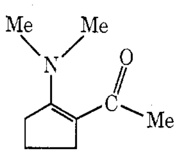
TABLE II

ACTIVATION FREE ENERGIES FOR ROTATION ABOUT THE C—N BOND IN ENAMINO KETONES

Compd	T_c, C°	$\Delta\nu$	ΔG^*, kcal/mol	$\Delta\Delta G^*$
33	−9	17.5	13.5	2.4
34	33	12.0	15.9	

The qualitative observation was made that in the ambident temperature spectra of **29** and **30** the signals for the CH_2N protons of **30** were partially resolved into a set of triplets. The analogous signals for **29** were unresolved, indicating a lower coalescence temperature and probably a lower free energy of activation for the six-membered-ring derivative **29**.

To determine the effect on rotational barriers of fixed trans *vs.* cis geometry of the enamine double bond, an attempt was made to obtain comparative data on the *cis*-enamino ketones **35** and **36**. The syntheses of **35** and **36** involved acetylation of the 1-dimethylaminocyclopentene and 1-dimethylaminocyclohexene, respectively. Inspection of the nmr spectra of the distilled products of these reactions indicated that both **35** and **36** were present in ~1:1 ratio with the corresponding unconjugated double-bond isomers, an observation similar to other reported cases of acetylation of enamines.[15] No convenient separation of these isomeric product mixtures was devised, but the nmr spectra of both product mixtures containing **35** and **36** were examined at various temperatures. No significant changes were noted in either spectra at temperatures as low as −60°, an indication that the coalescence temperatures and rotational barriers for **35** and **36** are relatively low compared to those of **33** and **34**.



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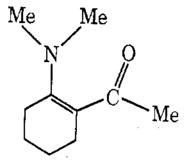

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Experimental Section

Nmr spectra were obtained on a Varian HA-100 spectrometer using solutions in deuterated chloroform. Chemical shifts are reported in parts per million downfield from tetramethylsilane used as an internal standard. Mass spectra were obtained using a CEC 21-104 spectrometer. Ir spectra were taken on a Perkin-Elmer Model 337 spectrophotometer. Uv spectra were obtained on a Perkin-Elmer Model 202 spectrophotometer. Melting and boiling points are uncorrected.

General Procedures for Preparation of Morpholino and Pyrrolidino Enamines and Enamino Ketones.—Enamines **14**, **15**, and **17** were prepared by the method of Stork, *et. al.*[16] The same procedure was used for the preparation of enamino ketones **24–26** using 1.75:1.00 molar ratios of pyrrolidine and the appropriate diketones in refluxing benzene. Enamines **18** and **19** were prepared by the method of Blanchard.[17] Enamino ketones **27–32**

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[11] (a) H. E. A. Kramer and R. Gompper, *Z. Phys. Chem.* (*Frankfurt am Main*), **43**, 292 (1964); (b) H. E. A. Kramer, *Justus Liebigs Ann. Chem.*, **696**, 28 (1966).

[12] S. Glasstone, K. J. Laidler, and H. Erying, "The Theory of Rate Processes," McGraw-Hill, New York, N. Y., 1951, p 195.

[13] J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, p 223.

[14] G. Binsch in "Topics in Stereochemistry," Vol. 3, E. J. Elliel and N. L. Allinger, Ed., Interscience, New York, N. Y., 1968, p 97.

[15] G. Opitz and E. Tempel, *Angew. Chem., Int. Ed. Engl.*, **3**, 754 (1964).

[16] G. Stork, A. Brizzolara, H. Landesman, J. Szmusovisz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 345 (1963).

[17] E. P. Blanchard, *J. Org. Chem.*, **28**, 1397 (1963).

TABLE III
PHYSICAL DATA FOR ENAMINES AND ENAMINO KETONES

Compd	Bp (mm) or mp, °C	Lit. bp (mm) or mp, °C	Nmr, δ[a] (J, Hz)	Mass spectrum (70 eV) M+ (rel intensities)
14	108–109 (20)	105–107 (13)[b]		
15	93–94 (18)	88–92 (13)[b]		
17	111–115 (19)	104–106 (12)[b]		
18	80–85 (35)	81 (35)[c]		
19	72–84 (95)	85–86 (104)[c]		
24	68–70 (0.1)	70–71 (0.2)[d]		165 (87), 150 (31), 137 (38), 136 (100), 109 (35), 108 (39), 81 (45), 70 (58)
25	83–84 (0.5)		5.82 (t, $J = 3$, 1 H, $=CH$) 3.1–3.4 (t, $J = 7$, 4 H, CH_2) 2.25–2.55 (m, 4 H, CH_2CH_2CO) 1.65–2.0 (m, 4 H, CH_2)	
26	69–70 (1.0)	85–90 (0.4)[e]	5.72 (apparent t, $J = 3.5$, 1 H, $=CH$) 3.1–3.5 (m, 4 H, CH_2N) 2.05–2.7 (m, 3 H CH_2CH) 1.9 (m, 4 H, CH_2CH_2) 1.1 (d, $J = 7$, 3 H, CH_3)	
27		59–60	6.32 (apparent t, $J = 3$, 1 H, $O{=}CH$) 3.74 (m, 4 H, OCH_2) 3.07 (m, 4 H, NCH_2) 2.44 (m, 4 H, $=CCH_2CH_2CO$)	
28	86–88	84–88[f]		
29	134–135	131–133[g]		
30[b]	104–105		4.87 (s, 1 H, $=CH$) 3.10–3.55 (2 t, $J = 6$, 4 H, CH_2N) 2.25–2.70 (2 t, $J = 4$, 4 H, CH_2CH_2CO) 1.90–2.20 (m, 4 H, CH_2)	151 (77), 123 (24), 122 (100), 108 (38), 95 (67), 44 (32), 81 (16), 70 (27)
31[b]	93–95		5.24 (s, 1 H, $=CH$) 3.67 (m, 4 H, OCH_2) 3.25 (m, 4 H, NCH_2) 1.80–2.45 (m, 6 H, $=CCH_2CH_2CH_2CO$)	
32[b]	106–107		5.05 (s, 1 H, $=CH$) 3.7–3.8 (t, $J = 6$, 4 H, OCH_2) 3.35–3.45 (t, $J = 6$, 4 H, NCH_2) 2.3–2.7 (2 t, $J = 7$, 4 H, CH_2CH_2CO)	167 (100), 137 (4), 110 (29), 109 (26), 108 (29), 85 (38), 81 (48), 55 (70)

[a] s, singlet; d, doublet; t, triplet; 2 t, two triplets partially resolved; m, multiplet. [b] Reference 16. [c] Reference 17. [d] R. A. Jerussi, *J. Org. Chem.*, **34,** 3648 (1969). [e] R. T. Dahill, Jr., *ibid.*, **31,** 2694 (1966). [f] Reference 18. [g] Reference 7.

were prepared using the procedure reported by Panouse and Sannie[18] for the preparation of **28**. Physical data on these compounds are recorded in Table III. In the case of compounds previously reported comparative literature physical constants are recorded. Mass spectral and nmr data are included for compounds not previously reported in the literature. Difficulties in purification prevented satisfactory characterization of these compounds by elemental analysis. However, in all cases spectral evidence supports the assigned structures.

General Procedure for Preparation of Dimethylamino Enamino Ketones.—A pressure bottle was charged with ~0.03 mol of the appropriate diketone in 100 ml of either anhydrous ether or *p*-dioxane and an excess of either anhydrous calcium chloride or sodium carbonate and cooled in an ice bath. After the addition of a fourfold excess of dimethylamine, the bottle was sealed and heated at ~80° in an oil bath overnight. After cooling the bottle was opened and the reaction mixture filtered. The residue was washed sparingly with chloroform and the organic phases were combined. After removal of the solvent, the residual oil or solid was crystallized (ether for **33**, 1:5:10 methylene chloride–ether–pentane for **34**) to yield 60–70% of the dimethamino enamino ketone containing a small amount of the starting diketone. Physical data on these compounds are included in Table III.

Registry No.—**24,** 18543-93-6; **25,** 36287-24-8; **26,** 4933-43-1; **27,** 24454-33-9; **28,** 19805-73-3; **29,** 3357-16-2; **30,** 36287-28-2; **31,** 16179-67-2; **32,** 36287-30-6; **33,** 31039-88-0; **34,** 36287-32-8.

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[18] J. J. Panouse and C. Sannie, *Bull. Soc. Chim. Fr.*, 1374, (1956).