Basicity of the Carbonyl Group. Part 9.[1] Lewis and Brønsted Basicities of Enamino-ketones

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pK_{BH^+} Values and enthalpies of complex formation between boron trifluoride and 30 3-aminocyclohex-2-enones have been investigated. A collection of thermodynamic and spectroscopic arguments, in particular derived from a ^{13}C dynamic n.m.r. study, showed the carbonyl oxygen to be the basic site for protonation in aqueous or organic solvents as well as the site for BF_3 co-ordination in dichloromethane. Experimental and theoretical (*ab initio* calculations) observations in favour of an interaction between H^+ or BF_3 and the nitrogen atom are discussed. Structural effects on the basicities have been examined and linear correlations between pK_{BH^+} or $\Delta H^\circ_{BF_3}$ and nitrogen substituent constants σ^* have been established and discussed. A single extra thermodynamic relationship between pK_{BH^+} and $\Delta H^\circ_{BF_3}$ is found for a large series of unsaturated ketones, including enamino-ketones. This relationship shows that Lewis basicity ($\Delta H^\circ_{BF_3}$) may be used as an indirect measure of pK in a homogeneous series of weak bases for which acidity functions are difficult or impossible to find.

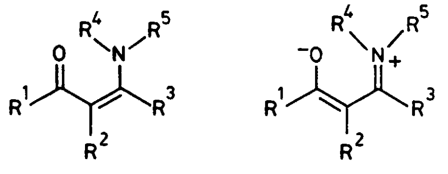
For many years, enamino-ketones have been of great interest as synthetic intermediates, especially in heterocyclic chemistry.[2-8] The fact that their structure and reactivity are governed primarily by the dipolar form (B) has led to their use as carriers of biologically active groups.[9,10] On account of their usefulness in pharmacology, the study of the basicity of these compounds has led to several investigations. Nevertheless, the results available are inadequate in some important respects.

(i) As far as protonation in aqueous media is concerned, the thermodynamics have been little studied; pK_{BH^+} values have been measured only for a few of these compounds [11-13] and no conclusion has been drawn about the role played by substituents on the enaminone moiety. (ii) No structural or thermodynamic study has been undertaken concerning Lewis basicity. (iii) Finally, although some spectroscopic arguments [2,14-17] have been put forward to support the predominance of *O*-protonation over *N*- or *C*-protonation, no exhaustive study has been carried out in order to define the protonation site in regard to the nature and state (solution, solid) of the enamino-ketone and the experimental conditions (acid agent, concentration, solvent, *etc.*).

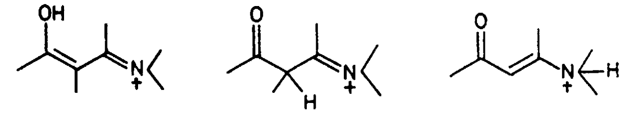
Leonard and Adamcik [15] who were the first to suggest the predominance of *O*-protonation in some cases, pointed out that 4-*NN*-diethylaminopent-3-en-2-one, for instance, does not conform to the spectroscopic criteria that led them to propose *O*-protonation for other compounds. Thus, these authors concluded that it is necessary to be extremely cautious when defining the basic site of each type of structure.

In this study, we examine the various methods which allow definition of the protonation site in aqueous solution and the complexation site by a Lewis acid in an organic solvent (BF_3 in CH_2Cl_2) for a series of 3-amino-5,5-dimethylcyclohex-2-enones. The methods are: (i) the determination of equilibrium constants of protonation (pK_{BH^+}) and enthalpies of complex formation with BF_3 (ΔH°); (ii) the study of protonation effects on $\pi\pi^*$ transitions; (iii) *ab initio* calculations of a free and a protonated model of an enamino-ketone; and (iv) a ^{13}C n.m.r. study of the free and protonated or complexed compounds with a determination of the ^1H chemical shifts and C(3)–N rotational barriers in the adducts.

We also discuss the nitrogen substituent effects on the two acid–base equilibria, and then examine the relationship between the Brønsted and Lewis basicities of these compounds (1)—(30). The choice of the cyclohexene structure for these compounds is dictated by the following considerations. On the one hand, enamino-ketones derived from cyclohexane-1,3-diones show some interesting therapeutic properties related to their low toxicity and analeptic properties.[18] On the other hand, the fixed *trans-s-trans* conformation precludes the *cis-trans*-isomerization and the existence of intramolecular hydrogen bonds observed in some open-chain enamino-ketones.[19]


(A) (B)

R^1,R^2,R^3,R^4,R^5 = H, alkyl or aryl


O- protonation *C*- protonation *N*- protonation

Results

(a) *Basicity Measurements*.—Measurement of the protonation equilibrium (1) of enamino-ketones in aqueous solution has been carried out by Albert and Sergeant's method [20] combining u.v.–visible spectrophotometry with electrometry.

$$B_{(aq)} + H^+_{(aq)} \underset{K_{BH^+}}{\rightleftharpoons} BH^+_{(aq)} \qquad (1)$$

BF_3 complex formation (2) enthalpies ΔH° are measured in CH_2Cl_2 by a microcalorimetry method previously described.[21]

$$B_{(CH_2Cl_2)} + BF_{3(g)} \xrightarrow{\Delta H^\circ} 1:1\ \text{complex}_{(CH_2Cl_2)} \qquad (2)$$

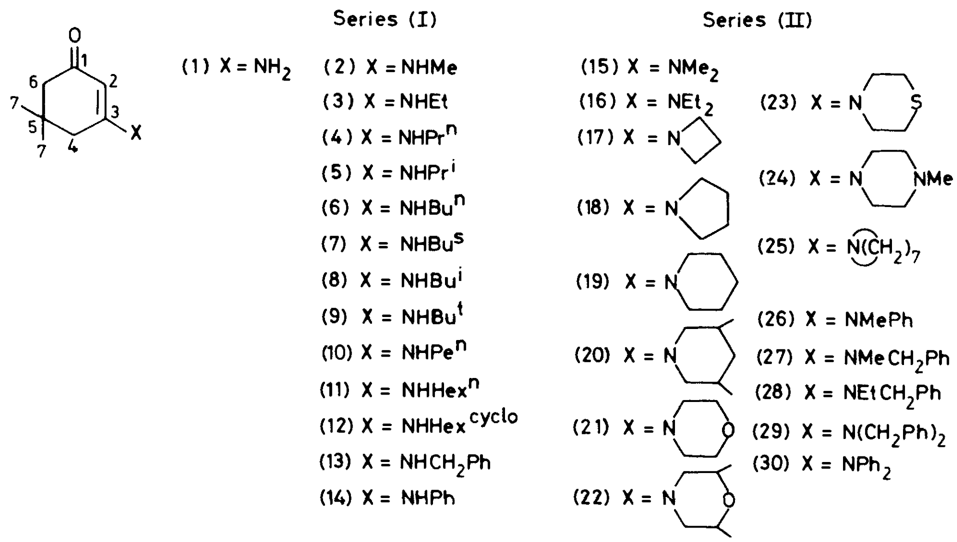


Table 1. pK_{BH^+} and ΔH° values of enamino-ketones at 298.15 ± 0.1 K

Compound	$\Sigma\sigma^*$ [a]	Brønsted basicity pK_{BH^+} [b]	Compound	$\Sigma\sigma^*$ [a]	Brønsted basicity pK_{BH^+} [b]	Lewis basicity $-\Delta H^\circ$/kJ mol^{-1} [b]	n [c]
(1)	0.98	2.82 ± 0.04	(15)	0	3.14 ± 0.02	132.43 ± 0.47	13
(2)	0.49	2.84 ± 0.01	(16)	−0.20	3.28 ± 0.02	135.05 ± 0.39	7
(3)	0.39	2.92 ± 0.01	(17)	−0.24	3.45 ± 0.01	136.00 ± 0.49	15
(4)	0.375	2.95 ± 0.01	(18)	−0.26	3.38 ± 0.03	134.74 ± 0.44	9
(5)	0.30	3.02 ± 0.01	(19)	−0.18	3.28 ± 0.03	134.15 ± 0.60	16
(6)	0.36	2.95 ± 0.03	(20)		3.29 ± 0.02	132.51 ± 0.81	8
(7)	0.28	3.08 ± 0.01	(21)	0.67	2.53 ± 0.04	128.06 ± 0.36	9
(8)	0.365	2.96 ± 0.01	(22)		2.56 ± 0.03	128.90 ± 0.46	9
(9)	0.19	2.81 ± 0.01	(23)		2.57 ± 0.03	129.25 ± 0.44	7
(10)		2.99 ± 0.02	(24)		1.36 ± 0.15 [d]	129.60 ± 0.39	7
(11)	0.361	2.93 ± 0.02	(25)		3.20 ± 0.01	132.76 ± 0.54	7
(12)	0.283	3.08 ± 0.01	(26)	0.60	2.40 ± 0.01	127.32 ± 0.74	8
(13)	0.705	2.57 ± 0.02	(27)	0.215	2.71 ± 0.02	129.11 ± 0.71	7
(14)	1.09	2.15 ± 0.06	(28)	0.115	2.77 ± 0.01	130.45 ± 0.62	9
			(29)	0.43	2.24 ± 0.01	122.85 ± 0.47	7
			(30)	1.20	1.72 ± 0.07	120.75 ± 0.34	6

[a] $\Sigma\sigma^* = \sigma^*_{R1} + \sigma^*_{R2}$, where R^1 and R^2 are the nitrogen substituents. [b] Quoted errors are at the 95% confidence level. [c] Number of measurements. [d] The actual substituent is 1-methylperhydropyrazinium in the pK measurement.

The pK_{BH^+} and ΔH° values obtained are listed in Table 1.

In the case of compounds (1)—(14) bearing one or two hydrogens at the nitrogen atom, it was impossible to measure the enthalpies of complex formation. In fact, at the level of concentration needed for our microcalorimetry study, these compounds are partially associated and the recorded heat change corresponds to the dissociation of these aggregates as well as to the complex formation with the Lewis acid. The existence of these associations is shown by the observation of characteristic free and bonded ν_{N-H} bands in the i.r. spectra. The band intensities vary with the concentration. In the same manner ΔH° is not constant when concentration is varied. Attempts to circumvent these problems with other solvents inert towards boron trifluoride ($C_6H_5NO_2$, $CHCl_3$) were unsuccessful.

We had previously measured the pK_{BH^+} in aqueous sulphuric acid of some 5,5-dimethylcyclohex-2-enones with substituents of widely differing electronic character (from CN to OH) [22] at position 3; these cyclohexenones follow the H_A acidity function.[22,23] The variation of the pK_{BH^+} in the series is particularly well related to the $\sigma_p{}^+$ constants of substituent in position 3.[22] Nevertheless, we observe a significant deviation in the relationship of pK_{BH^+} with $\sigma_p{}^+$ for compounds (1), (14), and (15) which show a higher basicity than expected according to their $\sigma_p{}^+$ value. This anomaly cannot result from misuse of the acidity function H_A [22] and the same deviations are seen for the relationship of ΔH° and $\sigma_p{}^+$ [24] (Figure 1).

(b) *U.v. Spectra.*—The wavenumbers of the $\pi\pi^*$ absorption maxima in free (B) and in protonated (BH^+) enamino-ketones and 3-substituted 5,5-dimethylcyclohex-2-enones are reported in Table 2. The hypsochromic shift observed for protonation of enamino-ketones induced some authors [16] to argue in favour of *O*-protonation. However, a reverse effect inside an apparently homogeneous series of cyclohexenones led us to re-examine the matter.

(c) Ab initio *Calculations.*—*Ab initio* STO 3G calculations [25] on *trans-s-trans*-4-*NN*-dimethylaminopent-3-en-2-one as the model compound, free and protonated, taken in its standard geometry [26,27] gave the results in Table 3.

From these results, we can see that (i) considering the relative total energies of protonated systems (C) and (D), protonation on the oxygen atom is thermodynamically favoured

Table 2. Wavenumbers of the $\pi\pi^*$ electronic transition in free (B) and protonated (BH^+) enamino-ketones and 3-substituted cyclohexenones

Enamino-ketone	B $\tilde{\nu}_{max.}/cm^{-1}$	BH^+ $\tilde{\nu}_{max.}/cm^{-1}$	Cyclohexenone substituent in position 3	B $\tilde{\nu}_{max.}/cm^{-1}$	BH^+ $\tilde{\nu}_{max.}/cm^{-1}$
(1)	34 810	36 270	H	42 920	36 360
(2)	34 340	35 780			
(3)	34 190	35 710	CH_3	41 240	35 520
(4)	34 100	35 620			
(5)	34 100	35 050	Cl	41 070	35 340
(6)	34 130	35 620			
(7)	34 010	35 620	Br	39 920	33 270
(8)	34 070	35 520			
(9)	39 990	35 340	OCH_3	39 140	36 230
(10)	34 100	35 590			
(11)	34 070	35 590	OC_2H_5	38 840	36 230
(12)	33 900	35 460			
(13)	34 070	35 120	OH	38 680	36 230
(14)	32 420	33 610			
(15)	33 060	34 900	SC_2H_5	33 390	29 370
(16)	32 840	34 720			
(17)	33 110	35 180	CO_2CH_3	41 070	35 840 [b]
(18)	32 950	34 900			
(19)	32 570	34 600	CN	41 580	34 840 [b]
(20)	32 520	34 450			
(21)	32 680	33 960	$CH_2CO_2C_2H_5$	41 840	35 840
(22)	32 650	33 930			
(23)	32 550	33 640	CH_2CN	42 920	36 560
(24)	33 280 [a]	33 760 [a]			
(25)	32 490	34 280	$CH_2COC_2H_5$	41 240	35 270
(26)	32 710	33 840			
(27)	32 900	34 190	C_6H_5	34 580	26 920
(28)	32 730	34 160			
(29)	32 710	33 610			
(30)	32 100	32 520			

[a] The actual substituent is 1-methylperhydropyrazinium. [b] The base is not fully protonated.

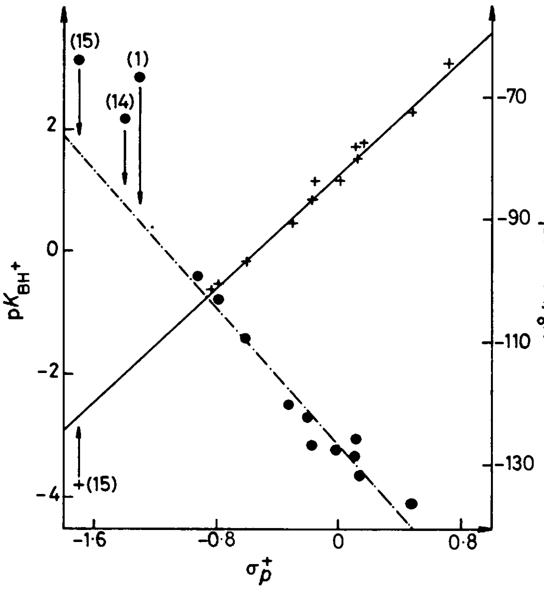


Figure 1. Relationship of pK_{BH^+} and σ_p^+ (●) and ΔH° and σ_p^+ (+) in 3-substituted 5,5-dimethylcyclohex-2-enones

in the gas phase.[28] System (C) is more stable by 0.012 a.u. (31.5 kJ mol^{-1}). (ii) A hypsochromic shift is revealed on passing from the uncharged molecule to the *N*-protonated form. This finding agrees with the relative values of atomic coefficients for the nitrogen atom in π and π^* orbitals. Conversely, a bathochromic effect is expected for *O*-protonation with $C_O{}^{\pi^*}$ larger than $C_O{}^{\pi}$ [29] (Table 3).

(d) C(3)–N *Rotational Barriers.*—Taking in consideration the obvious analogy between amides and enamino-ketones, we transposed to the latter the n.m.r. experiments carried out to estimate the basic site of the former. We have determined the rotational barrier around the C(3)–N bond for a few enamino-ketones in free, protonated, and co-ordinated forms (Table 4) and found, as with amides,[30] a high rotation barrier in all three forms.

For compound (18), the higher barrier in water (pH 6) relative to $CDCl_3$ results from an increase in solvent polarity and from the greater strength of hydrogen bonds between the solvent and the carbonyl oxygen. These two factors stabilize the ground state energy level more than the less polar, less basic transition state.[31,32] On the other hand, the significantly lower barrier from pH to 0.8 does not seem in accord with *O*-protonation.

(e) ^1H *and* ^{13}C *N.m.r. Spectra.*—We have also measured the effects induced by protonation or complexation on ^1H and ^{13}C chemical shifts (Tables 5 and 6). We can see that the effect of protonation on the chemical shifts of C(1)—(3) and those of the methyl substituents on the nitrogen atom is consistent, whatever the medium, for both (15) and the open-chain enamino-ketone. Moreover, the effect of co-ordination with BF_3 is similar to the effect of protonation. From Table 6, it appears that whatever the nature of substituent, boron trifluoride complex formation always leads to a downfield shift of the olefin proton relative to the free system.

Table 3. Results of *ab initio* STO 3G calculations on 4-*NN*-dimethylaminopent-3-en-2-one (*trans-s-trans*)

		Free form [b]	*O*-Protonated form (C) [b]	*N*-Protonated form (D) [c]
E_{tot}/a.u.[a]		−396.820 053	−397.264 449	−397.252 573
$\lvert\Delta H_{prot}\rvert$			0.444 396	0.432 520
E_{π}/a.u.		−0.214	−0.432	−0.480
E_{π^*}		0.263	−0.015	0.045
$\Delta E_{\pi\pi^*}$		0.477	0.417	0.525
Absolute values of atomic coefficient in MO structure	$C_O{}^{\pi}$	0.350		
	$C_N{}^{\pi}$	0.624		
	$C_O{}^{\pi^*}$	0.576		
	$C_N{}^{\pi^*}$	0.281		

[a] 1 a.u. ≃ 2 625.5 kJ mol^{-1}. [b] Nitrogen atom is sp^2. [c] Nitrogen atom is sp^3.

Table 4. The free energy of activation * for the hindered internal rotation C(3)−N in some free, protonated, and co-ordinated enamino-ketones of series (II)

Form (solvent)	Conc. (M)	(15) $\Delta G^{\ddagger}_{298}$/ kJ mol^{-1}	(18) $\Delta G^{\ddagger}_{298}$/ kJ mol^{-1}	(19) $\Delta G^{\ddagger}_{298}$/ kJ mol^{-1}
Free ($CDCl_3$)	0.5	55.5	66.7	49.4
Free (H_2O, pH 6)	0.5		73.4	
Protonated (H_2O, pH 0.8)	0.5		70.9	
Co-ordinated BF_3 (CH_2Cl_2)	0.3	70.8		

* Obtained by total line shape analysis of ^{13}C n.m.r. signals of C_{α} and C_{β} in $N(C_{\alpha}-C_{\beta}-)_2$

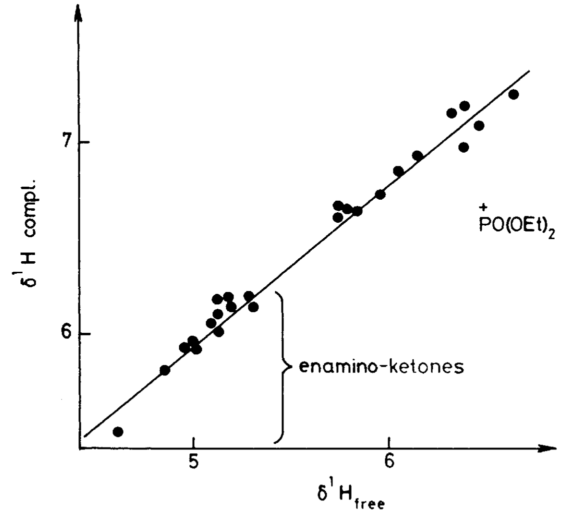


Figure 2. Relationship of δ^1H_2 (complex) and δ^1H_2 (free base) for enamino-ketones of series (II) and 3-substituted cyclohexenones

Discussion

(a) *Nature of the Protonation and Co-ordination site:* N *or* O ?—The n.m.r. results clearly show that the carbonyl oxygen is the preferred basic site, for both protonation (in water or trifluoroacetic acid) and for BF_3 co-ordination.

(i) As far as rotational barriers are concerned, the increase in $\Delta G^{\ddagger}$ for compound (15) on going from free to co-ordinated form (Table 4) is in agreement with a higher π character of the C(3)−N bond; this phenomenon can only be induced by *O*-co-ordination.[34-36] Although the barrier is slightly smaller for compound (18) at pH 0.8 than at pH 6, its value is still too high to result from *N*-protonation. In the case of *N*-protonation, the π-character of the C(3)−N bond would have been destroyed leaving a correspondingly small barrier. The observed decrease may be explained by the presence of a very small amount of the *N*-protonated form. An analogous observation was made by Stilbs[37] in the case of amides where many authors have established the *N*-protonation : *O*-protonation ratio to be 10^{-3}—10^{-4}.[38-42] As for as we are aware, Liler[43] is the only author to propose a ratio of 10^4. This value is obtained from a linear relationship between pK_{BH^+} and $\nu_{C=O}$ of various compounds; however, it is known that such a relationship is applicable only in a truly homogeneous series of carbonyl compounds.[22,44,45]

The large values of the rotational barrier in free enamino-ketones indicate that the nitrogen atom has a hybridization state closer to sp^2 than to sp^3. Considering that atoms of five-membered rings resist a change from sp^2 to sp^3 hybridization, while those of six-membered rings favour it,[46] the *N*-protonation would be more favourable for compound (19) (piperidino) than for compound (18) (pyrrolidino), just as *N*-(*p*-nitrophenyl)piperidine (pK_{BH^+} +1.8) is more basic than *N*-(*p*-nitrophenyl)pyrrolidine (pK_{BH^+} + 1.1).[47] However, (18) is more basic than (19) (Table 1) thus ruling out *N*-protonation for these compounds.

(ii) The comparison of the ^{13}C chemical shifts of 4-*NN*-dimethylaminobut-3-en-2-one and its quaternary ammonium salt with those of enamino-ketone (15) ($CDCl_3$ or H_2O) and its protonated (H_2O, pH 0.8 and CF_3CO_2H) or co-ordinated (BF_3 in CH_2Cl_2) form, shows (Table 5) that the formation of an ammonium ion induces a downfield shift of C(1) and (2) and an upfield shift of C(3) bonded to the nitrogen atom. Protonation or co-ordination induces the opposite effect suggesting the oxygen atom as the basic site.

(iii) For the chemical shifts of the olefinic proton, there is the very good relationship (3) between the free and the co-ordinates forms (Table 6) both for enamino-ketones of series (II) and for a series of 3-substituted cyclohexenones (Figure 2).

$$\delta^1H_2\ (\text{complex}) = (0.84 \pm 0.02)\ \delta^1H_2\ (\text{free base}) + 1.74 \qquad (3)$$

r 0.9929, s 0.058 p.p.m., n 28

O-Co-ordination is the only possibility for the latter series[24] and it is very improbable that two different co-ordination sites (oxygen for cyclohexenones and nitrogen for enamino-ketones) can lead to two straight lines with the same slope and intercept. Further, the only aberrant point is due to

Table 5. ^{13}C Chemical shifts (in p.p.m. relative to Me_4Si) of free and protonated 4-*NN*-dimethylaminobut-3-en-2-one and of free, protonated, and co-ordinated enamino-ketone (15)

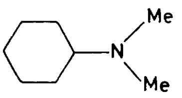
Compound (solvent)	C(1)	C(2)	C(3)	$N(CH_3)_2$
$CH_3C(1)OC(2)HC(3)HN(CH_3)_2$ [a] (neat liquid)	194.4	98.2	154.2	
$CH_3COCHCHN^+(CH_3)_3Cl^-$ [b] (CD_3OD)	197.5	126.9	148.6	
	(+3.1) [d]	(+28.7)	(−5.6)	
$CH_3COCHCHN(CH_3)_2$ [b,c] (CF_3CO_2H)	187.2	97.3	164.9	
	(−7.2) [d]	(−0.9)	(+10.7)	
(15) ($CDCl_3$)	196.1	97.5	164.3	39.8
(15) (H_2O, pH 6)	198.5	95.9	171.2	41.1
	(+2.4) [e]	(−1.6)	(+6.9)	(+1.3)
(15) (H_2O, pH 0.8)	184.9	96.5	177.2	43.3
	(−11.2) [e]	(−1.0)	(+12.9)	(+3.5)
(15) (CF_3CO_2H)	187.0	97.4	178.0	43.3
	(−9.1) [e]	(−0.1)	(+13.7)	(+3.5)
(15) (BF_3 complex, CH_2Cl_2)	188.1	96.7	176.2	41.8 41.7
	(−8.0) [e]	(−0.8)	(+11.9)	(+2.0) (+1.9)

[a] Ref. 33. [b] Ref. 14. [c] Average chemical shifts of *s-cis-* and *s-trans*-isomers. [d] Δδ relative to chemical shifts of free base. [e] Δδ relative to chemical shifts of (15) in $CDCl_3$.

Table 6. ^{1}H Chemical shifts of the olefinic proton in free and complexed 3-substituted cyclohexenones and enamino-ketones of series (II) (in p.p.m. relative to Me_4Si; 0.3M in CH_2Cl_2)

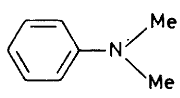
Cyclohexenone substituent in position 3	Free	Complex	Enaminoketone	Free	Complex
H	5.97	6.73	(15)	4.98	5.93
CH_3	5.78	6.63	(16)	5.02	5.94
Cl	6.16	6.93	(17)	4.63	5.50
Br	6.40	7.19	(18)	4.87	5.81
OCH_3	5.30	6.17	(19)	5.13	6.03
OC_2H_5	5.30	6.15	(20)	5.13	6.03
SC_2H_5	5.78	6.65	(21)	5.13	6.10
CO_2CH_3	6.66	7.25	(22)	5.14	6.18
CN	6.48	7.08	(23)	5.13	6.03
$CH_2CO_2CH_3$	5.85	6.65	(24)	5.13	6.03
CH_2CN	6.06	6.83	(25)	5.00	5.96
$CH_2COC_2H_5$	5.82	6.63	(26)	5.20	6.15
C_6H_5	6.34	7.15	(27)	5.12	6.04
$PO(OC_2H_5)_2$	6.49	6.67 *	(28)	5.13	6.07
			(29)	5.17	6.08
			(30)	5.14	5.82

* The first complexation takes place on the oxygen of the phosphoryl group.



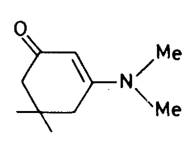
(31)

ΔH° −137·9



(32)

−109·2



(15)

$-132{\cdot}4\ kJ\ mol^{-1}$

5,5-dimethyl-3-oxocyclohex-1-enyl diethylphosphonate where the Lewis acid addition now takes place on the phosphoryl oxygen (as shown by i.r. and n.m.r. spectra and calorimetry[24]).

In order to examine the possibility of *N*-co-ordination with BF_3, we measured the $\Delta H^\circ_{BF_3}$ values of three different models exhibiting very similar steric effects around the nitrogen atom, but different electronic effects on the nitrogen basicity. The decrease of the basicity on going from (31) to (15) is a result of delocalization of the nitrogen lone pair and of the electron-withdrawing effect of the sp^2 carbon bonded to the nitrogen atom. For the enamino-ketone (15), *N*-co-ordination would be subject to (i) an identical or slightly larger (two methyls in position 5) steric requirement than (31) and (32); (ii) an inductive effect close to that in (32); (iii) a higher delocalization effect than in (32). Experimental results show that it is not the case. It is the *O*-co-ordination along with the mesomeric effect of $N(CH_3)_2$ that is responsible for the high basicity of (15). Comparison of the pK_{BH^+} of these models is meaningless because the solvation varies greatly for ammonium and oxonium ions.

The nature of the basic site for our compounds now seems definitively assigned as far as protonation in water and co-ordination with boron trifluoride in an organic solvent is concerned. However, three pieces of experimental and theoretical data appeared to invalidate *O*-protonation or co-ordination and merit discussion and refutation: (i) deviation of the points for NR^1R^2 from the relationships of pK_{BH^+} and σ_p^+ and ΔH° and σ_p^+ (Figure 1); (ii) the singular protonation effect on $\pi \rightarrow \pi^*$ transitions for amino-substituents relative to all other substituents of 3-substituted cyclohexenones (Table 2); (iii) the bathochromic effect resulting from *O*-protonation, predicted by *ab initio* calculations for the $\pi \rightarrow \pi^*$ transition.

We can reject these arguments by considering the following. The mode of determination of σ_p^+ constants. For substituents other than amino-groups, we used Brown and Okamoto's constants[48] established by the solvolysis of αα-dimethylbenzyl chlorides; as the rate of this reaction cannot be meas-

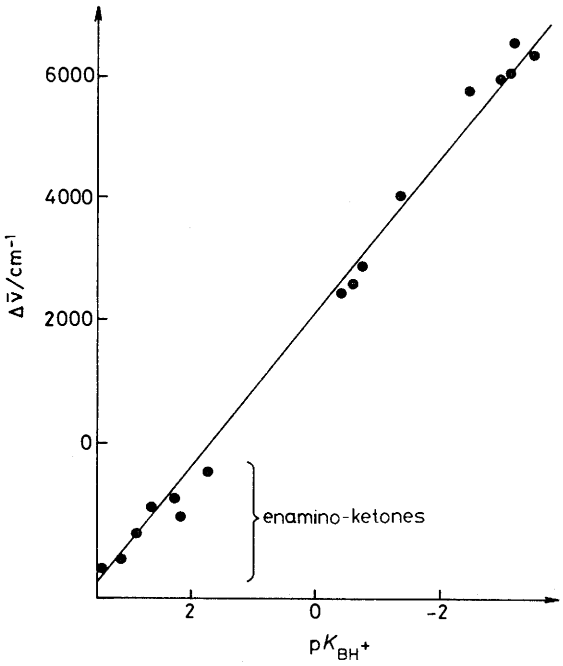


Figure 3. Relationship of $\Delta\tilde{\nu}$ and pK_{BH^+} in 3-substituted cyclohexeenones and enamino-ketones. For the sake of clarity only some enamino-ketone points are drawn.

ured for NH_2, NHC_6H_5, and $N(CH_3)_2$ *para*-substituted compounds, Brown and Okamoto estimated their σ_p^+ by averaging values derived from other reactions[48] [σ_p^+ $N(CH_3)_2$ -1.7 is the average for -1.74, -2.00, -1.55; our relationships would require σ_p^+ *ca.* -2.1].* The problem of the inaccuracy of Brown and Okamoto's σ_p^+ constants for amino-groups has attracted the attention of many authors, but no reliable solution has been found.[49,50] Taking into account the high quality of the correlations for pK_{BH} and σ_p^+ and ΔH° and σ_p^+, it is understandable that inaccurate σ_p^+ values could induce significant deviations.[51]

The difference $\Delta\tilde{\nu} = \tilde{\nu}_{max.}^{BH+} - \tilde{\nu}_{max.}^{BH+}$ for 3-substituted cyclohexenones can be derived from Table 2. For electron-releasing substituents and for hydrogen, we can see that the magnitude of this difference decreases with increasing electron-donating properties ($\Delta\tilde{\nu}$ 6 560 for H and 2 450 cm⁻¹ for OH). Extrapolation to amino-substituents much more electron-donating than OH leads logically to a cancellation and eventually to an inversion of $\Delta\tilde{\nu}$ (negative value). This assumption could be confirmed by substituents, yet unknown, that possess electronic effects intermediate between OH and NH_2; nevertheless, we observe the linear relationship (4) between $\Delta\tilde{\nu}$ and pK_{BH^+} for electron-donating substituents (amino-groups included) (Figure 3).

$$\Delta\tilde{\nu}/\text{cm}^{-1} = -(1\,251 \pm 18)\,pK_{BH^+} + 2\,080 \qquad (4)$$
$$r\ 0.9960,\ s\ 250\ \text{cm}^{-1},\ n\ 39$$

Solvation effects are neglected in the *ab initio* energy level calculations and we suggest this as one possible cause of the calculated bathochromic shift. Another suggestion is that STO 3G calculations with standard geometry are unable to describe u.v. transitions.

On the other hand, *ab initio* calculations usually give consistent results for the energies of isodesmic processes (like $H\overset{+}{O}-C-C=C-N \longrightarrow O=C-C=C-\overset{+}{N}H$). Theoretical (Table 3) and experimental results obtained in the gas phase[28] (*i.e.* favouring *O*-protonation) could differ from those derived from aqueous solution because of the different solvation energies between *O*- and *N*-protonated forms. However, Taft's investigations[52–54] show that solvation of the protonated carbonyl group by water is much stronger than that of a tertiary ammonium ion.†

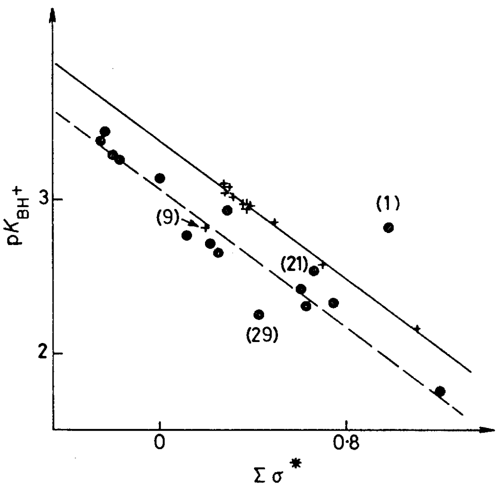


Figure 4. Relationship of pK_{BH^+} and $\Sigma\sigma^*$ for series (I) (+) and (II) (●)

(b) *Influence of the Nitrogen Substituents on the Basicities.*— The results of Table 1 show that pK_{BH^+} and ΔH° are strongly influenced by the nature of the nitrogen substituents. Variations of *ca.* 2 p*K* units and of *ca.* 16 kJ mol⁻¹ are observed for pK_{BH^+} and ΔH°, respectively. Comparison of values corresponding to compounds (16), (18), and (19), (19) and (20), and (21) and (22) shows a slight influence by steric effects on the basicity. Therefore we established the linear relationships (5)—(7) between the basicity parameters (pK_{BH^+} and ΔH°) and the electronic constants of alkyl and aryl substituents of the nitrogen atom [Figures (4) and (5)]. The σ^* constants of Taft[55] and Hall[56] (Table 1) seemed to be the most adequate.

Series (I) [(9) excepted] $pK_{BH^+} =$
$$-(1.12 \pm 0.03)\,\Sigma\sigma^* + 3.37 \qquad (5)$$
$$r\ 0.9976,\ s\ 0.02\ pK\ \text{unit}$$

Series (II) [(21),(29) expected] $pK_{BH^+} =$
$$-(1.16 \pm 0.07)\,\Sigma\sigma^* + 3.06 \qquad (6)$$
$$r\ 0.9887,\ s\ 0.09\ pK\ \text{unit}$$

$$\Delta H^\circ = (9.91 \pm 0.60)\,\Sigma\sigma^* - 132.49 \qquad (7)$$
$$r\ 0.9874,\ s\ 0.82\ \text{kJ mol}^{-1}$$

Thus, the inductive effects of the nitrogen substituents are the main factors influencing the two types of basicity. The sensitivity to inductive effects is higher than expected for a substituent located four bonds away from the basic site. However the absolute values of the slopes for the straight lines are much smaller than would be expected if the basic site were

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* A redetermination of σ_p^+ for the amino-substituent, including other series, will be published separately.

† For instance, protonated acetone is more solvated than protonated trimethylamine by 71 kJ mol⁻¹.

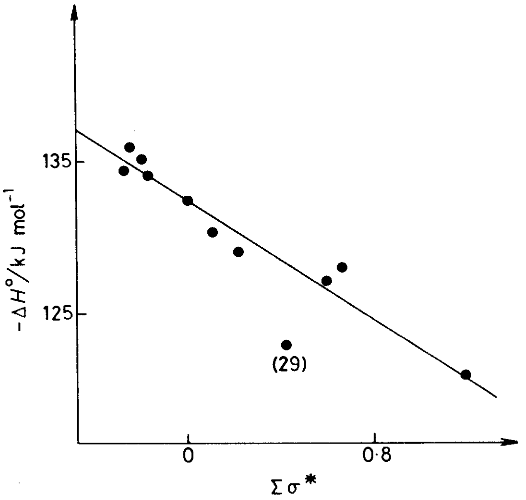

Figure 5. Relationship of ΔH° and $\Sigma\sigma^*$ for series (II)

the nitrogen atom. The substituent inductive effect therefore acts indirectly, affecting the delocalization of the nitrogen lone pair. In these series, the correlations of pK_{BH^+} and $\Sigma\sigma^*$ and ΔH° and $\Sigma\sigma^*$ are representative of what we call a ' p–π inductive effect '. For enthalpies of complexation, it is particularly important that such relationships can be established showing no participation of any steric effect. Concerning either BF_3 co-ordination of aliphatic ketones [57] and *ortho*-substituted pyridines [58] or BMe_3 co-ordination of amines,[59–61] it has been shown that basicity polar effect relationships cannot be obtained without taking steric effects into account. Thus, we have yet another argument in favour if *O*-co-ordination of BF_3 on enamino-ketones.

The exclusion of compounds (9) and (29) bearing respectively the bulky t-butyl and dibenzyl groups deserves some comment. Very large nitrogen substituents can interact with the cyclohexenone moiety thus hindering the overlap between the nitrogen lone pair and the π system. The steric inhibition of resonance decreases the basicity [less stabilization of canonical form (B) protonated or co-ordinated] expected from the linear relationship with σ*. Small deviations occur for some cyclic substituents [(17),(21)]. The corresponding σ* values are derived from p*K* measurements of alkylamines [56] and may contain a steric effect contribution (steric inhibition of solvation).[59]

It is noteworthy that for correlations of pK_{BH^+} and $\Sigma\sigma^*$, the enamino-ketones must be separated into two groups depending on whether they are derived from primary [series (I)] or secondary [series (II)] amines. The two straight lines have an intercept difference of *ca.* 0.3 p*K* unit. As compared to secondary and tertiary amines whose intercept difference is equal to 2.5 p*K* unit,[56] this small value is consistent with the large separation between the substituents and the basic site. It is unlikely that in our series, where the nitrogen is linked to an sp^2 carbon, nitrogen protonation gives only a 0.3 p*K* unit difference. Indeed, in secondary and tertiary anilines where the basic nitrogen is linked to an sp^2 carbon, the intercept difference is 2.5 p*K* unit,[62] *i.e.* the same as for aliphatic amines. We assign the parallelism of the straight lines to a constant difference of solvation between the free and the oxygen-protonated base in each series. The protonated enamino-ketones bear a partial positive charge on nitrogen, thus increasing the acidity of the hydrogen bonded to this atom [series (I)]. Further stabilization of the protonated form by $^{\delta+}$NH hydrogen bonding to the solvent is expected. This effect should be weaker than that for a true charge-localized ammonium ion.[52–54]

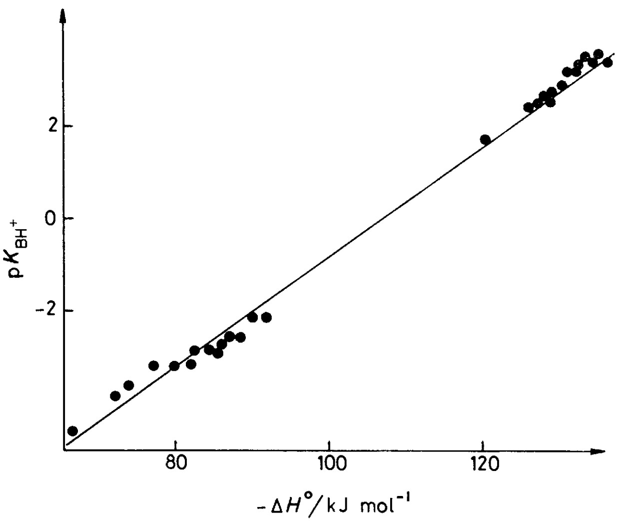

Figure 6. General extrathermodynamic relationship of pK_{BH^+} and ΔH°

(c) *Extrathermodynamic Relationship between the Two Basicity Parameters.*—From the correlations of pK_{BH^+} and $\Sigma\sigma^*$ and ΔH° and $\Sigma\sigma^*$ (limited by the σ* values available), we can predict an extrathermodynamic relationship of the form (8). The most significant point is that both the slope and the intercept are close to those obtained for a similar relationship for series of *p*-substituted 3-phenyl-5,5-dimethylcyclohex-2-enones and *p*-substituted acetophenones [63] Including the basicity parameters of enamino-ketones, we obtained a single relationship (9) covering 7.5 p*K* units (Figure 6). In this relationship, the pK_{BH^+} values of phenylcyclohexenones and acetophenones calculated [63] from the two negative H_A scales of Katritzky *et al.*[64] have been corrected by 0.33 p*K* unit.[65]

Series II [(29) not included] pK_{BH^+} =

$$-(0.121 \pm 0.006)\Delta H^\circ - 12.90 \quad (8)$$

$$r\ 0.9834,\ s\ 0.09\ pK \text{ unit}$$

$$pK_{BH^+} = -(0.120 \pm 0.001)\Delta H^\circ - 12.79 \quad (9)$$

$$r\ 0.9984,\ s\ 0.18\ pK \text{ unit},\ n\ 29$$

One use of this relationship is the possibility of estimating unknown pK_{BH^+} (or ΔH°) values when experimental difficulties preclude their direct determination [for instance, difficulties associated with use of acidity functions as in the acetophenone series, or with interfering phenomena in ΔH° determination as in series (I)].

This unique extrathermodynamic relationship for unsaturated ketones is the ultimate proof for *O*-protonation and *O*-co-ordination of enamino-ketones.

Conclusion

A string of converging arguments allows us to ascertain that oxygen is the preferred basic site in enamino-ketones. Both experimental and theoretical results seemingly against this position were analysed and rational explanations proposed. A general relationship of pK_{BH^+} with ΔH° shows that complexation enthalpies are an adequate measure of the basicity of enamino-ketones. Microcalorimetry may then be considered as an excellent indirect method for pK_{BH^+} determinations, particularly for homogeneous series of weak bases where spectroscopic studies using acidity functions are difficult [66] or even impossible.[22] Finally, considering the distance between the carbonyl oxygen and the various perturbing groups, the large differences in the measured basicities of enamino-ketones definitely do not result from direct field inductive effects of nitrogen substituents. The relationships of $\mathrm{p}K_{\mathrm{BH^+}}$ and $\Sigma\sigma^*$ and ΔH° and $\Sigma\sigma^*$ allow us to consider the possibility of these effects influencing the conjugation between the nitrogen lone pair and the π system, thereby being regarded as p–π inductive effects.

Experimental

Compounds (1)—(8) were prepared as described;[67] the other compounds were prepared by the method of Kashima *et al.*[68]

$\mathrm{p}K_{\mathrm{BH^+}}$ *Measurements*.—Determination of $\mathrm{p}K_{\mathrm{BH^+}}$ values has been achieved by spectrophotometry on a Cary 118C spectrophotometer (recording speed 0.2 nm $\mathrm{s^{-1}}$; slit width 0.25 mm; 1 cm quartz cell; 298.15 ± 0.1 K). Aqueous solutions of enamino-ketones * (10^{-3} M) were diluted with aqueous solutions of hydrochloric, acetic, and formic acids. The pH values of solutions were measured on a Metrohm E 150 pH meter fitted with a Metrohm AG 9100 glass electrode at 298.15 ± 0.1 K. To record the u.v. spectra, the buffer solution was placed in the reference cell. It was verified that no important variation in the absorption curve of enamino-ketones protonated at pH 0.8 occurs when the acid concentration is strongly increased.

ΔH° *Measurements*.—The apparatus used for determining enthalpies of reaction between a gas ($\mathrm{BF_3}$) and a liquid has already been described.[21] All measurements were performed on 0.3—0.5M base solutions in dichloromethane. Previously, this solvent had been treated by concentrated sulphuric acid, washed until neutrality, then distilled from $\mathrm{P_2O_5}$ and stored over 4 Å molecular sieves in the dark. The gaseous Lewis acid is injected in small increments into a 3 $\mathrm{cm^3}$ base solution. Before saturation, each injection gives an enthalpy calculated by $\Delta H^\circ = \Delta Q/\Delta n$ where ΔQ is the produced heat and Δn is the number of moles of injected boron trifluoride. The stoicheiometry of the complex may be calculated from the total amount of injected Lewis acid and the total recorded heat.[1]

^{1}H *and* ^{13}C *N.m.r. and Activation Parameters for* C(3)–N *Rotation*.—^{1}H N.m.r. spectra were recorded on a Varian A 60 A spectrometer at normal probe temperature (*ca.* 40 °C). ^{13}C N.m.r. spectra was recorded on a Bruker WH 90 spectrometer with Fourier transform. For variable-temperature studies line shape analyses were carried out with a classical dynamic n.m.r. CLATUX program;[69] activation parameters were calculated using the Eyring relationship.[70]

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* Sparingly soluble compounds (aromatic substituents) are first solubilized in a small amount of methanol.

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