

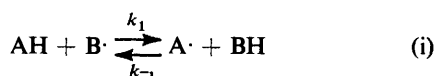
Acyl Nitroxides. Part 4.¹ Estimation of OH Bond Dissociation Energies for *N*-*t*-Butylhydroxamic Acids

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E.s.r. spectroscopy has been used to determine the equilibrium constants for the hydrogen exchange reactions between *N*-*t*-butylhydroxamic acids and the stable piperidine *N*-oxyl (1); since the O-H bond strength in (1)-H is known, this gives an estimate of the O-H bond strengths in the hydroxamic acids. These are found to be stronger than those in dialkyl nitroxides and increase with increasing electron demand in the acyl group.

If an equilibrium constant K for the hydrogen atom transfer process (i) can be determined, either directly, or by separate



measurements of k_1 and k_{-1} , then in general ΔS is assumed to be negligible and the value of ΔG may be taken as an approximate measure of the difference between the A-H and B-H bond dissociation energies.^{2,3} If $D(\text{B-H})$ is known, measurement of K therefore gives an estimate of $D(\text{A-H})$. Mahoney *et al.*³ have used this procedure to estimate solution O-H bond strengths of a series of ketoximes and dialkylhydroxylamines by direct e.s.r. measurements of radical concentrations in mixtures prepared from AH and B· where both A· and B· were relatively persistent radicals. These experiments depended on a knowledge of $D(\text{B-H})$ which, for compounds (1)-H-(3)-H, were determined by a microcalorimetric procedure involving the stoichiometric oxidation of hydrazobenzene to azobenzene by each of the radicals (1)-(3). The result for (1)-H of 71.8 kcal mol⁻¹ was in excellent agreement with the value of 71.9 (±2.7) kcal mol⁻¹ obtained by Lebedev *et al.*,⁴ by direct measurements of heats of combustion and sublimation for the nitroxide and its corresponding hydroxylamine. In general, it was concluded that the O-H bond strengths in dialkylhydroxylamines are between 70 and 74 kcal mol⁻¹ (the lower values being for the more sterically crowded molecules) although a slightly lower figure of 69.5 ± 2 kcal mol⁻¹ has since been suggested for *NN*-diethylhydroxylamine.⁵

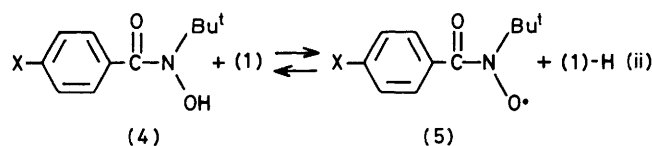
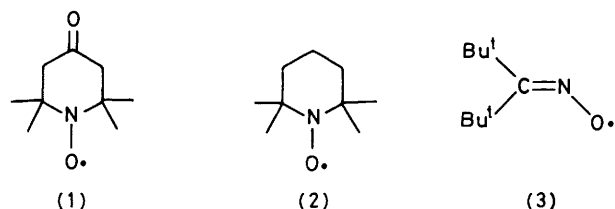
Recent applications of the equilibration technique⁶ include the estimation of the O-H bond strength in *NN*-bistrifluoromethylhydroxylamine.⁷

In a preliminary report,⁸ we summarized data on the equilibration of (1) with four *N*-*t*-butylhydroxamic acid derivatives (4a-d). The ΔG value for the parent *N*-*t*-butylbenzohydroxamic acid [equation (ii)] was *ca.* 6 kcal mol⁻¹, implying a greater O-H bond strength in the hydroxamic acid than in the hydroxylamine (1)-H and, correspondingly, a greater radical reactivity in (5a) than in (1), a point which we have exploited in inter-^{1,9-11} and intra-molecular¹² oxidation reactions using acyl nitroxides.

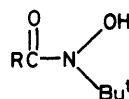
In the present paper, we give details of the equilibration experiments as well as the results of measurements on other *N*-*t*-butylhydroxamic acids.

Results

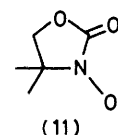
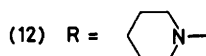
The preparations of the hydroxamic acids (4a-d), (6)-(9), *N*-hydroxycarbamates (10) and (11), and *N*-hydroxyurea (12) were described in Part 1.¹³ 2,2,6,6-Tetramethyl-4-piperidone *N*-oxyl (1) was obtained from Aldrich. Equilibrium was established in benzene or other solvent starting with de-



- a; X = H
b; X = Ph
c; X = NO₂
d; X = OMe



- (6) R = PhCH=CH-
(7) R = PhCH₂CH₂-
(8) R = CH₃(CH₂)₉-
(9) R = (CH₃)₂CHCH₂-
(10) R = C₂H₅O-



oxygenated stock solutions of (1) and the appropriate *N*-hydroxy-compound each of accurately known concentration (both *ca.* 2.5mm). These were mixed using a range of initial reactant ratios (usually from 1:1 to 40:1 [AH]:[B·]) in order to identify any concentration dependence of the measured equilibrium constant. The mixtures were diluted with further oxygen-free solvent such that the total radical concentration did not exceed 5 × 10⁻⁴M, and the resulting solutions were again carefully deoxygenated and then allowed to stand in the dark at room temperature for 24 h before measuring the ratio of concentrations of the two nitroxides by e.s.r. (Varian E4). This procedure was routinely adopted, although equilibrium was in most instances established within minutes. One further precaution was that stock solutions of *N*-hydroxy-compounds were checked before mixing for the

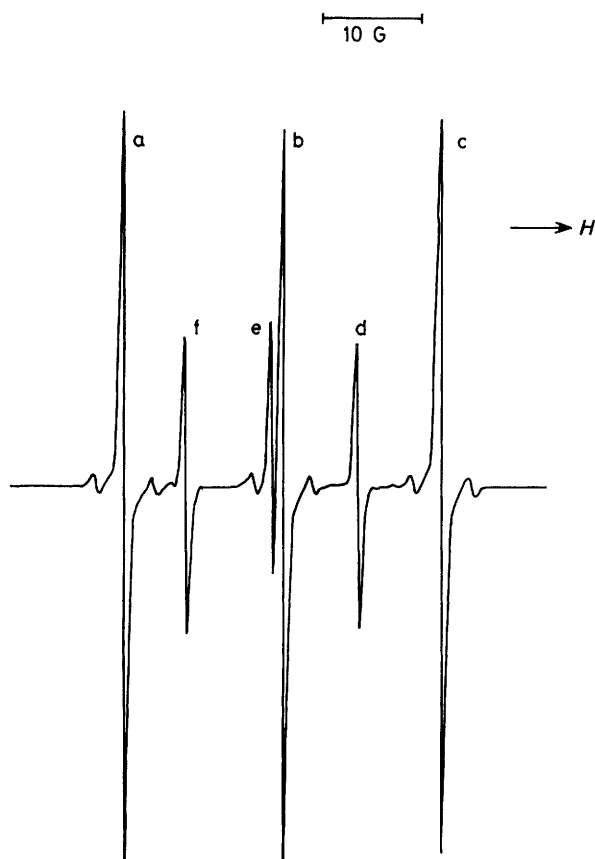


Figure E.s.r. spectrum of equilibrium mixture obtained by mixing a solution of (1) with a solution of (9); peaks a—c are due to the piperidine *N*-oxyl, and d—f arise from the acyl nitroxide

presence of radical. Normally, concentrations were close to, or below, spectrometer detection limits. When this was not the case, fresh solutions were prepared and checked; in these instances special care was taken to minimize exposure to oxygen throughout the handling procedure.

The ratio of radical concentrations was obtained using single electronic integration¹⁴ followed by peak area measurement on the absorption spectra. Control experiments showed that a plot of [(peak area)/(receiver gain)] against relative concentration of (1) passed through the origin and was accurately linear over more than two orders of magnitude. It is not necessary to measure absolute radical concentrations in these experiments if it is assumed that no loss of total radical concentration occurs during the equilibrium. A representative first derivative spectrum from an equilibrium experiment is presented in the Figure. It will be seen that individual peaks from the two nitroxides are well separated, but, because of the slightly different *g* values for the two species, integration of peak d of the acyl nitroxide spectrum and peak c of the piperidine *N*-oxyl give the most satisfactory results with minimum complication from overlap of the ¹³C satellite lines. In many instances, the acyl nitroxide lines were much weaker than shown in the illustration and had to be recorded at higher gain than those used for the piperidine *N*-oxyl.

A typical set of results is given in Table 1 for *N*-*t*-butylbenzohydroxamic acid (4a) in benzene at 15 °C; from the figures, it will be seen that there is no perceptible trend in the values of *K* as the initial concentration ratio is altered. The mean value is calculated to be $(1.89 \pm 0.24) \times 10^{-5}$.

Table 2 summarizes results for the four benzohydroxamic

Table 1. Equilibrium measurements on mixtures of (4a) (= BH) and (1) (= A·) in benzene at 15 ± 1 °C

Approximate initial concentration ratio [BH] ₀ : [A·] ₀	Calculated equilibrium constant 10 ⁵ K
1 : 1	1.91
2 : 1	2.12
4 : 1	1.64
6 : 1	1.95
10 : 1	2.30
20 : 1	1.74
10 : ½	1.57

Table 2. Equilibrium data for the reactions of (4a—d) with (1) at 15 ± 1 °C

Substituent X in (4)	Solvent	Calculated <i>K</i>	Δ <i>G</i> /kcal mol ⁻¹
NO ₂	PhH	$(5.4 \pm 3.34) \times 10^{-7}$	8.41 ± 0.45
H	PhH	$(1.89 \pm 0.24) \times 10^{-5}$	6.23 ± 0.07
H	Hexane	$(15.11 \pm 4.03) \times 10^{-5}$	5.06 ± 0.17
H	CCl ₄	$(8.14 \pm 1.18) \times 10^{-5}$	5.40 ± 0.08
Ph	PhH	$(5.20 \pm 2.54) \times 10^{-5}$	5.74 ± 0.38
OMe ^a	PhH	$(7.39 \pm 0.42) \times 10^{-4}$	4.13 ± 0.06

^a Equilibrium required 48 h.

Table 3. Equilibrium data for the reactions of compounds (6)—(9) and (12) with (1) in CCl₄ at 15 ± 1 °C

Hydroxamic acid	<i>K</i> ^a	Δ <i>G</i> /kcal mol ⁻¹
(6)	$(1.56 \pm 0.16) \times 10^{-4}$	5.02 ± 0.06
(7)	$(5.08 \pm 0.97) \times 10^{-4}$	4.35 ± 0.11
(8)	$(9.16 \pm 1.48) \times 10^{-4}$	4.01 ± 0.09
(9)	$(1.22 \pm 0.10) \times 10^{-3}$	3.84 ± 0.05
(12)	$(1.16 \pm 0.29) \times 10^{-2}$	2.57 ± 0.13

^a Mean value from eight independent estimations.

acids (4a—d), as well as the results for (4a) redetermined using hexane and CCl₄ as solvents. In the final column, the Δ*G* values obtained from the equilibrium measurements are listed. Table 3 gives similar data (CCl₄) for the hydroxamic acids (6)—(9), and the *N*-hydroxyurea (12). Experiments with the two *N*-hydroxycarbamates (10) and (11) were unsatisfactory, in that acyl nitroxide levels never rose above the low background values present in the reactant solutions.

Finally, as a check on the method, CCl₄ solutions of (5a)¹³ and of the *N*-hydroxyurea (12) were mixed, and an equilibrium constant of 76.2 ± 6.7 was found. This is in reasonable agreement with the calculated figure of 140 ± 50 based on equilibrations of (4a) and (12) with the piperidine *N*-oxyl. It equates to Δ*G* -2.54 kcal mol⁻¹ (calculated -2.83).

Discussion

Determination of O—H bond strengths of hydroxamic acids by the equilibration procedure outlined in the Introduction is perhaps open to greater criticism than are measurements on other systems because of the possibility of intramolecular hydrogen bonding in the hydroxamic acids which could contribute to Δ*S* and especially to Δ*H* in the equilibria. Because of the rather wide error limits in these experiments, no attempt has been made to study the temperature dependence of *K* for any of the equilibria. In any case, it might reasonably be expected that hydrogen bonding effects will be similar in

Table 4. Summary of estimated O-H bond dissociation energies for *N*-*t*-butylhydroxamic acids

Compound	O-H Bond strength (kcal mol ⁻¹)
(4a)	77.2
(4b)	76.7
(4c)	79.4
(4d)	75.1
(6)	76.8
(7)	76.2
(8)	75.8
(9)	75.6
(12)	74.4

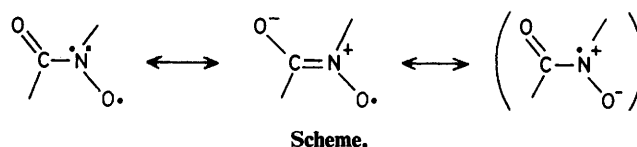
most of the systems studied, and from the high reactivity of the acyl nitroxides in hydrogen abstraction reactions⁹⁻¹² it is at least clear that we are dealing with nitroxides which have an unusually high affinity for hydrogen. Hydrogen bonding in the hydroxamic acids will be discussed further below, but with the above reservation in mind, Table 4 has been prepared as a summary of the hydroxamic acid O-H bond dissociation energies obtained from the experimental ΔG (CCl₄) values by addition to the O-H bond strength (71.8 kcal mol⁻¹) for (1)-H.³

One problem, removed as the investigation developed, was the original choice of benzene as solvent. Weak radical solvation by benzene has often been discussed,¹⁵ and at least one specific instance concerns nitroxides.¹⁶ For this reason, the equilibrium measurements with the parent benzohydroxamic acid (4a) were repeated in *n*-hexane and in CCl₄. There is an appreciable difference between the *K* value found in benzene and those in the other two solvents (Table 2), and the O-H bond strengths for the substituted benzohydroxamic acids recorded in Table 4 have all been corrected downwards from the benzene results by 0.8 kcal mol⁻¹.

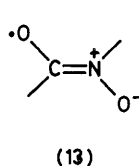
A prime objective in this investigation was to relate O-H bond strength to nitroxide structure, it being considered that a strengthening of the O-H bond could be related to a destabilisation of the nitroxide moiety relative to that in dialkyl nitroxides. We,⁸ and others before us,¹⁷ have argued that lone-pair delocalisation from nitroxide nitrogen would tend to 'fix' the unpaired electron on oxygen (Scheme).

The importance we attached to this¹⁸ has been reappraised,¹⁹ and we have ourselves measured an isotropic ¹⁷O coupling from carbonyl oxygen in isotopically enriched (4a) of 4.4 G¹⁸ consistent with ca. 12% *p*-orbital spin density on carbonyl oxygen [structure (13)]. Nevertheless, the role of lone-pair delocalisation seems to be supported by an excellent correlation between the O-H bond strengths of the four benzohydroxamic acids and Brown's σ^+ constants. Using $\log(K/K_0) = \rho\sigma^+$ for the mean values of *K* (in benzene) gives $\rho = 2.07$ with $r = 0.999$. It is worth recalling that, although a_N for these nitroxides does not change very markedly with substituent, there is nevertheless an equally good correlation between a_N and σ^+ over the range *p*-NO₂-*p*-NMe₂, including eight *p*-substituted aroyl nitroxides.⁸

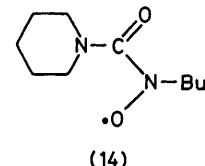
The equilibrium data for the *N*-hydroxyurea (12) are also in good agreement with the destabilisation argument, for in the corresponding nitroxide (14) the demand for electrons by the carbonyl can be largely satisfied by the lone pair on piperidine nitrogen. Accordingly, the nitroxide grouping in (14) is less perturbed by the adjacent carbonyl, and the radical has much of the character of a dialkyl nitroxide. This is reflected not only in the lower O-H bond strength in (12), but also in the relatively high a_N value for the radical (11.73 G in benzene), which is intermediate between those of (1) and (5a) (15.2 and



Scheme.



(13)



(14)

7.98 G, respectively), as is the visible absorption maximum (ca. 555 nm compared with ca. 425 and 645 nm, respectively). Furthermore, in crystals of (14) there is a substantial torsion angle (117°) in the O-C-N-O group, in contrast with the near planarity of this moiety in 3,5-dinitrobenzoyl *t*-butyl nitroxide (166°).²⁰ On the other hand, the piperidine nitrogen and the carbonyl group in (14) are essentially coplanar.

The alkanoyl nitroxides seem to be very slightly less destabilised than their aroyl analogues whilst the data for the styrylcarbonyl derivative are similar to those for (4a). Possibly the small differences here may be attributed to different electronegativities of *sp*² and *sp*³ bonded carbon groupings.

The failure to obtain data for the *N*-hydroxycarbamates is puzzling. Analogy with the discussion so far would tend to suggest that the strengths of the O-H bonds in (10) and (11) might have been found to be between those of (4a) and (12). Whether intramolecular hydrogen bonding might be especially important in these hydroxy-compounds, and impede atom transfer to (1), is not clear. But this cannot be the explanation for the curious fact that, amongst the *successful* equilibrations, by far the slowest was that involving the carbonate 'phenylogue', *p*-methoxybenzohydroxamic acid (4d).

The general conclusion that the acyl *t*-butyl nitroxides have a higher affinity for hydrogen than do the dialkyl nitroxides seems indisputable. But whilst the O-H bond in the hydroxamic acids is unusually strong, there must be some contribution to the equilibria from intramolecular hydrogen bonding in these acids. Its occurrence²¹ seems clear from the broad O-H and C-O absorption bands in solutions of e.g. *N*-*t*-butylbenzohydroxamic acid (4a) at 3180 and 1605 cm⁻¹, respectively; the latter sharpens and shifts to 1636 cm⁻¹ in DMSO which competes as a hydrogen bond acceptor. It is very difficult to attempt to quantify the hydrogen bond contribution to ΔG ; on balance we believe it to be small, probably less than 2 kcal mol⁻¹, since the chelate five-membered ring requires distortion from a preferred geometry in which the O-H bond is bent out of the CONO plane in order to minimize lone-pair-lone-pair repulsion across the N-O bond. This effect is clearly seen in the large N-O rotational barrier in *O*-alkyl derivatives of these hydroxamic acids.²²

One of the most reactive nitroxides known is bistrifluoromethyl nitroxide; using procedures similar to those described here, this has been shown to form bonds to hydrogen with *D*(O-H) 82.6 kcal mol⁻¹. Qualitatively, the explanation is similar to that presented here, in that the strongly electron-withdrawing substituents denude nitrogen of its lone-pair and concentrate spin on oxygen. An estimate of the *p*-orbital spin density on oxygen in (CF₃)₂NO[•] suggests a value of 67%, in contrast with ca. 54% for dialkyl nitroxides.²³ A figure of at least 60% has been suggested¹⁷ for benzoyl *t*-butyl nitroxide, and there may be a simple correlation between these numbers and the corresponding O-H bond strengths. However, as we

have pointed out,¹⁸ deduction of precise information on spin density distribution in nitroxides may be less straightforward than is indicated by a direct proportionality²⁴ between a_N and a_O , and the spin densities ρ_N and ρ_O , respectively. Finally, we recall that the results of INDO calculations mentioned in the preliminary report supported the contention that ρ_O is greater in the model acyl nitroxide HCONHO· than it is in H₂NO·.^{8,25}

Acknowledgements

We thank the SRC for a studentship (T. C. J.) and a grant to purchase the spectrometer. M. J. P. also thanks D. Griller and K. U. Ingold for their hospitality at N.R.C.C., Ottawa, where this manuscript was prepared, and NATO for a travel grant.

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Received 3rd August 1982; Paper 2/1360