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The solvation properties of nitric oxide

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Literature values for the partition of nitric oxide between the gas phase and water and between the gas phase and organic solvents have been combined to yield water–solvent partition coefficients. Analysis of the gas–solvent and water–solvent partition coefficients using the solvation equations of Abraham shows that nitric oxide is only a very weak hydrogen-bond base. The various solvation descriptors of Abraham for nitric oxide can be obtained, and are shown to be similar to other inorganic gases; the descriptors can be used to predict a large number of physicochemical properties of nitric oxide. A key property of nitric oxide is the lipophilicity, as the water–octanol partition coefficient, that we calculate to be quite small at 0.74 (log P_{oct}), about the same as that for argon or nitrogen.

Introduction

Although nitric oxide is now a well-studied compound, remarkably few physicochemical properties are available. Zhu *et al.*[1] have noted that 'little is known about its fundamental chemistry', but showed that nitric oxide could act as an acceptor of an electron pair from carbanions to give a species of the type $(R\text{-}NO^{\bullet})^-$. Alternatively, if the substrate is a better electron donor, then electron transfer to nitric oxide, yielding NO^- is observed. Schonafinger[2] has suggested that nitric oxide can penetrate cell membranes very easily because of its low molecular weight and its rather lipophilic properties. Vetrovsky and Entlicher[3] also refer to the hydrophobicity (*i.e.* the lipophilicity) of nitric oxide and its ability to penetrate cell membranes, but to our knowledge no determination of the lipophilicity of nitric oxide has been published. Indeed, the comprehensive data base of water–octanol partition coefficients, that are widely used as an index of lipophilicity, does not even list nitric oxide.[4] It is known[5] that nitric oxide has a high diffusion coefficient in both water and biological tissues but this is not very relevant to lipophilicity, which depends on the ratio of the forward and backward diffusion coefficients across a phase boundary. Our aim in this paper is to attempt to estimate physicochemical properties of nitric oxide that are relevant to passive transport of compounds through biological membranes; these properties will include lipophilicity as well as hydrogen-bond properties (but not electron transfer).

Methodology

We have previously investigated several processes that involve passive transport of solutes through biological systems.[6] These include blood–brain distribution,[7] saline–brain perfusion,[8] water–skin permeability,[9] partition between water and plant cuticular matrix,[10] and permeation from water into plant cells.[11] All of these processes can be examined and analysed through the general solvation eqn. (1),[12] where SP is the solute property.

$$\log SP = c + eE + sS + aA + bB + vV \qquad (1)$$

We use a simplified notation for the independent variables in eqn. (1), which are solute descriptors, as follows.[6,12] In parentheses is given our original notation for the descriptors. E (R_2) is an excess molar refraction in units of (10^{-1} cm^3 mol^{-1}), S (π_2^H) is the dipolarity/polarizability, A ($\Sigma\alpha_2^H$) is the overall or summation hydrogen-bond acidity, B ($\Sigma\beta_2^H$) is the overall or summation hydrogen-bond basicity, and V (V_x) is the McGowan volume in units of (10^{-2} cm^3 mol^{-1}).[13] For transport from the gas phase to condensed phases, an alternative equation is used [eqn. (2)]. The final descriptor in eqn.(2) is L

$$\log SP = c + eE + sS + aA + bB + lL \qquad (2)$$

(log L^{16}), where L^{16} is the solute Ostwald solubility coefficient (or gas–liquid partition coefficient) in hexadecane at 298 K,[14] defined in eqn. (3) where the solvent is hexadecane.

$$L^S = [\text{concentration in solvent, } s]/[\text{concentration in the gas phase}] \qquad (3)$$

Eqn. (2) has been applied to biochemical processes such as the solubility of gaseous solutes in blood and tissues[15] and the partition of solutes between the gas phase and plant cuticular matrix.[10] If the descriptors in eqns. (1) and (2) were known, a variety of biochemical and also physicochemical properties of nitric oxide could be predicted. The descriptors themselves are valuable, because they correspond to fundamental chemical properties.

Our general methods of obtaining the solute descriptors in eqns. (1) and (2) have been recently detailed.[16,17] In brief, the McGowan volume, V, can easily be calculated,[13] and so there remain five solute descriptors in eqns. (1) and (2) to obtain. Equations along the lines of eqns. (1) and (2) are set out for processes in which values for nitric oxide are available, so that we have values of log SP from several equations for which all the coefficients are known. The only unknowns are the solute descriptors themselves, which are obtained by a least squares method that assigns values of descriptors that minimise the differences between the observed and calculated log SP values.

With regard to the calculation of descriptors, the most useful log SP values are those that refer to gas–solvent or to water–solvent partitions. Solubilities, as gas–water partitions, are known for nitric oxide in water[18–20] at 298 K and at 313 K, with log $L^W = -1.327$ at 298 K, and in a number of organic solvents,[21–25] but no water–solvent partitions, P, seem to have

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Table 1 Coefficients in eqn. (2) for gas–solvent partitions at 298 K[a]

Solvent	c	e	s	a	b	l	$\theta^b/°$
Methanol (dry)	−0.004	−0.215	1.173	3.701	1.432	0.769	0
Ethanol (dry)	0.012	−0.206	0.789	3.635	1.311	0.853	5
Hexane	0.292	−0.169	0.000	0.000	0.000	0.979	79
Cyclohexane	0.163	−0.110	0.000	0.000	0.000	1.013	79
Benzene	0.107	−0.313	1.053	0.457	0.169	1.020	53
Toluene	0.121	−0.222	0.938	0.467	0.099	1.012	52
Tetrachloromethane	0.282	−0.303	0.460	0.000	0.000	1.047	74
Ethyl acetate (dry)	0.203	−0.335	1.251	2.949	0.000	0.917	21
Acetonitrile (dry)	−0.007	−0.595	2.461	2.085	0.418	0.738	34
Nitrobenzene (dry)[c]	−0.273	0.039	1.803	1.231	0.000	0.929	43
Octanol (wet)	−0.198	0.002	0.709	3.519	1.429	0.858	

[a] From refs. 26–29. [b] The Ishihama and Asakawa value, see text. [c] Provisional equation.

Table 2 Coefficients in eqn. (1) for water–solvent partitions at 298 K[a]

Solvent	c	e	s	a	b	v	$\theta^b/°$
Methanol (dry)	0.329	0.299	−0.671	0.080	−3.389	3.512	0
Ethanol (dry)	0.208	0.409	−0.959	0.186	−3.645	3.928	3
Hexane	0.361	0.579	−1.723	−3.599	−4.764	4.344	30
Cyclohexane	0.159	0.784	−1.678	−3.740	−4.929	4.577	30
Benzene	0.142	0.464	−0.588	−3.099	−4.625	4.491	27
Toluene	0.143	0.527	−0.720	−3.010	−4.824	4.545	25
Tetrachloromethane	0.260	0.573	−1.254	−3.558	−4.588	4.589	29
Ethyl acetate (dry)	0.358	0.362	−0.449	−0.668	−5.016	4.155	10
Acetonitrile (dry)	0.413	0.077	0.326	−1.566	−4.391	3.364	21
Nitrobenzene	−0.181	0.576	0.003	−2.356	−4.420	4.263	23
Octanol (wet)	0.088	0.562	−1.054	0.034	−3.460	3.814	

[a] From refs. 26–29. [b] The Ishihama and Asakawa value, see text.

Table 3 Calculated[a] and observed[b] log L^S and log P values for nitric oxide at 298 K

Solvent	Log L^S(calc)	Log L^S(obs)	Log P(calc)	Log P (obs)
Methanol (dry)	−0.391	−0.457	0.838	0.870
Ethanol (dry)	−0.450	−0.594	0.819	0.733
Hexane	−0.348	−0.329	1.010	0.998
Cyclohexane	−0.475	−0.348	0.928	0.980
Benzene	−0.575	−0.520	0.912	0.854
Toluene	−0.531	−0.595	0.832	0.732
Tetrachloromethane	−0.439	−0.445	0.981	0.882
Ethyl acetate (dry)	−0.479	−0.397	0.857	0.930
Acetonitrile (dry)	−0.445	−0.483	0.829	0.844
Nitrobenzene	−0.771	−0.721	0.515	0.606
Diethyl ether (dry)[c]		−0.391		0.854

[a] From eqns. (2) and (1) with the coefficients in Table 1 and Table 2, and with the descriptors for nitric oxide as in the text. [b] From refs. 21–25. The values of log P have been obtained using a value of −1.327 for log L^W from refs. 18–20. [c] No equations available.

been measured. As mentioned above, the most extensive compilation of log P values[4] does not refer to nitric oxide at all. However, the value of L^S for nitric oxide in a given solvent may be combined with the corresponding L^W value in water to give a value for the partition between water and the solvent through eqn. (4).

$$L^S/L^W = P \quad \text{or} \quad \log L^S - \log L^W = \log P \qquad (4)$$

In Table 1 are given the coefficients in eqn. (2) for various gas–solvent partitions, and in Table 2 are the coefficients for the corresponding water–solvent partitions.[17,26–29] Note that some of the water–solvent partitions refer to partition from pure water to the pure dry solvent, and are not ‘practical’ partitions. The observed log L^S values for nitric oxide, and the ‘observed’ log P values obtained through eqn. (4), are given in Table 3.

Results and discussion

There are 10 log L^S values and 10 log P values for nitric oxide for which we have the relevant equations. Now it is very important that the 10 equations in Table 1 (and the 10 in Table 2) are substantially different, that is that they contain different information that can be used to obtain descriptors. A very elegant method of comparison of solvation equations is that of Ishihama and Asakawa.[30] They regard our five-descriptor equation as a line in five dimensions. Then for two equations, the angle, θ, between the lines is a measure of how close the lines (*i.e.* the equations) are. In order to calculate values of θ for 10 equations, one equation has to be taken as the standard, and we have chosen the first equation in Table 1 and in Table 2 as the arbitrary standard. The calculated θ values are in the last column of Tables 1 and 2. There are huge variations in θ, and so we are confident that the equations in Table 1 (and those in Table 2) are sufficiently different for us to be able to obtain descriptors for nitric oxide with some confidence.

The McGowan characteristic volume can be calculated[13] as 0.2026, in units of 10^{-2} cm^3 mol^{-1}, and we can then assign the remaining descriptors as those that best reproduce the 20 observed values. We find that with $E = 0.370$, $S = 0.02$, $A = 0.00$,

$B = 0.086$, and $L = -0.590$, the 10 log L^S values are reproduced with a standard deviation, sd, of 0.081 log units, the 10 log P values with sd = 0.069 log units, and the entire set of 20 values with sd = 0.071 log units.

Because the analysis yields the one set of descriptors that best reproduce the observations, there are no statistics as regards standard deviation in the values of the descriptors. We can rectify this by adopting the method of 'leave-one-out', as described previously.[16] The first equation is left out and a set of descriptors is calculated from equations 2–20. Then the second equation is left out and a set of descriptors calculated from equations 1, 3–20. Each equation is left out in turn, and so we arrive at 20 sets of descriptors from which we can derive the statistics shown in Table 4. The 'leave-one-out' values are almost exactly the same as those obtained from the entire 20 solvent set, but we can now assess the internal self-consistency of the calculations through, for example, the sd values for each individual descriptor. These sd values are very small indeed.

The obtained descriptors for nitric oxide can be compared with those for various gaseous solutes,[12,26] as shown in Table 5. There is nothing very exceptional at all in the solvation descriptors of nitric oxide. It is almost nonpolar/polarizable, and has a small hydrogen-bond basicity, about the same as nitrous oxide or carbon dioxide. The absence of specific properties of nitric oxide means that solute–solvent interactions will just be of a very general type. This results in the solubilities of nitric oxide in solvents being nearly all the same (see Table 3); there is only a difference of 0.39 log units between the highest and lowest observed values of log L^S. Only for solubility in water, where log L^W is −1.33, is there any marked difference. However, this is not due to specific nitric oxide–water interactions, because the same effect is observed for the solubility of methane in water and organic solvents.[31] What is of interest, is that with a knowledge of the solvation descriptors, a number of passive transport properties can be deduced, especially those relevant to passage through membranes.

Table 4 Calculation of solvation descriptors by the method of 'leave-one-out'[a]

Descriptor	E 10^{-1} cm^3 mol^{-1}	S	B	L
Max. value[b]	0.468	0.039	0.100	−0.567
Min. value[b]	0.262	0.009	0.074	−0.620
Mean value[b]	0.373	0.020	0.086	−0.593
sd[b]	0.043	0.007	0.005	0.014
All equations[c]	0.370	0.020	0.086	−0.590

[a] The A-descriptor is zero. [b] By the 'leave-one-out' method. [c] All 20 equations used.

Previously, we have applied eqns. (1) and (2) to a large number of processes,[6–11,15,32,33] and have obtained the corresponding coefficients that are required for any prediction of physicochemical properties. In Table 6 we give some predicted properties of nitric oxide, together with details of the observed range of such properties. Also given are the corresponding values for nitrogen; bearing in mind the range of properties, these are all quite close to those for nitric oxide, showing again the non-specific character of the interactions between nitric oxide and solvents or phases. The lipophilicity of nitric oxide, taken as log P_{oct}, where P_{oct} is the water–octanol partition coefficient, is rather small, 0.74, about the same as that for argon (0.74) or nitrogen (0.67), and less than that for methane (1.09), so the idea[2,3] that nitric oxide is rather liphophilic is not substantiated by our calculations. Nitric oxide is believed to be unstable in physiological solutions,[34] but since various workers[2,3] have suggested that nitric oxide can penetrate cell membranes easily, we thought it useful to calculate a number of quantities relevant to simple passive transport.

The partition between water and plant cuticular matrix can be calculated from the equation given by Platts and Abraham[10] as log $P = 0.22$ which is a rather small value (see Table 6). An air–plant cuticular matrix partition can similarly be calculated, and is actually much smaller than any other such partition observed to date.[10] The rate of permeation of plant cells, as log (k/cm s^{-1}), is −2.25 which is about the same as the very hydrophilic compound methylurea.[11] The range of log k values for permeation of plant cells (see Table 6) is somewhat misleading because nearly all the compounds studied were very hydrophilic, ranging from methanol with log $k = 0.00$ to pentaerythritol with log $k = -9.77$. Our conclusion is that, judged on the basis of our assigned descriptors (Table 4), nitric oxide is

Table 5 Comparison of solvation descriptors

Solute	E/10^{-1} cm^3 mol^{-1}	S	A	B	L	V/10^{-2} cm^3 mol^{-1}
NO	0.370	0.02	0.00	0.09	−0.590	0.2026
Ar	0.000	0.00	0.00	0.00	−0.688	0.1900
N_2	0.000	0.00	0.00	0.00	−0.978	0.2222
O_2	0.000	0.00	0.00	0.00	−0.723	0.1830
N_2O	−0.080	0.15	0.00	0.11	0.220	0.2810
CO	0.000	0.00	0.00	0.04	−0.836	0.2222
CO_2	0.000	0.28	0.05	0.10	0.057	0.2809
SO_2	0.403	0.66	0.29	0.09	0.780	0.3465
CH_3CHO	0.208	0.67	0.00	0.45	1.230	0.4061
NH_3	0.139	0.39	0.16	0.56	0.680	0.2084
CH_3OH	0.278	0.44	0.43	0.47	0.970	0.3082

Table 6 Predicted properties (log values) of nitric oxide

Property	Prediction	Min. value[a]	Max. value[a]	Nitrogen
Water–wet octanol partition[b]	0.74	−2.0	8.0	0.67
Water–chloroform	0.92	−3.25	6.01	0.93
Ethylene glycol–heptane	0.51	−3.69	2.99	1.16
Water–plant matrix partition	0.22	−0.86	4.47	0.45[c]
Water–plant cell permeation[d]	−2.25	−9.77	0.00	−2.07[c]
Gas–wet octanol[b]	−0.56	−1.7	7.8	−1.13
Gas–chloroform	−0.49	−1.18	8.19	−0.87
Air–plant matrix partition	−0.99	1.60	4.52	−1.46[c]

[a] Recorded values for various solutes. [b] The minimum and maximum values for various solutes are approximate only. [c] Calculated value. [d] In cm s^{-1}.

not very lipophilic, and can permeate membranes only poorly by simple passive diffusion.

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