An NMR Shift Reagent Method for the Determination of Micelle/Water Partition Coefficients

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An NMR shift reagent method has been developed which makes the measurement of micelle/water partition coefficients more accessible.

Partition coefficients play an important role in determining the physicochemical behaviour of solutes when they are transferred to immiscible solvent systems. These coefficients have been discussed with regard to solvent extraction in analytical chemistry and also to oil/water partition of drugs and toxicants in medicinal and environmental chemistry.[1] In the latter field partition coefficients have been used as a hydrophobicity parameter and the data have been collected mainly from octan-1-ol/water systems in order to pursue the study of structure–activity relationships.[2] Partition coefficients are also measured in micelle/water systems. These systems are characteristic among different systems because of an organised structure of chain molecules in a micelle which resembles that in a lipid membrane. Hitherto, partition coefficients in such micelle/water systems have been obtained by several methods such as the measurement of solubility[3] or vapour pressure,[4] calorimetry[5] and micelle electrophoresis.[6] These methods are, however, not easy to use for a variety of

Table 1 Micelle/water partition coefficients measured by the NMR shift reagent method[a]

Solute	δ_{obs}	δ_{aq}	$\delta_{obs}{}^s$	$\delta_{aq}{}^s$	ρ	$\log K_p$	$\log K_p$[b]
Phenol	7.221 ± 0.001	7.275 ± 0.000	7.201 ± 0.002	7.241 ± 0.001	0.398 ± 0.086	1.60 ± 0.15	1.70 1.72[c]
4-Chlorophenol	7.084 ± 0.002	7.188 ± 0.001	7.066 ± 0.000	6.848 ± 0.002	0.946 ± 0.006	3.02 ± 0.05	3.31
Benzoic acid	7.947 ± 0.000	7.941 ± 0.001	7.941 ± 0.001	7.902 ± 0.001	0.846 ± 0.035	2.36 ± 0.12	2.48
4-Hydroxybenzoic acid	7.873 ± 0.001	7.881 ± 0.000	7.915 ± 0.001	7.999 ± 0.001	0.644 ± 0.012	1.87 ± 0.02	1.89
Propionic acid	2.343 ± 0.001	2.352 ± 0.001	2.388 ± 0.001	2.407 ± 0.002	0.182 ± 0.045	0.96 ± 0.13	—

[a] The chemical shift (δ) is measured for the *ortho*-protons in phenols and benzoic acids and for the α protons in propionic acid; it is expressed in ppm from TMS. Susceptibility corrections are made by dual measurements on the SCM and permanent magnet instruments. See text for further detail. [b] Measured from the relaxation-reagent method in DTAB/water system. [c] Measured by electrophoresis in the SDS micelle.

molecules including drugs and related compounds, preventing a systematic collection of data in this system. An NMR paramagnetic relaxation method has been proposed[7] as a simple alternative to the NMR pulsed gradient spin-echo self-diffusion technique.[8] This method involves the measurement of the relaxation time of solute in a micelle/water system in the presence and absence of a low concentration of relaxation reagent such as Mn^{2+} ion. In a routine NMR measurement, however, the precise measurement of relaxation times is not easy to accomplish because of the special attention and machine times needed in the experiment. In the present study we have developed a novel method which utilizes NMR shift reagents instead of the relaxation reagents.

Dysprosium trichloride (Nakarai Chemicals, 99.9%), sodium dodecyl sulfate (SDS) (Kishida Chemicals, 98%), dodecyltrimethylammonium bromide (DTAB) (Tokyo Kasei Kogyo Co., 99%) and sodium tripolyphosphate (Wako Pure Chemical Ind.) were used without further purification. Phenols, benzoic acids and propionic acid from commercial sources were purified by distillation or recrystallization before use. The shift reagent $[Dy(ppp)_2]^{7-}$ was made *in situ* from dysprosium trichloride and sodium tripolyphosphate.[9] NMR spectra were obtained using a Hitachi R250H (SCM magnet, 250 MHz) and Hitachi R90H (permanent magnet, 90 MHz) spectrometers at 35.0 °C. A digital resolution of 0.001 ppm or better was achieved by setting the spectral width and data memory. Chemical shifts were measured relative to external TMS ($SiMe_4$) sealed in a capillary tube located at the coaxial centre of a 5 mm (o.d.) NMR tube; the bulk magnetic susceptibility was corrected by weighting the data obtained from the SCM and permanent magnets at the same temperature in the ratio 1 : 2.[10] Here, an external reference was used to exclude a problem of solvent effect on the standard, although a proper choice of internal reference would be possible and widen the applicability of the method.

In the micelle/water partition system the observed chemical shift of a solute (δ_{obs}) can be related to the shift pertinent to the solute in micelle (δ_{mic}) and that in aqueous phase (δ_{aq}) as in eqn. (1), where ρ is the fraction of residence time a solute molecule spends in micelle phase. A similar equation holds when the NMR shift reagent is added [eqn. (2)], where the shift reagent is assumed not to affect the chemical shift inside the micelle phase. This assumption was confirmed to be correct below 6 mmol dm^{-3} of the added shift reagent by monitoring the chemical shifts of micelle itself. By eliminating δ_{mic} from above equations eqn. (3) is obtained. The partition coefficient (K_p) is expressed as in eqn. (4),

$$\delta_{obs} = \rho\delta_{mic} + (1 - \rho)\delta_{aq} \tag{1}$$

$$\delta_{obs}{}^s = \rho\delta_{mic} + (1 - \rho)\delta_{aq}{}^s \tag{2}$$

$$\rho = 1 - \frac{\delta_{obs}{}^s - \delta_{obs}}{\delta_{aq}{}^s - \delta_{aq}} \tag{3}$$

$$K_p = \frac{\rho}{1 - \rho}\,\frac{V_{aq}}{V_{mic}} \tag{4}$$

where V_{aq}/V_{mic} is the ratio of the volume of the aqueous phase relative to that of the micelle phase. V_{mic} was obtained by the use of the partial molar volume of SDS.[11]†

The determination of micelle/water partition coefficients is shown in Table 1 for several solutes; standard deviations on repeated measurements are also given. In Table 1, except for the last column, phenols were measured in 75 mmol dm^{-3} SDS solution using 30 mmol dm^{-3} solute and 5 mmol dm^{-3} shift reagent $[Dy(ppp)_2]^{7-}$: benzoic acids and propionic acid were measured in 80 mmol dm^{-3} DTAB solution using 30 mmol dm^{-3} solute and 4 mmol dm^{-3} shift reagent $Dy(NO_3)_3{\cdot}5H_2O$ or $Yb(NO_3)_3{\cdot}3H_2O$ (for benzoic acid), the pH being adjusted to 2.0 by aqueous DCl.

The proposed method facilitates the simple but precise determination of micelle/water partition coefficient, if only a small amount of solute is available for a routine NMR experiment and if special care is taken to perform an accurate measurement of chemical shifts.

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References

1 R. Franke, in *Theoretical Drug Design Methods, Pharmacochemistry Library*, ed., W. Th. Nauta and R. F. Rekker, Elsevier, Tokyo, 1984, vol. 7.
2 C. Hansch and A. Leo, in *Substituent Constants for Correlation Analysis in Chemistry and Biology*, Wiley, New York, 1979.
3 P. Ekwall, L. Mandell and K. Fontell, *Mol. Cryst. Liq. Cryst.*, 1969, **8**, 157.
4 K. Hayase and S. Hayano, *Bull. Chem. Soc. Jpn.*, 1977, **50**, 83.
5 H. Fujiwara, Y.-Z. Da, K. Ito, T. Takagi and Y. Nishioka, *Bull. Chem. Soc. Jpn.*, 1991, **64**, 3707.
6 S. Terabe, K. Otuka and T. Ando, *Anal. Chem.*, 1985, **57**, 834.
7 Z. Gao, R. E. Wasyueshen and J. C. T. Kwak, *J. Phys. Chem.*, 1989, **93**, 2190.
8 P. Stilbs, *Prog. Nucl. Magn. Reson. Spectrosc.*, 1987, **19**, 1.
9 R. K. Gupta and P. Gupta, *J. Magn. Reson.*, 1982, **47**, 344.
10 J. Homer, *Appl. Spectrosc. Rev.*, 1975, **9**, 1.
11 K. Shinoda and T. Soda, *J. Phys. Chem.*, 1963, **67**, 2072.

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† That the aqueous phase was not saturated with the solute is evident from experiments in which the same concentration was dissolved in water without micelle and NMR spectra measured. As further evidence, $\log K_p$ was remeasured for concentration of phenol of half of the original one. The resulting $\log K_p$ value decreased by only 0.03, supporting the reliability of the original value.

V_{mic} was calculated from the partial molar volume after correcting for the micelle compounds below the critical micellization concentration (cmc). The cmc value was also confirmed not to change appreciably on dissolving solutes of the concentration used in the experiment. Calculation of V_{mic} in this way has been done in other papers, *e.g.* in ref. 7.