Kinetics of acetonitrile-assisted oxidation of tertiary amines by hydrogen peroxide

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The rate of oxidation of tertiary amines by aqueous hydrogen peroxide is increased in the presence of acetonitrile due to the formation of a reactive intermediate. The active oxidant, presumably peroxyacetimidic acid, was quantified by a photometric method. Activation parameters of the acetonitrile-assisted and non-assisted oxidations are given in the temperature range 20 to 40 °C. The increased rate of the assisted oxidation is explained by the low enthalpy of activation although the entropy of activation is more negative due to a highly ordered transition state.

Introduction

In the course of studies on alkaloidal constituents of the South American vines *Uncaria tomentosa* (Willd.) DC. and *Uncaria guianensis* (Aubl.) Gmel. (Rubiaceae),[1] *N*-oxides of oxindole alkaloids† were required as reference compounds. A simple process was desired to yield pure *N*-oxide samples in aqueous solutions which can be used directly for reversed-phase HPLC. Hydrogen peroxide was chosen as the oxidant. Because of the known tendency of spiro oxindole alkaloids to isomerize in aqueous solution[2] and due to their poor solubility in water, the effect of organic co-solvents was to be examined. Of course these co-solvents had to be compatible with the requirements of HPLC. During this work the rate-enhancing effect of acetonitrile on oxidations in neutral aqueous solutions was discovered and shown to be a general phenomenon.

Results

Effect of solvent polarity

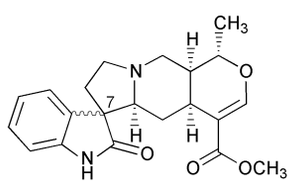
The rate of isomerization of oxindole alkaloids is controlled by solvent polarity. Therefore, admixture of organic solvents to the buffered aqueous medium (pH 7) is a logical approach to avoid or minimize the problem of isomerization. Oxidations were carried out with an alkaloid concentration of 10^{-5} mol dm^{-3} and an excess of hydrogen peroxide from 0.2 to 2.4 mol dm^{-3}. As expected,[3,4] the reaction was pseudo-first-order, and the second-order rate coefficients k_2 were calculated from the slope of a linear graph of k_1 *vs.* $[H_2O_2]$. When the oxidation of pteropodine **1** was conducted in water–methanol mixtures in order to suppress the isomerization, a decrease of the rate of reaction was observed with a linear correlation between the free energy of activation and the mole fraction of water χ in the range $\chi = 1.0$ to 0.45 (four points, eqn. (1)). The use of less polar

$$\log (k_2/\mathrm{dm^3\ mol^{-1}\ s^{-1}}) = 1.13\,\chi - 4.83 \quad r^2 = 0.989 \quad (1)$$

co-solvents like dioxane or *tert*-butyl alcohol suppressed the isomerization but decreased the rate of oxidation even more. Therefore, these solvents do not appear to be advantageous.

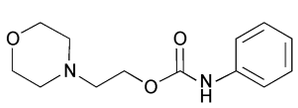
Effect of acetonitrile

Nitriles promote oxidations by hydrogen peroxide of sulfides, sulfoxides and alkenes in alkaline solution.[5] In the present work it was found that admixture of small amounts of acetonitrile (mole fraction of water χ from 1.0 to 0.8) to buffered solutions (pH 7) of pteropodine **1** accelerated the observed rate of oxidation by a factor of approximately 200. Oxidations were carried out with an alkaloid concentration of 10^{-5} to 10^{-4} mol dm^{-3} and an excess of hydrogen peroxide from 0.02 to 0.2 mol dm^{-3}. Over a wide range of mixtures (χ from 0.8 to 0.2) the observed rate coefficients were independent of χ. Addition of still more acetonitrile ($\chi < 0.2$) resulted in a sudden drop of the rate of reaction. This unusual behaviour is illustrated in Fig. 1a. The results with the weaker base isopteropodine **2** were similar, although this alkaloid is oxidized more slowly than the 7-epimer **1** (Fig. 1b). Fortunately, this alkaloid also isomerizes more slowly. The polarity of the solutions at a mole fraction of $\chi = 0.5$ is sufficiently low to inhibit the undesired isomerization. Thus, oxidation of the oxindole alkaloids was 4 to 5 orders of magnitude faster than isomerization at $\chi = 0.5$.



1 7*R*
2 7*S*

3



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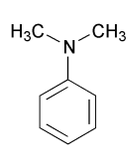

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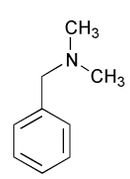

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In acetonitrile–water mixtures the assisted and non-assisted oxidations take their course as parallel reactions, and the formation of peroxyacetimidic acid or its anion peroxyacetimidate in a pre-equilibrium is assumed (Scheme 1). Peracids typically have pK_a values of approximately 8 and, therefore, are mostly undissociated in neutral solution.[6] According to this mechanistic concept, the rate law of the total reaction can be described by eqn. (2), where k_W is the rate coefficient for the non-assisted reaction in water, and k_2 that for the reaction of the assumed active oxidant peroxyacetimidate with the amine.

† The numbering system is based on that customarily used for the hetero-yohimbinoid alkaloids.

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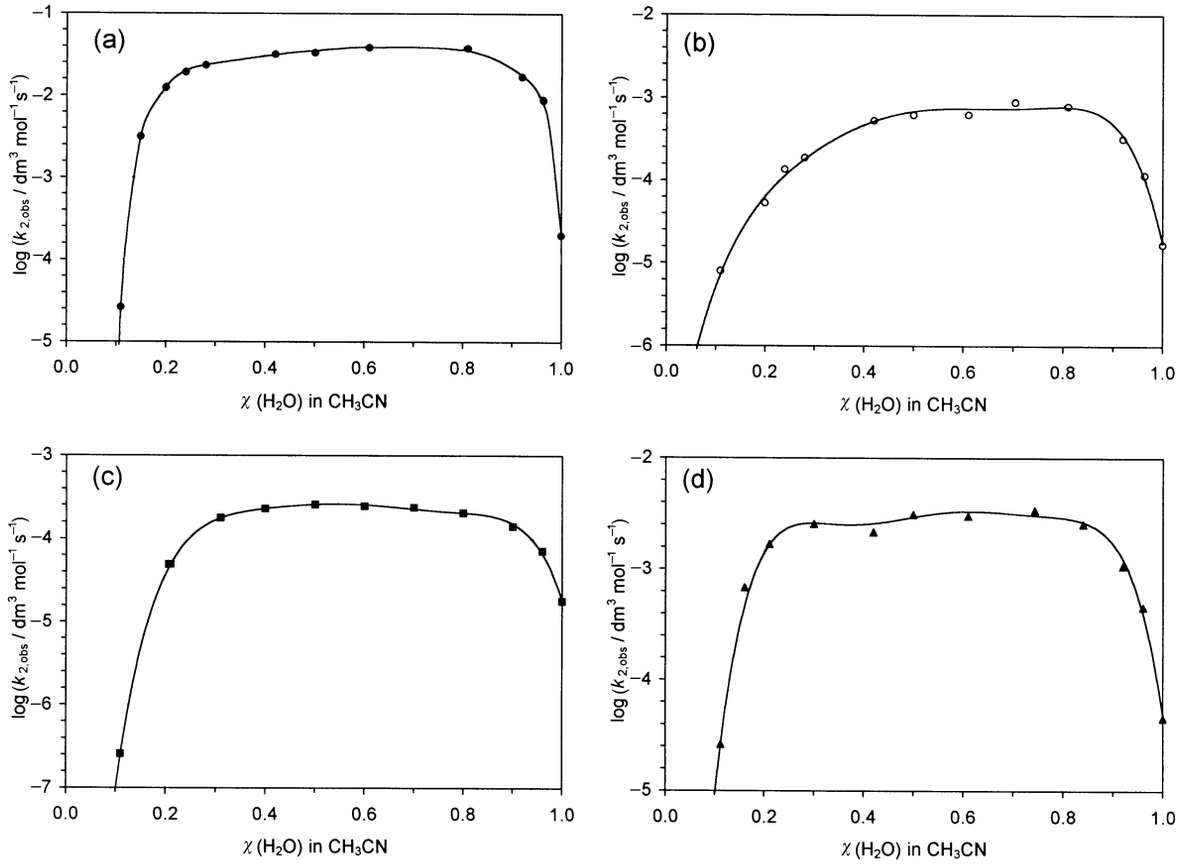
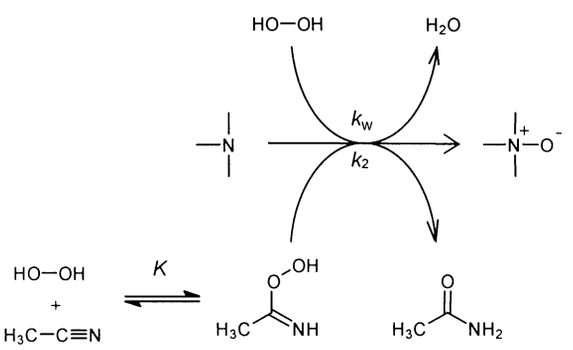


Fig. 1 Dependence of the observed second-order rate coefficients of the oxidation of (a) pteropodine **1**, (b) isopteropodine **2**, (c) pyridine **3** and (d) 2-morpholinoethyl *N*-phenylcarbamate **4** by hydrogen peroxide at 30 °C on the mole fraction χ of water in acetonitrile.



Scheme 1

From eqns. (3) and (4), eqn. (5) follows and thus the practical rate law in eqn. (6) is derived, where $k_W << k_2'$, and k_W may be assumed to decrease further with decreasing solvent polarity, and therefore eqn. (7) holds.

$$-\frac{d[amine]}{dt} = k_1[amine] = k_W[H_2O_2][amine] + k_2[CH_3C(=NH)OOH][amine] \quad (2)$$

$$[CH_3C(=NH)OOH] = K[CH_3CN][H_2O_2] \quad (3)$$

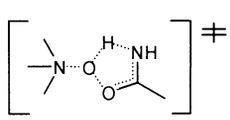
$$k_2K[CH_3CN] = k_2' \quad (4)$$

$$k_2[CH_3C(=NH)OOH] = k_2'[H_2O_2] \quad (5)$$

$$-\frac{d[amine]}{dt} = (k_W + k_2')[H_2O_2][amine] = k_{2,obs}[H_2O_2][amine] \quad (6)$$

$$k_2 = \frac{k_{2,obs}}{K[CH_3CN]} \quad (7)$$

From the second-order rate coefficients k_2 and k_W at 20, 30 and 40 °C, the enthalpy and entropy of activation, $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$, for both the assisted ($\chi = 0.5$) and non-assisted oxidation ($\chi = 1.0$) were calculated and are summarized in Table 1. While a negative entropy of activation is expected for a bimolecular mechanism due to the loss of translational and rotational degrees of freedom, the presumed cyclic activated complex (Scheme 2) involving peroxyacetimidic acid would be highly



Scheme 2

ordered and therefore possess still less vibrational entropy. Unexpectedly, the assisted oxidation of pteropodine **1** has a less negative entropy of activation and is exceptional in this respect compared with the other amines. The activated complex is obviously perturbed in this case, which is possibly due to interaction with the hydrogen bond donor carbonyl group on the same side of the molecule as the lone pair of the nitrogen atom. The epimer **2** shows the expected behaviour. In general, it can be seen that, although the loss of entropy in the activation step is large, the enthalpies of activation of the reactions in water–acetonitrile mixtures are much lower than those in water, which suggests an early (reactant-like) transition state and causes the overall higher rates of the assisted reactions. Surprisingly, at $\chi = 0.1$ and 20 °C the oxidation of pteropodine **1** becomes pseudo-zero-order ($k_1/s^{-1} = 10^{-9}$), the rate being independent of substrate concentration, whereas the oxidation of isopteropodine **2** is immeasurably slow under these conditions. A likely

Table 1 Second-order rate coefficients and activation parameters

Amine	$\chi = 1.0$ $k_w/10^{-5}$ dm^3 mol^{-1} s^{-1} $T = 293$ K	303 K	313 K	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}
Pteropodine **1**	7.6	20	36	57	−129
Isopteropodine **2**	1.0	2.3	5.1	59	−139
Pyridine **3**	1.2	1.8	2.4	25	−254
2-Morpholinoethyl *N*-phenylcarbamate **4**	1.6	4.5	11	71	−95
N,*N*-Dimethylaniline **5**	3.2	6.5	13	52	−153
N,*N*-Dimethylbenzylamine **6**	0.30	0.50	0.83	36	−229
	$\chi = 0.5$ k_2/dm^3 mol^{-1} s^{-1}				
Pteropodine **1**	4.7	8.3	11.6	43	−83
Isopteropodine **2**	0.037	0.065	0.091	31	−165
Pyridine **3**	0.052	0.054	0.056	0.76	−267
2-Morpholinoethyl *N*-phenylcarbamate **4**	0.40	0.65	1.15	37	−125
N,*N*-Dimethylaniline **5**	0.68	1.01	1.34	23	−169
N,*N*-Dimethylbenzylamine **6**	2.27	2.33	2.47	0.77	−235

explanation could be that (1) the low solvent polarity and (2) the low temperature decrease the rate of formation of the reactive intermediate. Acetamide, which arises as a secondary product, was identified and quantified by GC-MS and shown to be present in equimolar amounts based on amine consumed.

Other tertiary amines

In order to prove that the acetonitrile-assisted oxidation of tertiary amines in neutral solution is a general phenomenon, the oxidations of some other tertiary amines were studied. The substrates were selected to represent as wide a scope as possible. Pyridine **3** was chosen as an aromatic heterocyclic amine. In industry, *N*-alkylmorpholine *N*-oxides are important solvents for cellulose. Therefore a representative of this class of compounds was of interest, and the phenylcarbamate of 2-morpholinoethanol **4** was used to enable UV detection. Again, the typical dependence of the rate coefficient on the mole fraction χ was observed (Fig. 1c, d). In addition, the oxidations of *N*,*N*-dimethylaniline **5** and *N*,*N*-dimethylbenzylamine **6** as further examples of distinct structural classes were examined at $\chi = 0.5$ and $\chi = 1.0$. All these substrates showed a similar behaviour. Rate coefficients and activation parameters are given in Table 1. In all cases, the enthalpy of activation is considerably lower for the nitrile-assisted oxidation which explains the increased rate.

Effects of co-solvents and pH

The rates of the assisted oxidations showed a dependence on solvent polarity similar to that of the non-assisted reactions when methanol or *tert*-butyl alcohol was added. When the oxidation of pteropodine **1** was performed in a mixture of acetonitrile and methanol (75:25, same molar acetonitrile concentration as in $\chi = 0.5$) at 30 °C it became pseudo-zero-order ($k_1/s^{-1} = 10^{-7}$). This implies that the formation of peroxyacetimidic acid becomes rate-determining under these conditions. *N*,*N*-Dimethylbenzylamine **6** showed a similar behaviour, whereas isopteropodine **2**, pyridine **3**, 2-morpholinoethyl *N*-phenylcarbamate **4** and *N*,*N*-dimethylaniline **5** did not react at all in this solvent mixture. It was ascertained that the rate of oxidation of **1** and **2** at 30 °C ($\chi = 1.0$) is not significantly different at pH 6 and 8. The assisted oxidation of **1** at 30 °C ($\chi = 0.5$) did not show any pH-dependence when pH 6, 7, 8 or 9 buffers were used, either. It was also demonstrated that the buffer concentration (0.005, 0.010 M) does not affect the rate.

Detection and quantification of peroxyacetimidic acid

The presumed peroxyacetimidic acid was detected using a modified spectrophotometric method which allows determination of peracids in the presence of a large excess of hydrogen peroxide.[7] Thermostatted mixtures of acetonitrile and aqueous buffer pH 7 ($\chi = 0.5$) were equilibrated with two different concentrations of hydrogen peroxide. Then a solution of potassium iodide was added, and the iodine liberated was determined by measuring the absorbance at 352 nm every 10 seconds. Peroxyacetimidic acid concentration was calculated from the absorbance at zero time by second-order extrapolation. It was confirmed that, without the equilibration period prior to the measurement, no peroxy acid species could be detected. 3-Chloroperbenzoic acid was used for calibration. It was also established that the resulting 3-chlorobenzoic acid does not interfere with the measurement at 352 nm. The accuracy of the method was estimated as ±2.5% using known amounts of 3-chloroperbenzoic acid in the presence of a 20-fold excess of hydrogen peroxide. The determinations were carried out at 20, 30 and 40 °C. The equilibrium constants (Scheme 1) $K \times 10^4$ at these temperatures were calculated as 2.0, 3.3 and 5.2, respectively. Thus, the molar heat change of reaction ΔH_R between acetonitrile and hydrogen peroxide was found to be 35 kJ mol^{-1} under these conditions. Overnight equilibration was necessary for the mixtures containing methanol or *tert*-butyl alcohol to form the peroxyimidic acid, and $K \times 10^4$ at 30 °C was approximately 1.

Discussion

Peroxybenzimidic acid or its anion peroxybenzimidate has been proposed as a reactive intermediate in the conversion of benzonitrile to benzamide by alkaline hydrogen peroxide.[8] More recently, spectroscopic evidence has been put forward which supports the existence of peroxyacetimidate as an intermediate in the reaction of hydrogen peroxide, acetonitrile and alkali.[9,10] Admittedly, the photometric assay used in this work does not prove the structure but it does prove the presence of a peroxy acid species. Little doubt remains that the active oxidant is indeed peroxyacetimidic acid.

It is noteworthy that the oxidations described in this report were carried out in phosphate-buffered solution at pH 7 (phosphate ions reportedly suppress the Radziszewski hydrolysis of nitriles,[11] and eliminate metal ion involvement[12]), whereas the literature so far describes nitrile-assisted oxidations of amines only in alkaline solutions. For instance, pyridine was oxidized by hydrogen peroxide in the presence of benzonitrile in methanol only after the addition of sodium hydroxide solution.[13] A likely explanation for the observations in the literature[13] is that methanol was used as the solvent. Solvents which are less polar than water have now been shown (1) to decrease the rate of formation of the active oxidant and (2) to decrease the rate of oxidation in general. In fact, the oxidation of pyridine by hydrogen peroxide in acetonitrile is started by addition of water.

It has also been reported that the effect of pH on the rate of epoxidation of styrenes with a mixture of nitrile and hydrogen peroxide is less than expected.[11] In the present work it has been found that the oxidation of tertiary amines, assisted or not, is not affected by pH in the range 6 to 9, either.

For alkene epoxidation in 75% methanol, the oxidation step is rate-determining and the pre-equilibrium is attained, whereas the oxidation is fast for the case of dimethyl sulfoxide, a much more reactive substrate than alkenes, and hence the rate is governed by the formation of peroxyimidic acid.[14] In contrast, epoxidation in methanol has been reported to be independent of alkene structure, indicating that the slow step has to be the formation of the intermediate.[13] It has now been demonstrated that, for the oxidation of tertiary amines, the experimental conditions, *i.e.* solvent polarity and temperature, determine which step becomes rate-limiting.

In the absence of a substrate, the intermediate peroxyimidic acid has been postulated to react with the peroxide anion to yield amide and oxygen, the classic Radziszewski hydrolysis of nitriles.[13] However, it has been concluded that this cannot be a major pathway because the overall rate should be second-order in hydrogen peroxide which is not the case.[14] An experiment with doubly isotope-labelled $H_2{}^{18}O_2$ has also refuted this mechanism.[12] Rather, at high alkalinity (pH > 10), the peroxyimidate decomposes homolytically, inducing radical decomposition of hydrogen peroxide.[14]

Finally, it must be noted that the described kinetic experiments were conducted in very dilute solutions which show a reasonably ideal behaviour, whereas at higher amine concentrations the kinetics become less transparent; for instance, a 3/2-order in H_2O_2 has been observed.[15] Similarly, the decrease of rate of styrene epoxidation with increasing styrene concentration has been attributed to the decrease of polarity of the reaction mixture.[11] Moreover, in acetonitrile-rich mixtures the hydrogen ion activity is significantly increased[16] which may contribute to the sudden drop of the rate at $\chi < 0.2$.

Thus, from a synthetic point of view, the optimum conditions for the oxidation of tertiary amines by hydrogen peroxide to *N*-oxides are (1) a solvent system of high polarity, (2) pH higher than 6 but lower than 10, and (3) the mole fraction χ of acetonitrile at least 0.2 but not higher than 0.7.

These results shed new light on previous work and provide more insight into the mechanistic aspects of the nitrile–hydrogen peroxide–solvent–substrate system.

Experimental

Materials

The alkaloids **1** and **2** were obtained by supercritical fluid extraction of *Uncaria tomentosa* root with CO_2, followed by conventional acid–base work-up and separation by column chromatography (silica gel, EtOAc–hexane = 9:1). All other reagents were of analytical grade (Merck, Darmstadt). Concentration of H_2O_2 was determined iodometrically. ^{1}H-NMR spectra were recorded in $CDCl_3$ at 200 MHz (*J* values in Hz). Optical rotation was measured using a Perkin-Elmer 141 polarimeter and is given in units of 10^{-1} deg cm^2 g^{-1}. Peroxyacid assays were performed on a Shimadzu UV-160A spectrophotometer.

Kinetic procedures

Typically, $10 - A$ cm^3 reagent mixture (hydrogen peroxide, 0.005 M phosphate buffer pH 7, optional co-solvent, with or without acetonitrile) were pre-equilibrated for 10 min, and A cm^3 of concentrated amine solution (in buffer, acetonitrile or co-solvent as required) were added in order to obtain a final amine concentration of 10^{-4} to 10^{-5} mol dm^{-3} in a volume of 10 cm^3. Oxidations were followed by monitoring the thermostatted (±0.1 K) reaction mixture by HPLC analysis, using an RP-18 (5 μm) column (125 × 4 mm id, Merck). A mixture of acetonitrile and 0.01 M aqueous phosphate buffer pH 7.0 (45:55) with a flow of 1.3 cm^3 min^{-1} at 80 °C was used as eluent for compounds **1** (t_R 3.0 min), **2** (t_R 4.4 min), **7** (t_R 1.3 min), **8** (t_R 1.4 min), and a mixture of methanol and buffer (45:55) with a flow of 1.0 cm^3 min^{-1} at 50 °C for compounds **3** (t_R 2.2 min), **4** (t_R 3.3 min), **9** (t_R 1.4 min), and **10** (t_R 2.0 min) with detection at 247 nm. A mixture of methanol and buffer (55:45) with a flow of 1.0 cm^3 min^{-1} at 50 °C was used for compounds **5** (t_R 4.5 min), **6** (t_R 6.2 min), **11** (t_R 1.5 min), and **12** (t_R 1.7 min) with detection at 205 nm. Aliquots of the reaction mixture were diluted with buffer (1:10) immediately prior to analysis. Relative standard deviation (RSD) of the primary HPLC measurements was 0.8%. In each experiment, 3 to 5 data points were used to determine a single rate coefficient k_1 using the absolute values of peak areas, and 3 to 4 concentrations of hydrogen peroxide were used to obtain k_2' values. The kinetic experiments were reproduced 3 to 7 times, and RSD of k_2' was ≤10%.

Photometric determination of peroxyacetimidic acid

2 cm^3 of a mixture of acetonitrile and 0.005 M phosphate buffer pH 7 (75:25 by volume, $\chi = 0.5$) were thermostatted (±0.1 °C) in a quartz cuvette, 20 or 40 μl of 0.3% hydrogen peroxide added, and the mixture equilibrated for at least 10 min. Then, 1 cm^3 thermostatted 0.2 M potassium iodide solution was added and the photometric program started. The wavelength was set at 352 nm. The first measurement was recorded 20 s after mixing, and then every 10 s for as long as 80 s. An identical mixture of acetonitrile, buffer and iodide solution was used as a blank. From these data the absorbance at zero time was extrapolated and used for the calculation of peroxyacetimidate concentration. Six determinations were made at 20, 30 and 40 °C each. An eight-level calibration in the range 0.5 to 20 μmol dm^{-3} was performed using 3-chloroperoxybenzoic acid, the potency of which was assayed by titration. Finally, from the peroxyacetimidate concentration and the known concentrations of acetonitrile and hydrogen peroxide, the equilibrium constants K were calculated. Calibrations were also performed in methanol and *tert*-butyl alcohol mixtures which were used for the determination of K.

Synthetic procedures

2-Morpholinoethyl *N*-phenylcarbamate 4. 2-Morpholinoethanol (656 mg, 5.0 mmol) was refluxed with phenyl isocyanate (667 mg, 5.6 mmol) in 50 cm^3 hexane for 2 h. The product crystallized readily upon cooling. Yield: 1.01 g (81%); mp 73 °C, δ_H 2.52 (4H, AA′), 2.67 (2H, t, *J* 6), 3.73 (4H, BB′), 4.30 (2H, t, *J* 6), 6.76 (1H, br s), 7.06 (1H, tt, *J* 7, *J* 2), 7.26–7.40 (4H, m) ppm.

Pteropodine *N*-oxide 7. Pteropodine **1** (90 mg, 0.24 mmol) was dissolved in 5 cm^3 acetonitrile, 5 cm^3 30% hydrogen peroxide were added, and the mixture was allowed to stand at 22 °C. After 12 h, 30 cm^3 water and 20 mg manganese dioxide were added. The excess hydrogen peroxide was destroyed and acetonitrile was distilled off under reduced pressure. The remaining aqueous solution was cooled and extracted five times with dichloromethane. The extracts were combined, dried over anhydrous sodium sulfate and evaporated. The residue was chromatographed on silica gel using ethyl acetate–methanol = 1:1 as the eluent. The respective fraction ($R_f = 0.23$) crystallized upon concentrating and yielded 70 mg pteropodine *N*-oxide (75%); mp 173 °C (dec.), $[a]_D^{21} = -79°$ ($c = 1.02$ in CH_2Cl_2), δ_H 1.51 (3H, d, *J* 6), 1.80 (1H, m), 1.90 (1H, d, *J* 12), 2.0 (1H, m), 2.18 (1H, m), 2.30 (1H, ddd, *J* 13, *J* 13, *J* 13), 2.53 (1H, m), 3.24 (1H, m), 3.55 (1H, m), 3.62 (3H, s), 3.7 (1H, m), 4.32 (1H, m), 4.38 (1H, m), 4.98 (1H, qd, *J* 6, *J* 10), 6.92 (1H, d,

J 7), 7.07 (1H, t, *J* 7), 7.23 (2H, m), 7.56 (1H, s), 9.0 (1H, br s) ppm.

Isopteropodine *N*-oxide 8. Oxidation of isopteropodine **2** (55 mg, 0.15 mmol) as described for pteropodine afforded 37 mg isopteropodine *N*-oxide (65%); mp 210 °C (dec.), $[\alpha]_D^{21} = -44°$ ($c = 0.75$ in MeOH), δ_H 1.51 (1H, m), 1.55 (3H, d, *J* 6), 1.77 (1H, td, *J* 5, *J* 10), 1.93 (1H, q, *J* 13), 2.39 (1H, dd, *J* 9, *J* 12), 2.69 (1H, td, *J* 5, *J* 12), 2.80 (1H, td, *J* 12, *J* 7), 3.54 (1H, dd, *J* 12, *J* 5), 3.61 (3H, s), 3.62 (1H, m), 3.75 (1H, dd, *J* 2, *J* 12), 4.00 (1H, t, *J* 9), 4.13 (1H, d, *J* 12), 5.06 (1H, dq, *J* 10, *J* 6), 6.83 (1H, d, *J* 7), 7.00 (1H, t, *J* 8), 7.18 (1H, t, *J* 8), 7.55 (1H, s), 8.01 (1H, d, *J* 7), 9.84 (1H, s) ppm.

Pyridine *N*-oxide 9. Pyridine **3** (1.0 g, 12.6 mmol) was dissolved in 2 cm^3 acetonitrile and 8 cm^3 water and heated to 75 °C. Then, 3 cm^3 30% hydrogen peroxide (26 mmol) were added dropwise with stirring. The reaction mixture was diluted with 20 cm^3 water and extracted three times with 20 cm^3 dichloromethane. The extracts were dried over anhydrous sodium sulfate and evaporated. Pure pyridine *N*-oxide was obtained after chromatography on silica gel (ethyl acetate–methanol = 1:1) in yields from 80 to 90% of the theoretical amount. According to TLC, HPLC and IR, the product was identical with commercial pyridine *N*-oxide; mp 61 °C.

2-Morpholinoethyl *N*-phenylcarbamate *N*′-oxide 10. 2-Morpholinoethyl *N*-phenylcarbamate **4** (100 mg, 0.40 mmol) was dissolved in 2 cm^3 acetonitrile, 2 cm^3 water and 0.1 cm^3 30% hydrogen peroxide (0.87 mmol) were added, and the mixture was stirred at 70 °C for 5 h. The mixture was diluted with 10 cm^3 water and extracted three times with dichloromethane. The extracts were dried and concentrated under reduced pressure. The product was precipitated with diethyl ether and dried. Yield: 80%; mp 190 °C (dec.), δ_H ($CDCl_3$) 3.22 (2H, d, *J* 11), 3.38 (2H, td, *J* 11, *J* 3), 3.60 (2H, AA′, *J* 5), 3.76 (2H, dd, *J* 11, *J* 1), 4.44 (2H, td, *J* 11, *J* 1), 4.89 (2H, BB′, *J* 5), 7.06 (1H, t, *J* 7), 7.31 (2H, td, *J* 7, *J* 1), 7.53 (2H, d, *J* 7), 9.18 (1H, br s) ppm.

***N*,*N*-Dimethylaniline *N*-oxide 11.** *N*,*N*-Dimethylaniline **5** (1.21 g, 10 mmol) was dissolved in 50 cm^3 acetonitrile and 40 cm^3 water and heated to 70 °C. Then, 10 cm^3 30% hydrogen peroxide (87 mmol) were added dropwise with stirring. The reaction was complete after 2 h, as indicated by HPLC. After distilling the acetonitrile under reduced pressure, the solution was extracted several times with chloroform. The extracts were dried and evaporated. After chromatography on silica gel (ethyl acetate–methanol = 1:1) 1.26 g *N*,*N*-dimethylaniline *N*-oxide was obtained (92%); mp 151 °C (lit.: 151–152 °C).[17] The hydrochloride had a melting point of 123 °C after crystallization from acetone (lit.: 124–125 °C).[18]

***N*,*N*-Dimethylbenzylamine *N*-oxide 12.** *N*,*N*-Dimethylbenzylamine **6** (1.35 g, 10 mmol) was dissolved in 50 cm^3 acetonitrile and 40 cm^3 water and heated to 70 °C. Then, 10 cm^3 30% hydrogen peroxide (87 mmol) were added dropwise with stirring. After distilling off the acetonitrile under reduced pressure, the solution was extracted several times with chloroform. The extracts were dried over anhydrous sodium sulfate and evaporated. According to TLC, HPLC and IR, the isolated compound was identical with the *N*-oxide prepared by a literature procedure.[19] The residue was redissolved in concentrated hydrochloric acid and evaporated again. The *N*,*N*-dimethylbenzylamine *N*-oxide hydrochloride crystallized from water–dioxane (1:1) as needles. Yield: 1.21 g (80%); mp 121 °C (lit.: 121–122.5 °C).[20]

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