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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 has no hydrogen bond acidity at all, and 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. The calculated lipophilicity of nitric oxide, as a water-octanol partition coefficient, is very small at 0.58 ($\log P_{\text{oct}}$), about the same as argon or nitrogen.

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 $(\text{R-NO})^-$. Alternatively, if the substrate is a better electron donor, then electron transfer to nitric oxide, yielding NO^- is observed. Schonafinger² has suggested that nitric oxide can penetrate cell membranes very

easily because of its low molecular weight and its rather lipophilic properties, but to our knowledge no quantitative 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.³ 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)..

We have previously investigated several processes that involve passive transport of solutes through biological systems.⁴ These include blood-brain distribution,⁵ saline-brain perfusion,⁶ water-skin permeability,⁷ partition between water and plant cuticular matrix,⁸ and permeation from water into plant cells.⁹ All of these processes can be examined and analysed through the general solvation equation,^{4,10}

$$\log SP = c + e\mathbf{E} + s\mathbf{S} + a\mathbf{A} + b\mathbf{B} + v\mathbf{V} \quad (1)$$

where SP is the solute property. We use a simplified notation for the independent variables in eq 1, which are solute descriptors as follows.^{4,10} In parentheses is given our original notation for the descriptors. \mathbf{E} (R_2) is an excess molar refraction, \mathbf{S} (π_2^H) is the dipolarity/polarizability, \mathbf{A} ($\Sigma\alpha_2^H$) is the overall or summation hydrogen-bond acidity, \mathbf{B} ($\Sigma\beta_2^H$) is the overall or summation hydrogen-bond basicity, and \mathbf{V} (V_x) is the McGowan volume in units of ($\text{cm}^3 \text{ mol}^{-1} / 100$).¹¹ For transport from the gas phase to condensed phases, an alternative equation is used,

$$\log SP = c + e\mathbf{E} + s\mathbf{S} + a\mathbf{A} + b\mathbf{B} + l\mathbf{L} \quad (2)$$

The final descriptor in eq 2 is \mathbf{L} ($\log L^{16}$) where L^{16} is the solute Ostwald solubility coefficient (or gas-liquid partition coefficient, K) on hexadecane at 298 K,¹² defined through eq 3 where the solvent is hexadecane.

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

Eq 2 has been applied to biochemical processes such as the solubility of gaseous solutes in blood and tissues¹³ and the partition of solutes between the gas phase and plant cuticular matrix.⁸ If the descriptors in eq 1 and eq 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 eq 1 and eq 2 have been recently detailed.¹⁴ In brief, the McGowan volume can easily be calculated,¹¹ and so there remain five solute descriptors in eq 1 and eq 2 to obtain. Equations on the lines of eq 1 and eq 2 are set out for processes in which values for nitric oxide are available, so that we have values of log SP in several equations for which all the coefficients are known. The only unknowns are the solute descriptors themselves, and are obtained by a least squares method that assigns values of descriptors that minimise the observed and calculated log SP values.

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 at 298 K and at 313 K¹⁵ and in a number of organic solvents,¹⁶⁻²⁰ but no water-solvent partitions, P, seem to have been measured. As mentioned above, the most extensive compilation of log P values³ 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 eq. 4,

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

In Table 1 are given the coefficients in eq 2 for various gas-solvent partitions, and in Table 2 are the coefficients for the corresponding water-solvent partitions.²¹ 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 eq 4, are 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. The McGowan characteristic volume can be calculated¹¹ as 0.2026, in units of ($\text{cm}^3 \text{mol}^{-1} / 100$), and we can then assign the remaining descriptors as those that best reproduce the 20 observed values. We find that with $\mathbf{E} = 0.37$, $\mathbf{S} = 0.02$, $\mathbf{A} = 0.00$, $\mathbf{B} = 0.086$, and $\mathbf{L} = -0.590$, 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. The obtained descriptors for nitric oxide can be compared with those for various gaseous solutes,^{10,21} as shown in Table 4. 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. 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.

Previously, we have applied eq 1 and eq 2 to a large number of processes, and have obtained the corresponding coefficients that are required for any prediction. In Table 5 we give some predicted properties of nitric oxide, together with details of the observed range of such properties. The lipophilicity, taken as $\log P_{\text{oct}}$ where P_{oct} is the water-octanol partition coefficient is rather small, about the same as that for argon (0.74) or nitrogen (0.67), and less than that for methane (1.09), so the idea² that nitric oxide is rather lipophilic is not substantiated by our calculations. Nitric oxide is believed to be unstable in physiological solutions,²² but since Schonafinger² has 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 Abraham⁸ as $\log P = 0.22$ which is a rather small value (see Table 5). An air-plant cuticular matrix partition can similarly be calculated, and is actually much smaller than any other such partition observed to date.⁸ The rate of permeation of plant cells, as $\log k/\text{cm s}^{-1}$, is -2.25 which is about the same as the very hydrophilic

compound methylurea.⁹ The range of log k values, see Table 5, is somewhat misleading because nearly all the compounds studied were 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 can permeate membranes only poorly by simple passive diffusion.

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Table 1. Coefficients in Equation (2) for Gas-solvent Partitions at 298 K^a

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

^a From ref. 21. ^b Provisional equation.

Table 2. Coefficients in Equation (1) for Water-solvent Partitions at 298 K ^a

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

^a From ref. 21.

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 eq 2 and eq 1 with the coefficients in Table 1 and Table 2, and with the descriptors for nitric oxide as in the text. ^b From refs. 16-20. The values of log P have been obtained using a value of -1.327 for log L^W from ref. 15. ^c No equations available.

Table 4. Comparison of Solvation Descriptors

Solute	E	S	A	B	L	V
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 ₂ O	-0.08	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 ₃ CHO	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 ₃ OH	0.278	0.44	0.43	0.47	0.970	0.3082

Table 5. Predicted Properties of Nitric Oxide

Log (Property)	Prediction	Min value	Max value
Water-octanol partition ^a	0.74	- 2.0	8.0
Water-plant matrix partition	0.22	- 0.86	4.47
Water-plant cell permeation ^b	-2.25	-9.77	0.00
Air-plant matrix partition	-0.99	1.60	4.52

^a The minimum and maximum values are approximate only. ^b In cm s⁻¹

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