Supplementary Material (ESI)

# Ammonia oxide makes up some 20% of hydroxylamine in water

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# Electronic Supporting Information

## Contents

## 1. Materials

*O-(Tetrahydro-2H-pyran-2-yl)hydroxylamine* ***3*** was obtained from Sigma-Aldrich.

*O-Cyclohexylhydroxylamine* ***5*** [1, 2] was a gift from Dr. Andreas Herrmann (Firmenich SA). We thank Dr. Herrmann warmly for his help.

*O-cyclohexylhydroxylammonium (**5**) chloride.*

A solution of O-cyclohexylhydroxylamine in dry ether was treated with a small volume of hydrogen chloride in ether (4.0 M solution) under dry conditions, to give a precipitate of the hydrochloride salt. Solvent was removed with a pipette and the precipitate washed several times with dry ether. Residual solvent was then removed by passing a stream of nitrogen over the precipitate. The hydrochloride salt was recrystallised from dry 1,4-dioxane, and crystals were selected for diffraction studies. The salt could also be recrystallised from MeOH-ether.

## 2. Kinetics of hydrolysis of O-(Tetrahydro-2H-pyran-2-yl)hydroxylammonium chloride 4, at T = 39 ± 1 ºC.

Reactions were followed in $D_2O$/DCl by $^1$H NMR, using a Varian Mercury spectrometer (400 MHz ). The NMR tube contained [Substrate **3**] = 0.17373 M and [HCl] = 0.17377 M (100%) in *ca.* 1 ml of water.

**Table S1. Integrated area of the C-2(H) peak of 4, as a function of time.**

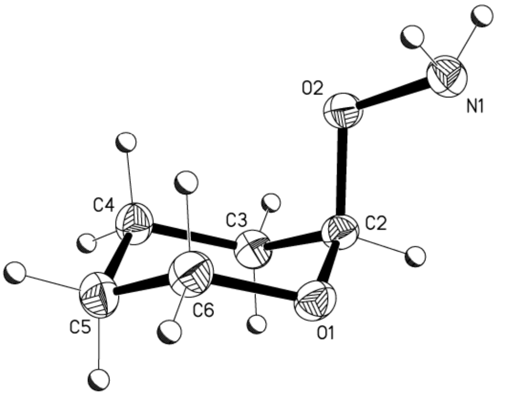
| **Time *t* (s)** | **Area A (%)** |
|---|---|
| 29.82 | 100 |
| 89.65 | 93.39 |
| 179.5 | 87.16 |
| 299.3 | 78.60 |
| 449.1 | 71.21 |
| 629.0 | 61.87 |
| 838.8 | 47.08 |
| 1079 | 42.80 |
| 1348 | 33.46 |
| 1648 | 32.68 |
| 1978 | 19.46 |
| 2338 | 17.90 |
| 2728 | 12.84 |
| 3148 | 8.56 |
| 3597 | 4.67 |

Plotting ln[A] vs. *t* gives slope = $-7.999 \pm 0.223 \times 10^{-4}\ s^{-1}$.

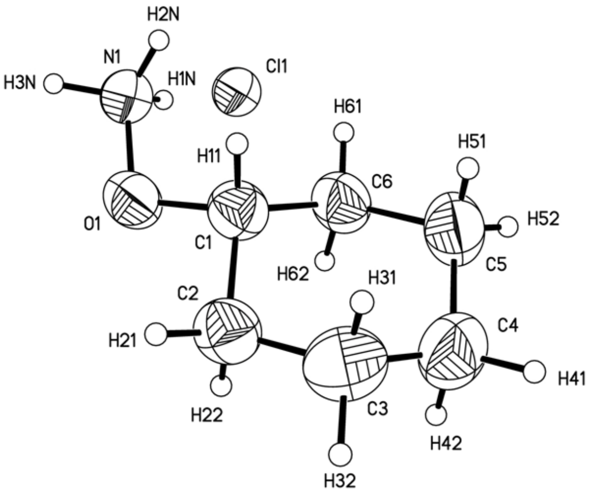
Interpolating into the original correlation,[3] $\log k_{hyd} = 4.39 - 1.11.pK_a$ (rate constants converted to $s^{-1}$) gives a value of $pK_a = 6.73$ for the leaving group. (The p$K_a$ of **4**, measured by titration at 20°C, is 4.06 ± 0.05.)

## 3. Crystal structures

We report new single crystal structure determinations of the structures of O-(tetrahydro-*2H*-pyran-2-yl)hydroxylamine **3** and O-cyclohexylhydroxylamine hydrochloride **5.HCl,** at 290(2)K)



**3**



**5.HCl**

Thermal ellipsoid (50%) plots for O-(Tetrahydro-*2H*-pyran-2-yl)hydroxylamine **3** (at 180(2)K) and O-Cyclohexylhydroxylamine hydrochloride **5.HCl,** at 290(2)K).

Uploaded files **Kirby.SI.3.cif** and **Kirby.SI.5.cif** refer.

*Crystal data* for **3:** $C_5H_{11}NO_2$, $M$=117.15, monoclinic, space group P2$_1$/c (no. 14), $a$ = 11.7328(7), $b$ = 5.1277(3), $c$ = 10.9693(6) Å, $\beta$ = 115.314(2)°, $U$ = 596.57(6) Å$^3$, $Z$ = 4, $\mu$(Mo-K$\alpha$) = 0.100 mm$^{-1}$, 7006 reflections measured at 180(2)K using an Oxford Cryosystems Cryostream cooling apparatus and Nonius Kappa CCD diffractometer: 1879 unique reflections ($R_{\text{int}}$ = 0.036); $R_1$ = 0.044, $wR_2$ = 0.112 [$I>2\sigma(I)$]. The structure was solved with *SHELXS-97** and refined with *SHELXL-97* .[4]

*Crystal data* for **5**. $C_6H_{14}ClNO$, $M$ = 151.63, orthorhombic, $a$ = 7.6236(4), $b$ = 9.2921(7), $c$ = 23.018(10) Å, $U$ = 1630.6(7) Å$^3$, $T$ = 290 K, space group Pbca (no. 61), $Z$ = 8, 6928 reflections measured, 1311 unique ($R_{int}$ = 0.0364) which were used in all calculations. The final $R(F)$ was 0.0351 (for $F^2 > 2\sigma(F^2)$) and the final $wR(F^2)$ was 0.1024 (all data).

Single-crystal X-ray diffraction data were collected on an Oxford Diffraction Gemini S Ultra diffractometer (Xcalibur goniometer, Sapphire3 detector) using an Enahnce Ultra Cu X-Ray Source (λ = 1.5418 Å) at 290(2) K. The crystal was mounted in a glass fibre using an epoxy resin. The temperature was kept stable at 290K using an Oxford Cryosystems Ltd. Cobra Cryostat. The data were collected and integrated using Oxford Diffraction CrysAlis software. The structure was solved using direct methods (SHELXS-97) [5] and refined by full-matrix least squares on F$^2$ (SHELXL-97).[5] H atoms were located in difference-Fourier maps and allowed to refine freely. However, isotropic thermal displacement parameters for the hydrogen atoms bound to carbon atoms were constrained to be 1.2 times those of the carbon atoms. Bond distances reported in the manuscript are those after correction for libration effects using PLATON. [6]

### 3.1 Crystal structure correlations: data and some discussion

For structure **3** we use the published correlations (equations (i) and (ii), respectively) between the lengths of the exocyclic (x) and endocyclic (n) C—OR bonds of tetrahydropyran acetals **2** and the p$K_a$ of the conjugate acid ROH of the leaving group:[7,8]

$$\text{Bond length (x) } C_5H_9O\text{—}OR = 1.493 - (6.495 \times 10^{-3})\, pK_a \qquad \text{(i)}$$

$$\text{Bond length (n) } C_5H_9O\text{—}OR' = 1.364 - (3.64 \times 10^{-3})\, pK_a \qquad \text{(ii)}$$

In the case of the cyclohexylamine derivative **5** the appropriate correlation is equation (iii): [8]

$$\text{Bond length } C_6H_{11}\text{—}OR = 1.475 - (2.90 \times 10^{-3})\, pK_a \ (r = 0.999) \qquad \text{(iii)}$$

The relationship (iii) is based on single crystal diffraction data for a substantial number of structures from the Cambridge Structural Database, purged of outliers and of structures with high R-factors. The excellent correlation obtained suggests that random factors such as crystal packing have been screened or averaged out.

The choice of the appropriate bond length (BL) for **5.HCl** presents a problem, because:

(a) BL is very insensitive to the p$K_a$, so that the calculated p$K_a$ is very sensitive to small differences in BL

(b) BL is significantly temperature dependent (in this system? – under investigation)

A first measurement at 100K gave a C—$ONH_3^+$ bond length of 1.4677(14) Å. According to the crystal structure correlation (iii) this would correspond to a p$K_a^O$ of 2.7±0.4 for the OH group of $NH_3^+$—OH, clearly not compatible with an observed global figure of 5.98. Using White's more recent correlation (iv),[9] specifically for structures measured at low temperature (130 K), gives a value for p$K_a^O$ of 3.85, also clearly incompatible with an overall p$K_a$ of 5.98.

$$\text{Bond length } C_6H_{11}\text{—}OR = 1.4787 - 2.86 \times 10^{-3}\, pK_a \qquad \text{(iv)}$$

Since the original correlation (iii) was based on pre-1990 structures, almost all collected at or around room temperature, we also collected a data set at room temperature.
Measurement at 290(2) K gave an initial C—O bond length for **4** of 1.454Å, sharpening up on refinement to 1.447(2)Å, corresponding to a high p$K_a^O$ of 9.65 Å for the OH group of $NH_3^+$—OH. We presume that the true figure lies between the two extremes of 3.85 and 9.65. Finally, correcting this last, refined figure for thermal libration [10] gave a best figure of 1.454(2) Å, corresponding to a p$K_a^O$ of 7.24 Å for the OH group of $NH_3^+$—OH.

Evidently the BL is remarkably temperature-sensitive, at the levels of accuracy required for the p$K_a$ estimation. Differences in BL not much greater than experimental error can make a big difference to estimated p$K_a$ s. More work needs to be done on this question: meanwhile we use the derived figure with appropriate caution.

## 4. Linear free energy relationships.

p$K_a$ s involving the ionizations of $^+NH_3OH$, $NH_2OH$, $^+NH_3O^-$ and $NH_2O^-$ are expected to be correlated by two separate linear free energy relationships, for the ionizations of hydroxy compounds ROH and substituted ammonium ions $R'NH_3^+$. In Figures S1 and S2 known p$K_a$s are plotted against sigma inductive values ($\sigma_i$) for the substituents R and R'. Values are taken from Charton's compilation,[11] apart from the value (0.12) corresponding to R' = $NH_2$.[12] Interpolation in Figure S1 using $\sigma_i$ values of 0.6 and 0.12, for $NH_3^+$ and $NH_2$, respectively, gives the p$K_a$ values for the OH groups of $NH_3^+OH$ and $NH_2OH$ of 6.29± 0.56 and 13.41±0.33 used in Table 1 of the paper.

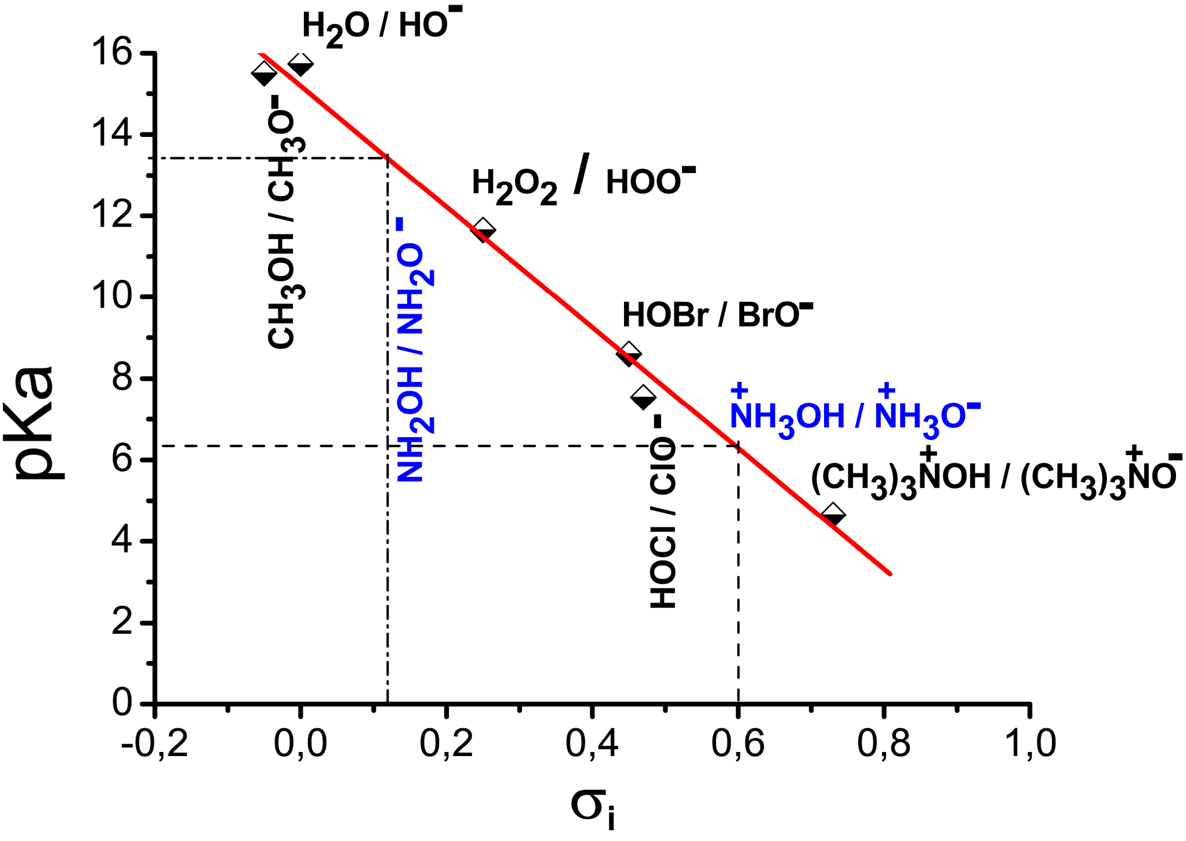


**Figure S1**. Linear free energy relationship for the p$K_a$s of systems ROH.
$\sigma_i$ values were taken from Charton's compilation,[11] with the exception of the value (0.12) [9] corresponding to R' = $-NH_2$.

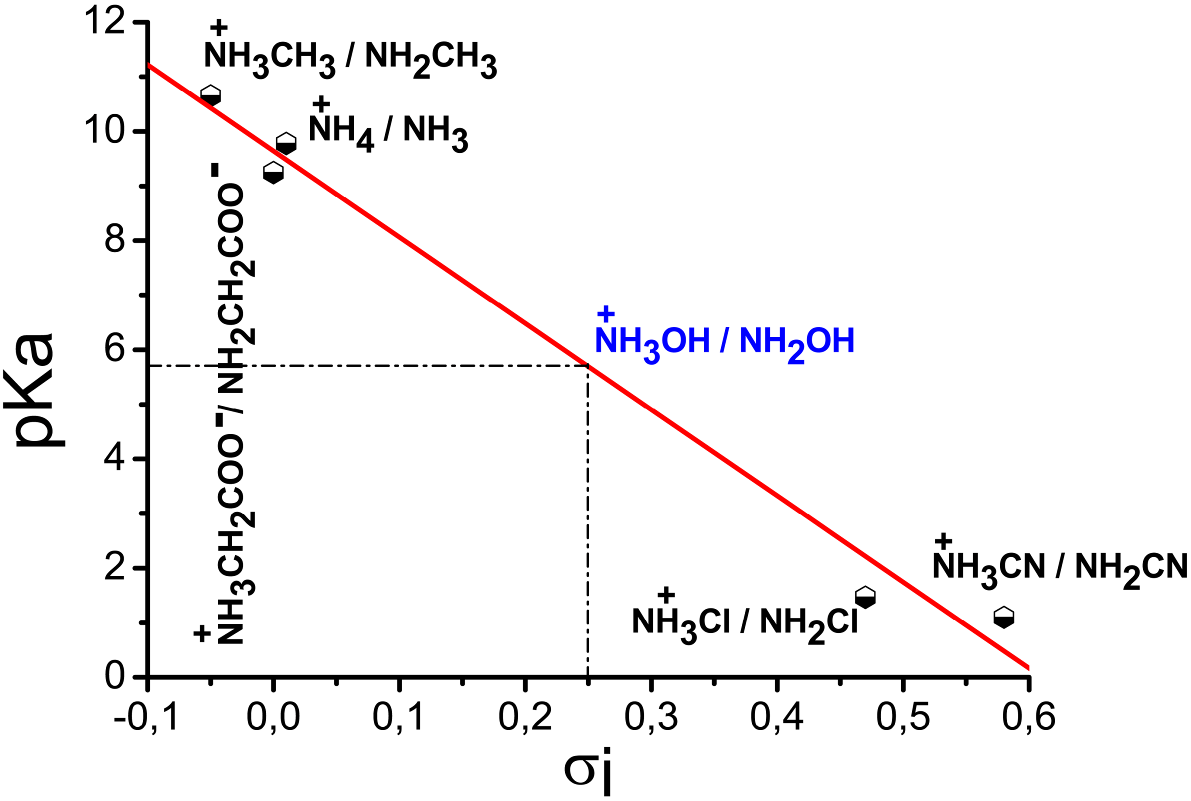


**Figure S2**. Linear free energy relationship for the p$K_a$s of systems R'$NH_3^+$. $\sigma_i$ values were taken from Charton's compilation.[11] The complete data sets used are given in Table S2.

**Table S2.** Literature values used for p$K_a$ and $\sigma_i$: and parameters obtained for the linear fits .

| **ROH** | **$\sigma_i$** | **p$K_a$** | **$RNH_3^+$** | **$\sigma_i$** | **p$K_a$** |
|---|---|---|---|---|---|
| $H_2O$ | 0 | 15.74 | $CH_3NH_3^+$ | -0.05 | 10.65 |
| $H_2O_2$ | 0.25 | 11.65 | $NH_4^+$ | 0 | 9.25 |
| HOCl | 0.47 | 7.54 | $ClNH_3^+$ | 0.47 | 1.47 |
| HOBr | 0.45 | 8.6 | $NCNH_3^+$ | 0.58 | 1.1 |
| $CH_3OH$ | -0.05 | 15.5 | $^-OOCCH_2NH_3^+$ | 0.01 | 9.78 |
| $(CH_3)_3N^+OH^-$ | 0.73 | 4.65 | | | |
| Linear fit | | | Linear fit | | |
| | value | error | | value | error |
| slope | -14.83 | 0.77 | slope | -15.79 | 1.07 |
| intercept | 15.19 | 0.32 | intercept | 9.64 | 0.36 |
| *r* | -0.995 | | *r* | -0.993 | |

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