Hydrogen-bond Basicity of Secondary and Tertiary Amides, Carbamates, Ureas and Lactams

Jean-Yves Le Questel,[a] Christian Laurence,[a] Abdeljalil Lachkar,[b] Maryvonne Helbert[a] and Michel Berthelot[a]
[a] *Laboratoire de Spectrochimie, Faculté des Sciences et des Techniques, 44072 Nantes, France*
[b] *Laboratoire de Spectroscopie, Université Cadi Ayyad, BP S15, Marrakech, Maroc*

The hydrogen-bond basicity scale pK_{HB} (logarithm of the formation constant of 4-fluorophenol–base complexes in CCl_4) has been measured for tertiary and secondary amides, carbonates, ureas and lactams. The hydrogen-bonding fixation site is the carbonyl group, even for the very hindered amide $Bu^tCON(C_6H_{11})_2$. In the amides $R^1CONR^2R^3$ the hydrogen-bond basicity is decreased more by bulky R^1 substituents on the carbonyl carbon than by bulky R^2 and R^3 substituents on nitrogen. The field effect of X substituents operates more effectively on hydrogen-bond basicity than the resonance effect in the $XCONMe_2$ series. The hydrogen-bond basicity is increased by six-membered cyclisation.

We are currently building a thermodynamic hydrogen-bond basicity scale based on pK_{HB}, the logarithm of the formation constant K_{HB} of the 1:1 4-fluorophenol–base complex in CCl_4 at 298 K [eqns. (1) and (2)]. In the proton-sharing equilibrium

$$B + 4\text{-}FC_6H_4OH \rightleftharpoons 4\text{-}FC_6H_4OH\cdots B \quad (1)$$

$$K_{HB} = [4\text{-}FC_6H_4OH\cdots B]/[4\text{-}FC_6H_4OH]\,[B]; \quad (2)$$
$$pK_{HB} = \log_{10}K_{HB}$$

(1), 4-fluorophenol is a reference hydrogen-bond donor (chosen for technical reasons) which plays the same role as H_2O, the reference Brønsted acid for proton-transfer equilibria.

We have already published data for various families of bases B: amidines,[1–3] alcohols,[4] 'push–pull' molecules[5] and nitriles.[6] We present here our pK_{HB} scale for amides, carbamates, ureas and lactams. A number of studies have investigated hydrogen bonding of phenols with tertiary amides,[7–9] secondary amides,[10] ureas,[11] lactams[12] and carbamates,[13] but they refer to a limited number of compounds, to various phenols and different experimental conditions. These data are not satisfactory as we are interested in building a scale defined from a reference process [eqn. (1)] rather than a statistical scale.[14]

We have both measured 33 primary pK_{HB} values and also calculated 27 secondary pK_{HB} values, from a linear correlation between pK_{HB} and $\Delta\nu$(OH), the lowering of the ν(OH) frequency of methanol on going from the free to the hydrogen-bonded OH group. Finally we have in hand 60 primary and secondary pK_{HB} values for secondary and tertiary amides, carbamates, ureas and lactams. Both primary and secondary values allow the calculation of β_2^H, a linear transform of pK_{HB} [eqn. (3)].[14] The β_2^H value permits a quantitative estimate of

$$\beta_2^H = (pK_{HB} + 1.1)/4.636 \quad (3)$$

the value of the formation constant for the hydrogen-bonded complex with any hydrogen-bond donor of known hydrogen-bond acidity α_2^H value.[15] However, only primary values have sufficient accuracy to achieve a correct understanding of small structural effects on hydrogen-bond basicity.

Experimental

Chemicals were either commercial or synthesized in our laboratory by known methods. Substituted *N,N*-dimethylbenzamides were kindly supplied by Dr. Morris (Glasgow).

Infrared measurements were carried out with a Fourier-Transform spectrometer Bruker IFS 45 by selecting 1 cm^{-1} resolution. A 1 cm quartz Infrasil cell was thermostatted at 25 ± 0.1 °C.

The IRTF spectroscopic method for measuring formation constants of hydrogen-bonded complexes of 4-fluorophenol has previously been described.[1–5] The maximum error in pK_{HB} is estimated to be ±0.04. Secondary amides are mainly in the s-*trans* conformation and self-associate in linear polymers[16] easily broken by the high dilutions used in this work. However acetanilide exists in both the s-*cis* and s-*trans* conformations. The very stable cyclic dimer formed from the s-*cis* monomer of acetanilide prevents determination of a meaningful pK_{HB} value for this secondary amide.

Results

The pK_{HB}, infrared frequency shifts $\Delta\nu$(OH), and β_2^H values are reported for the primary set in Table 1.

The correlation coefficient r and the standard deviation s show that a satisfactory correlation exists between pK_{HB} and $\Delta\nu$(OH) for 30 compounds [eqn. (4)].

$$pK_{HB} = 0.0127\,\Delta\nu(OH) + 0.137 \quad (4)$$
$$n = 30 \quad r = 0.9787 \quad s = 0.09$$

Hence eqn. (4) can safely be used for calculating secondary pK_{HB} (or β_2^H) values for those amides, carbamates and ureas for which only $\Delta\nu$(OH) has been measured. The experimental $\Delta\nu$(OH) and calculated pK_{HB} and β_2^H values are reported in Table 2. Secondary pK_{HB} values are less reliable than primary values since eqn. (4) is subject to $s = 0.09$ log units.

Discussion

Hydrogen Bonding Site.—The compounds studied have several potential acceptor sites available for hydrogen-bond formation, namely the oxygens and the nitrogens of the CO–N, N–CO–N and O–CO–N moieties. The lower carbonyl stretching vibration in the complex than in the free base shows, unambiguously, that in amides, lactams, carbamates and ureas, hydrogen bonding occurs on the oxygen of the carbonyl group

Table 1 Hydrogen-bond basicity of amides, carbamates, lactams and ureas: frequency shifts $\Delta\nu$(OH)/cm^{-1} and primary pK_{HB} and β_2^H values

Compounds	Formula	$\Delta\nu$(OH)	pK_{HB}	β_2^H
Secondary amides				
N-Methylformamide	HCONHMe	145	1.96	0.66
N-Methylbenzamide	PhCONHMe	152	2.03	0.68
N-Methylpropionamide	EtCONHMe		2.24	0.72
N-Ethylacetamide	MeCONHEt		2.29	0.73
N-Methylacetamide	MeCONHMe	167	2.30	0.73
Tertiary amides				
Dimethylcarbamoyl chloride	$ClCONMe_2$	70	1.00	0.45
N,*N*-Dimethyl-2,2,2-trifluoroacetamide	CF_3CONMe_2	81	1.04	0.46
N,*N*-Dimethyl-2-chloroacetamide	$ClCH_2CONMe_2$	133	1.74	0.61
N-Methylformanilide	HCONMePh	123	1.74	0.61
N,*N*-Diphenylacetamide	$MeCONPh_2$	130	1.94	0.66
N,*N*-Diisopropyl-2,2-dimethylpropionamide	$Bu^tCON(Pr^i)_2$	161	2.03	0.68
N,*N*-Dicyclohexyl-2,2-dimethylpropionamide	$Bu^tCON(C_6H_{11})_2$	160	2.06	0.68
N,*N*,2,2-Tetramethylpropionamide	Bu^tCONMe_2	161	2.10	0.69
N,*N*-Dimethylformamide	$HCONMe_2$	150	2.10	0.69
N-Methylacetanilide	MeCONMePh	150	2.19	0.71
N,*N*-Dicyclohexylpropionamide	$EtCON(C_6H_{11})_2$	170	2.22	0.72
N,*N*-Dimethylbenzamide	$PhCONMe_2$	159	2.23	0.72
N,*N*-Dicyclohexylisobutyramide	$Pr^iCON(C_6H_{11})_2$	174	2.24	0.72
N,*N*-Dimethylisobutyramide	Pr^iCONMe_2	171	2.26	0.72
N,*N*-Dimethylpropionamide	$EtCONMe_2$	166	2.36	0.75
N,*N*-Dicyclohexylacetamide	$MeCON(C_6H_{11})_2$		2.41	0.76
N,*N*-Dimethylacetamide	$MeCONMe_2$	179	2.44	0.76
N,*N*-Diethylacetamide	$MeCONEt_2$	184	2.47	0.77
Lactams				
1-Methyl-2-pyrrolidone		185	2.38	0.75
N-Methylcaprolactam		183	2.53	0.78
1-Methyl-2-pyridone		192	2.57	0.79
1-Methyl-2-piperidone		194	2.60	0.80
Carbamates				
Phenyl dimethylcarbamate	$PhOCONMe_2$	112	1.70	0.60
Ethyl dimethylcarbamate	$EtOCONMe_2$	137	1.83	0.63
Ureas				
1,1,3,3-Tetraethylurea	$Et_2NCONEt_2$	175	2.43	0.76
1,1,3,3-Tetramethylurea	$Me_2NCONMe_2$	177	2.44	0.76
N,*N*′-Dimethyl *N*,*N*′-ethyleneurea		183	2.46	0.77
N,*N*′-Dimethyl *N*,*N*′-trimethyleneurea		210	2.79	0.84

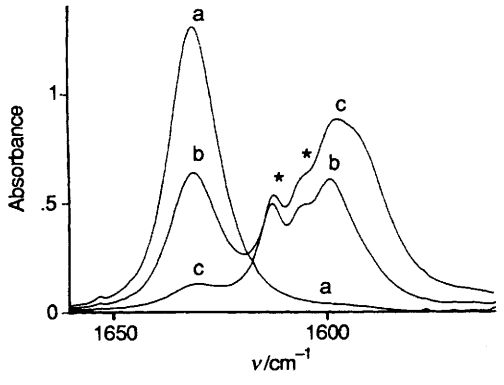

Fig. 1 FT–IR spectrum of $Bu^tCON(C_6H_{11})_2$ in the ν(CO) region: a, $Bu^tCON(C_6H_{11})_2$ (c = 0.03 mol dm^{-3}) in CCl_4; b, $Bu^tCON(C_6H_{11})_2$ (c = 0.03 mol dm^{-3}) and 4-fluorophenol (c = 0.03 mol dm^{-3}) in CCl_4; c, $Bu^tCON(C_6H_{11})_2$ (c = 0.03 mol dm^{-3}) and 4-fluorophenol (c = 0.13 mol dm^{-3}) in CCl_4. The bands marked with an asterisk at 1605 and 1612 cm^{-1} are the ring-valence vibrations of 4-fluorophenol.

and not on the other heteroatoms. However, for the sterically hindered amides $Pr^iCON(C_6H_{11})_2$ and $Bu^tCON(C_6H_{11})_2$ it has been suggested[17] that steric hindrance reduces the conjugation of the CO and $N(C_6H_{11})_2$ groups and hence the basicity of the carbonyl group and that, towards the Lewis acid I_2, nitrogen would become the basic site. Fig. 1 shows that the addition of 4-fluorophenol to a CCl_4 solution of $Bu^tCON(C_6H_{11})_2$ induces a lowering of 32 cm^{-1} of the carbonyl stretching vibration at 1629 cm^{-1}. Hence $Bu^tCON(C_6H_{11})_2$ behaves similarly to $MeCON(Me_2)$, for which $\Delta\nu$(C=O) is 25 cm^{-1}, and even for hindered amides the carbonyl remains the hydrogen-bonding site.

Steric Effects.—These are most easily studied by alkyl substitution on the CO–N function. In the trialkylated amide $R^1CONR^2R^3$, front strain between bulky substituents R^1 and/or NR^2R^3 and 4-fluorophenol must decrease the equilibrium constant, whereas back strain between R^1 and NR^2R^3 and also between R^2 and R^3 can be released by rotations and/or angle opening. It is clear that front strain occurs between bulky alkyl R^1 substituents on the carbonyl group and 4-fluorophenol since pK_{HB} decreases regularly when the size of R^1 increases in the R^1CONMe_2 series.

$$MeCONMe_2\ (2.44) > EtCONMe_2\ (2.36) > Pr^iCONMe_2\ (2.29) > Bu^tCONMe_2\ (2.10)$$

This decrease of 0.34 pK_{HB} unit on going from $MeCONMe_2$ to Bu^tCONMe_2 is also observed from $MeCON(C_6H_{11})_2$ to $Bu^tCON(C_6H_{11})_2$.

Table 2 Hydrogen-bond basicity of amides, carbamates and ureas: experimental frequency shifts $\Delta\nu$(OH)/cm^{-1} of methanol and secondary calculated pK_{HB} and β_2^H values

Compounds	Formula	$\Delta\nu$(OH)	pK_{HB}	β_2^H
Amides				
Diphenylcarbamoyl chloride	$ClCONPh_2$	48	0.75	0.40
Diethylcarbamoyl chloride	$ClCONEt_2$	74	1.08	0.47
N,N-Dimethyl-2,2,2-trichloroacetamide	CCl_3CONMe_2	81	1.17	0.49
N,N-Diphenylformamide	$HCONPh_2$	100	1.41	0.54
N,N-Diphenylbenzamide	$PhCONPh_2$	116	1.61	0.35
N,N-Diphenyl-2,2-dimethylpropionamide	Bu^tCONPh_2	118	1.64	0.59
N,N-Diphenyl-4-methoxybenzamide	$4\text{-}MeOC_6H_4CONPh_2$	121	1.67	0.60
N,N-Dimethyl-4-nitrobenzamide	$4\text{-}NO_2C_6H_4CONMe_2$	139	1.90	0.65
N,N-Dimethyl-4-(trifluoromethyl)benzamide	$4\text{-}CF_3C_6H_4CONMe_2$	144	1.97	0.66
N,N-Dimethyl-4-bromobenzamide	$4\text{-}BrC_6H_4CONMe_2$	152	2.07	0.68
1-Formylpiperidine		152	2.07	0.68
N,N-Diethylformamide	$HCONEt_2$	153	2.08	0.69
N,N-Dimethyl-4-fluorobenzamide	$4\text{-}FC_6H_4CONMe_2$	158	2.14	0.70
N,N-Diethylbenzamide	$PhCONEt_2$	167	2.26	0.72
N,N-Dimethyl-4-methylbenzamide	$4\text{-}MeC_6H_4CONMe_2$	168	2.27	0.73
N,N-Dimethyl-4-methoxybenzamide	$4\text{-}MeOC_6H_4CONMe_2$	171	2.31	0.74
N,N-Diethyl-4-methoxybenzamide	$4\text{-}MeOC_6H_4CONEt_2$	174	2.35	0.74
N,N-Dimethyl-4-dimethylaminobenzamide	$4\text{-}Me_2NC_6H_4CONMe_2$	185	2.49	0.77
Carbamates				
Phenyl diphenylcarbamate	$PhOCONPh_2$	82	1.18	0.49
Methyl diphenylcarbamate	$MeOCONPh_2$	100	1.41	0.54
Ethyl diphenylcarbamate	$EtOCONPh_2$	103	1.45	0.55
Methyl dimethylcarbamate	$MeOCONMe_2$	131	1.80	0.63
Ethyl diethylcarbamate	$EtOCONEt_2$	143	1.95	0.66
Ureas				
1,1,3,3-Tetraphenylurea	$Ph_2NCONPh_2$	126	1.74	0.61
1,1-Diphenyl-3,3-diethylurea	$Ph_2NCONEt_2$	152	2.07	0.68
1,1-Diphenyl-3,3-dimethylurea	$Ph_2NCONMe_2$	153	2.08	0.69
1,3-Diphenyl-1,3-diethylurea	PhEtNCONEtPh	159	2.16	0.70

In contrast, replacement of the methyl substituents on the nitrogen atom by bulky cyclohexyl substituents does not decrease significantly pK_{HB} when R^1 is small, *cf.* $MeCONMe_2$ (2.44) and $MeCON(C_6H_{11})_2$ (2.41).

Electrical Effects.—In the tertiary amides $XCONMe_2$ the electronic effects of the X substituents H, Me, Ph, Cl, CF_3, $ClCH_2$, OEt, OPh and NMe_2 on the hydrogen-bond basicity can be analysed by means of eqn. (5),[18] where pK°_{HB} refers to $HCONMe_2$, σ_F and σ_R measure the field and resonance

$$pK_{HB} = pK^{\circ}_{HB} + \rho_F\sigma_F + \rho_R\sigma_R \quad (5)$$

effects of X substituents,[18] and ρ_F and ρ_R measure the sensitivity of hydrogen-bond basicity to these effects.[18] It must be pointed out that eqn. (5) does not take into account (*i*) the steric effects of X substituents, (*ii*) possible non-additive effects[19] of X and NMe_2 substituents on the carbonyl group, which should require cross-terms in eqn. (5), and (*iii*) saturation effects of strongly electron-donating substituents.[20] Nevertheless, eqn. (6) has satisfactory statistics (*cf.* correlation coefficient *r* and standard deviation *s*).

$$pK_{HB} = 2.26 - 2.74\,\sigma_F - 0.78\,\sigma_R^+ \quad (6)$$
$$n = 9 \quad r = 0.969 \quad s = 0.15$$

The sensitivity coefficients ρ_F and ρ_R of eqn. (6) show that field effects play the leading part and that resonance effects are not very important. For example, in $ClCONMe_2$ the resonance electron-donating effect of chlorine is outweighed by its field electron-withdrawing effect, and $ClCONMe_2$ is the least basic amide of this study. Also, the strong resonance electron-donating effect of NMe_2 does not seem to be operative in $Me_2NCONMe_2$ since tetramethylurea is not more basic than dimethylacetamide.

In the secondary amides XCONHMe, the effects of the substituents H, Me, Et and Ph parallel those of tertiary amides:

HCONHMe (1.96) < PhCONHMe (2.03) < EtCONHMe (2.24) < MeCONHMe (2.30)

$HCONMe_2$ (2.10) < $PhCONMe_2$ (2.23) < $EtCONMe_2$ (2.36) < $MeCONMe_2$ (2.44)

Compared with H, the electron-donating effect of alkyl groups R and electron-withdrawing effect of phenyl easily explain the following sequence observed for substitutions on the nitrogen atom of the amide function:

$$MeCONR_2 > MeCONHR > MeCONRPh > MeCONPh_2$$

A ΔpK_{HB} increment of -0.25 can be calculated for the Me/Ph substitution on the nitrogen of the amide function from the following pK_{HB} values

$MeCONMe_2$ (2.44) > MeCONMePh (2.19) > $MeCONPh_2$ (1.94)

Cyclisation.—Cyclisation without cyclic strain (six-membered rings) increases the hydrogen-bond basicity of amides and ureas: 1-methyl-2-piperidone is more basic by 0.16 pK_{HB} units than is dimethylacetamide, and dimethyltrimethyleneurea is more basic by 0.35 pK_{HB} units than tetramethylurea.

The most basic cyclic ureas and lactams also seem to be six-membered since 1-methyl-2-pyrrolidone (five-membered) and *N*-methylcaprolactam (seven-membered) are less basic than 1-methyl-2-piperidone (six-membered) and dimethyltrimethyleneurea (six-membered) is more basic than dimethylethyleneurea (five-membered).

References

1 E. D. Raczynska, C. Laurence and P. Nicolet, *J. Chem. Soc., Perkin Trans. 2*, 1988, 1491.
2 E. D. Raczynska and C. Laurence, *J. Chem. Res. (S)*, 1989, 148
3 E. D. Raczynska, C. Laurence and M. Berthelot, *Can. J. Chem.*, in the press.
4 C. Laurence, M. Berthelot, M. Helbert and K. Sraïdi, *J. Phys. Chem.*, 1989, **93**, 3799.
5 C. Laurence, M. Berthelot, E. D. Raczynska, J. Y. Le Questel, G. Duguay and P. Hudhomme, *J. Chem. Res. (S)*, 1990, 250.
6 M. Berthelot, M. Helbert, C. Laurence and J. Y. Le Questel, *J. Phys. Org. Chem.*, submitted.
7 T. Gramstad and W. J. Fuglevik, *Acta Chem. Scand.*, 1962, **16**, 1369.
8 M. D. Joensten and R. S. Drago, *J. Am. Chem. Soc.*, 1962, **84**, 2697.
9 E. Kwiatkowsky, K. Kozubek and Z. Peplinski, *Z. Naturforsch., Teil B*, 1978, **33**(2), 230.
10 C. Dorval and Th. Zeegers-Huyskens, *Spectrosc. Lett.*, 1974, **7**(6), 247.
11 J. P. Muller, G. Vercruysse and Th. Zeegers-Huyskens, *J. Chim. Phys. Chim. Biol.*, 1972, **69**, 143.
12 T. Gramstad and W. J. Fuglevik, *Spectrochim. Acta*, 1965, **21**, 343.
13 K. Platteborze, J. Parmentier and Th. Zeegers-Huyskens, *Spectrosc. Lett.*, 1991, **24**(5), 635.
14 M. H. Abraham, P. L. Grellier, D. V. Prior, J. J. Morris and P. J. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1990, 521.
15 M. H. Abraham, P. L. Grellier, D. V. Prior, R. W. Taft, J. J. Morris, P. J. Taylor, C. Laurence, M. Berthelot, R. M. Doherty, M. J. Kamlet, J. L. M. Abboud, K. Sraïdi and G. Guihéneuf, *J. Am. Chem. Soc.*, 1988, **110**, 8534.
16 H. E. Hallam and C. M. Jones, *J. Mol. Struct.*, 1970, **5**, 1.
17 G. Guihéneuf, J. L. M. Abboud and A. Lachkar, *Can. J. Chem.*, 1988, **66**, 1032.
18 R. W. Taft and R. D. Topsom, *Prog. Phys. Org. Chem.*, 1987, **16**, 1.
19 O. Exner, *Collect. Czech. Chem. Commun.*, 1976, **41**, 1516.
20 C. A. Filgueiras and J. E. Huheey, *J. Org. Chem.*, 1976, **41**, 49.

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