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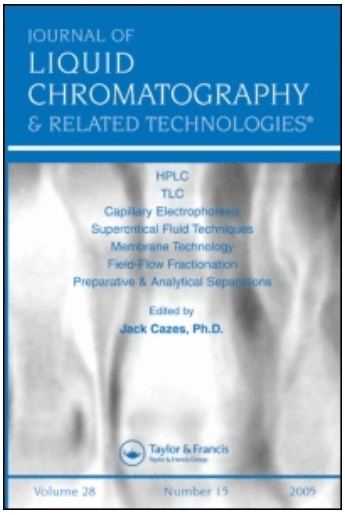

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Partition Coefficients (log P) and HPLC Capacity Factors (k') of Some Gd(III) Complexes of Linear and Macrocyclic Polyamino Carboxylates

Krishan Kumar[a]; K. Sukumaran[a]; S. Taylor[a]; C. Allen Chang[a]; A. D. Nunn[a]; M. F. Tweedle[a]
[a] The Bristol-Myers Squibb Pharmaceutical Research Institute, Princeton, New Jersey

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PARTITION COEFFICIENTS (log P) AND HPLC CAPACITY FACTORS (k') OF SOME Gd(III) COMPLEXES OF LINEAR AND MACROCYCLIC POLYAMINO CARBOXYLATES

KRISHAN KUMAR*, K. SUKUMARAN, S. TAYLOR,
C. ALLEN CHANG, A. D. NUNN, AND M. F. TWEEDLE
The Bristol-Myers Squibb Pharmaceutical Research Institute
P.O. Box 4000
Princeton, New Jersey 08543-4000

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ABSTRACT

The partition coefficients (log P) in n-butanol/water and n-octanol/water together with the HPLC capacity factors (k') in 2% and 4% acetonitrile (ACN) and aqueous buffered mobile phase were determined for 21 Gd(III) chelates of linear and macrocyclic polyamino carboxylates. A C_{18} reversed-phase (Nucleosil) column was used for determination of k'. The log P values were calculated (clog P) for the fully protonated form of the ligands. A reasonably good correlation (r = 0.76) between the measured log P values for the chelates in n-butanol/water and the calculated log P values for the ligands was observed. In general, the log P value in n-butanol/water for a chelate was 1.3 log unit different than that in n-octanol/water. The k' values in 2% and 4% acetonitrile/aqueous buffer were also correlated with measured log P values.

INTRODUCTION

Structure-activity relationships are useful in understanding certain biological effects of pharmaceuticals [1-3]. These include an understanding of biodistributions, effective dose, ED_{50}, and acute tolerance, LD_{50}. For a pharmaceutical to exhibit certain biological effects, it must interact with some cellular components of the site of action. The pharmaceutical must be transported through phase boundaries and undergo adsorption and desorption processes with

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proteins and membranes, as well as partitioning between different liquid phases before it reaches the site of action. Hansch and coworkers [4-6] proposed a model for understanding biological activity of potential pharmaceuticals. According to this model the lipophilic-hydrophilic balance of a compound, which is expressed by a partition coefficient is critical for drug absorption and transport. The n-octanol/water partition coefficient is a recognized model for biological lipids and aqueous phases. As the determination of lipophilicity by the traditional shake-flask method has certain limitations, the reversed-phase HPLC capacity factor is a useful alternative to the n-octanol/water system [7].

Our interest in lipophilicity determination resulted from a need to develop structure-activity relationships (SARs) in magnetic resonance imaging (MRI). MRI contrast agents are a class of pharmaceuticals [8,9] which utilizes gadolinium chelates, GdL (where L is a chelating agent or ligand). Four such chelates, e.g. the complexes of diethylenetriaminepentaacetic acid (DTPA), the bis methyl amide of DTPA (DTPA-BMA), 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA), and 10-(2-hydroxypropyl)-1,4,710-tetraazacyclododecane-1,4,7,10-tetraacetic acid (HP-DO3A), are being used clinically as extracellular contrast agents [9]. One of the requirements for intravenously administered gadolinium-based extracellular contrast agents is high hydrophilicity. This property is required to: (1) maintain water solubility, (2) minimize interaction of the pharmaceutical with plasma proteins, membranes, and other macromolecules, which allows for rapid equilibration of the complex in the extracellular space and efficient excretion, and (3) avoid permeation of the pharmaceutical through intact plasma membranes by diffusion. There is little published information on the lipophilicity (hydrophilicity) of this class of compounds [10].

The objectives of this investigation were to determine the lipophilicity (log P values) or hydrophilicity of 21 potential MRI contrast agents by the traditional shake-flask method [4] and by the reversed-phase HPLC method. Calculated log P values (clog P) for the ligands were compared to the measured log P values of the complexes to evaluate the predictability of log P for unknown gadolinium complexes. A general structure of the macrocyclic framework is shown in Table I. The structures of other ligands, e.g. EDTA, DTPA, and DTPA-BMA are well known [11].

MATERIALS AND METHODS

Instruments

The HPLC system used was a two pump, Rainin Instrument or Beckman model 110, with a Rheodyne injection valve containing a 20 µL sample loop. A C_{18} reversed-phase Nucleosil (Jones Chromatography or Alltech) (25.0 x 0.46 cm, 5µm) column was used. After each working period,

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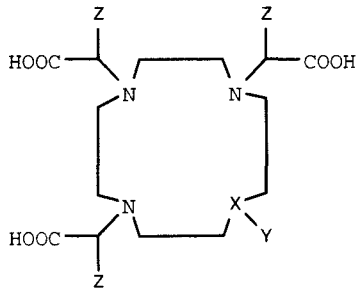
Table I. Structural Formulas of Macrocyclic Polyamino Carboxylates.



S.N.	X	Y	Z	Name
1	N	H	H	DO3A
2	N	$-CH_3$	H	Me-DO3A
3	N	$-CH_2CHOHCH_3$	H	HP-DO3A
4	N	$-CH_2CONHCH_3$	H	MA-DO3A
5	N	$-CH_2CONHC_6H_5$	H	PA-DO3A
6	N	$-(CH_2)_2CN$	H	CE-DO3A
7	O	-	H	OX-DO3A
8	N	$-CH_2C_6H_5$	H	BZ-DO3A
9	N	$-(CH_2)_2COOH$	H	HO-DO3A
10	N	$-CH_2CHOHCH_2OH$	H	PG-DO3A
11	N	$-CH2CHOHCH_2OCH_3$	H	HM-DO3A
12	N	$-CH_2COH(CH_2OCH_2)_3CH_3$	H	HD-DO3A
13	N	$-CH_2CHOH(CH_2)_3CH_3$	H	HH-DO3A
14	N	$-CH_2CH_2CH_3$	H	NP-DO3A
15	N	$-CH_2CONH(C_6H_4)(CONHCHOHCH_2OH)_2$	H	HAA-DO3A
16	N	-H	CH_3	DO3MA
17	N	$-CH_2COOH$	H	DOTA
18	N	$-CH(CH_3)COOH$	CH_3	DOTMA

the column was flushed with acetonitrile and then water/methanol. The column was stored in methanol. Integration of peak areas was performed either by a Shimadzu RC-3A chromatopac/ plotter or by using a Dynamax software. A Beckman 170 radioisotope detector was used for radioactivity and a Hitachi F-1050 or F-2000 detector for fluorescence.

A Radiometer PHM-82 pH meter with a combination glass electrode was used for all pH measurements. An LKB-Wallace gamma counter was used for the determination of radioactivity in the sample. The window used to count ^{153}Gd radioactivity was machine channels 20-140 inclusive. This window measures the gamma radiation at 97.4 and 103.2 keV.

Materials

Ethylenediaminetetraacetic acid (EDTA) (Fisher), diethylenetriaminepentaacetic acid (DTPA) (Aldrich) and DTPA-BMA (STREM) chemicals were used without further purification.

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The chelating agents and Gd(III) chelates were synthesized by literature procedures [12-16]. The purity of the chelating agents, ligands, and Gd(III) complexes was checked by elemental, mass spectral analysis, ^{1}H, ^{13}C NMR, and HPLC and the purity was >99% . HPLC grade methanol and acetonitrile were used for all chromatographic studies. Silica gel impregnated glass fiber sheets (ITLC-SG) were purchased from Gelman Sciences, Inc. (Ann Arbor, MI). The purity of $Gd(EDTA)^-$ was checked by using freshly prepared mobile phase, 10% ammonium acetate (Fisher) in 50% (v/v) aqueous methanol. This was prepared fresh daily. Stock solution of $GdCl_3$ was prepared from a solid sample of $GdCl_3$ purchased from Research Chemicals (Phoenix, AZ), and was used without further purification. The sample solution was standardized by a complexometric titration with xylenol orange as the indicator [17]. A stock solution of tris acetate buffered EDTA (Aldrich chemicals) was prepared for sample preparation and for the HPLC mobile phase. The tris acetate buffer was prepared from TRIZMA (Sigma) base and acetic acid (Fisher). Dilute solutions of hydrochloric acid and sodium hydroxide were used for adjustment of the pH. All other chemicals were reagent grade. Normal butanol and n-octanol (Aldrich) were greater than 99% pure. A sample of $^{153}GdCl_3$ ($t_{1/2}$ = 241.6 d) with a known specific activity and radioactivity concentration was purchased from the Oak Ridge National Laboratory, Oak Ridge (TN).

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Methods

The samples of $^{153}Gd/GdL$ were either prepared by a true tracer radiolabeling or by an isotope-exchange method [18]. In a true tracer radiolabeling procedure, a carrier-added sample of $^{153}GdCl_3$ was reacted with the free ligand. The pH of the reaction mixture was raised very slowly to 8 to avoid any $Gd(OH)_3$ formation. Any precipitated $^{153}Gd/Gd(OH)_3$ was removed by filtration through a 0.2 μm filter. The samples were purified by High Performance Liquid Chromatography [18].

In an isotope-exchange method, a solution of approximately 100 mM GdL was prepared. An aliquot of $^{153}GdCl_3$ was added to it. The pH was adjusted to 2 with 5 N HCl and the solution was heated to 80°C. Heating times varied for different chelates. The complexes of macrocyclic polyamino carboxylates were heated for 4 h, while the complexes of linear polyamino carboxylates required only 1 h. After heating, the solutions were neutralized with sodium hydroxide very slowly. The samples were analyzed by an ITLC or HPLC method for free Gd^{3+} [18-21]. In most of the samples the percentage of free Gd^{3+} was < 0.1%. High purity of these chelates is very important in these studies as free Gd^{3+} or free ligand, H_2L^{n-} at pH 7.4, will be very hydrophilic and influence the log P measurements.

The log P values were determined by a traditional shake-flask method. In a typical experiment, a 10 μL sample of a radiolabeled gadolinium chelate, ^{153}GdL ($[Gd]_T$ = 0.1 mmol/mL

and radioconcentration = 10-20 μCi/mL), and 2.0 mL of 25 mM tris acetate (pH 7.4) were mixed in a test tube. Two milliliters of either n-butanol or n-octanol were added and the test tube was vortexed for 2 min. The test tube was centrifuged for 2 min at 3000 rpm to insure complete separation of the two layers. Five hundred microliters of each phase were counted in an LKB gamma counter. The partition coefficient (P) values were calculated as follows:

$$P = \text{counts in organic phase/counts in aqueous phase} \quad (1)$$

Although the chelates used in this study are not protonated significantly above pH 3 [22], the tris acetate buffer was used to insure the presence of one species. The HPLC capacity factors (k') were determined for each complex using a silica-based reversed phase column. ^{153}GdL or GdL was used for these experiments. The mobile phase buffer containing 50 mM tris acetate and 10 mM EDTA (pH 7.4) was combined with 2% or 4% acetonitrile (v/v). Each chelate was injected in triplicate. The HPLC capacity factors (k') were determined using eq. 2.

$$k' = (t_r - t_o) / t_o \quad (2)$$

Where t_r is the retention time of the chelate, and t_o, the void volume or the time required to the mobile phase to move from one end of the column to the other. Normally a weaker solvent or non retained compound is used to determine the void volume of the column [23]. Recent work from this laboratory [21] has demonstrated that the percentage of acetonitrile does not affect the retention time of $Gd(EDTA)^-$, indicating that it is not retained. Consequently the retention time of $Gd(EDTA)^-$ has been taken as t_o. The calculation of the log P values (clog P) for the protonated form of the ligands was performed using MEDCHEM Vers. 3.42 [24].

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RESULTS AND DISCUSSION

Log P Values

The log P values for 21 potential extracellular MRI contrast agents were determined and are given in Table II. Impurities are obvious potential source of error in log P values measured by the shake-flask method. The samples used in this study were relatively pure and free from unbound Gd^{3+} or ligand. Free Gd^{3+} and H_2L^{n-} are more hydrophilic than the chelates and will affect the measurement considerably. All measurements were made in a buffered medium at pH 7.4 and there was <0.01% protonated chelate, GdL(H) [22]. Consequently the term log P rather than log D (distribution coefficient) was used. The data in Table II show that the log P values in n-octanol/water are always more negative than those in n-butanol/water indicating that all of the complexes are relatively hydrophilic. The linear-least squares fit of the plot of log P values in n-butanol/water vs. those in n-octanol/water gave a slope of 0.9 and an intercept of 1.3 with a

Table II. The Measured Values of Partition Coefficients (log P) in n-Butanol/Water and n-Octanol/Water Systems for Some Gd(III) Complexes, GdL, and the Calculated log P Values for Free Ligands

GdL	log P[a]	log P[b]	clog P[c]	GdL	log P[a]	log P[b]	clog P[c]
EDTA	-2.79	-3.91	-0.565	HO-DO3A	-2.84	d	0.527
DTPA	-3.16	d	-0.553	PG-DO3A	-2.22	-3.82	0.202
DTPA-BMA	-2.13	-4.14	-1.875	HM-DO3A	-1.99	-3.68	0.490
DO3A	-2.15	-3.86	-2.45	HD-DO3A	-1.60	-3.50	0.574
Me-DO3A	-1.94	-3.62	0.698	HH-DO3A	-0.81	-2.17	2.015
HP-DO3A	-1.98	-3.68	0.736	NP-DO3A	-1.42	-2.99	1.851
MA-DO3A	-2.28	-4.19	-0.038	HAA-DO3A	-2.62	d	-1.119
PA-DO3A	-1.22	-2.83	1.36	DOTMA	-2.21	d	1.69
CE-DO3A	-2.46	-3.97	0.403	DO3MA	-1.51	-3.31	-1.526
OX-DO3A	-2.76	d	0.169	DOTA	-2.87	-4.26	0.458
BZ-DO3A	-1.61	d	2.62				

[a]in n-butanol/water, [b]in n-octanol/water, and [c]calculated log P values for the protonated form of the ligand, [d]did not have enough counts in n-octanol layer to determine log P value.

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correlation coefficient (r) of 0.92 (Figure 1). Thus the following equation can be written to correlate log P data in n-butanol/water and in n-octanol/water for this series of Gd(III) complexes:

$$\log P_{\text{n-butanol/water}} = (0.9 \pm 0.2)\ \log P_{\text{n-octanol/water}} + (1.3 \pm 0.6) \qquad (3)$$

The correlation given in eq. 3 is very useful for highly hydrophilic compounds, as in some cases it is not possible to determine the log P value in the n-octanol/water system. Consequently, the log P determination in n-butanol/water is an alternative to n-octanol/water system. For example, from the correlation, the log P value in n-octanol/water system can be estimated as -4.9, -4.54, -4.73, -3.45, -4.3, and -4.12 for Gd(III) complexes of DTPA, HO-DO3A, OX-DO3A, BZ-DO3A, HAA-DO3A, and DOTMA, respectively, for which log P values could not be determined in n-octanol/ water. The n-octanol/water values were less accurate due to the lower number of counts in the n-octanol layer.

Correlation of the Measured log P Values for GdL and clog P for the Ligand

The log P values of the protonated form of the ligands were calculated by Hansch's fragmentation method (Table II) [24]. Deprotonation of the protonated form of the ligand is a

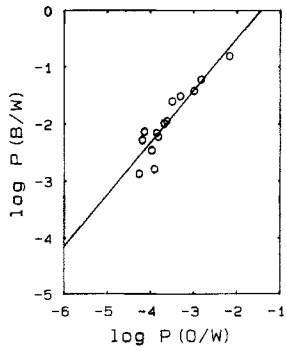

Fig. 1. Plot of log $P_{n\text{-butanol/water}}$ vs. log $P_{n\text{-octanol/water}}$.

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requirement for its complexation to Gd(III) (eq. 4). Five protons from DTPA, four protons from EDTA, DOTA, and some derivatives of DO3A and DOTA, and three protons from DTPA-BMA and most DO3A ligands are released upon reacting with Gd^{3+}. This variation in the overall

$$H_nL^o + Gd^{3+} <=====> GdL^{3-n} + n\,H^+ \qquad (4)$$

charge of the Gd(III) complexes might be expected to cause deviations from a linear relationship between the calculated and the measured lipophilicity unless a correction is made for the variable charge. However, the correction, clog P = 4.13 units for each unit of charge [5-7], is insignificant relative to the large clogP values and the existing scatter. As can be seen from Fig. 2, there is a linear relationship (eq. 5 and 6) between calculated and the measured log P values (in n-butanol/water and n-octanol/water systems) without any correction for charge.

$$\log P_{n\text{-butanol/water}} = (0.5 \pm 0.1)\ \text{clog P} - (2.5 \pm 0.1) \quad r = 0.74 \qquad (5)$$

$$\log P_{n\text{-octanol/water}} = (0.7 \pm 0.1)\ \text{c log P} - (4.1 \pm 0.1) \quad r = 0.84 \qquad (6)$$

It is apparent from equations 5 and 6 that measured n-octanol/water and n-butanol/water data correlate equally well with clog P values. It is possible to estimate the log P values for most of the gadolinium complexes of linear and macrocyclic polyamino carboxylates from clog P and using equations 5 and 6. However, the measured log P values for DTPA-BMA, DO3A, and DO3MA complexes were 2-3 orders of magnitude less hydrophilic than predicted by the correlation. Our measured log P value in n-butanol/water for Gd(DTPA-BMA) is in excellent agreement with the literature value [11].

The HPLC Capacity Factors

The compounds given in Table II were chromatographed on a silica based reversed-phase Nucleosil column with C_{18} support. The HPLC capacity factors (k') were determined using either

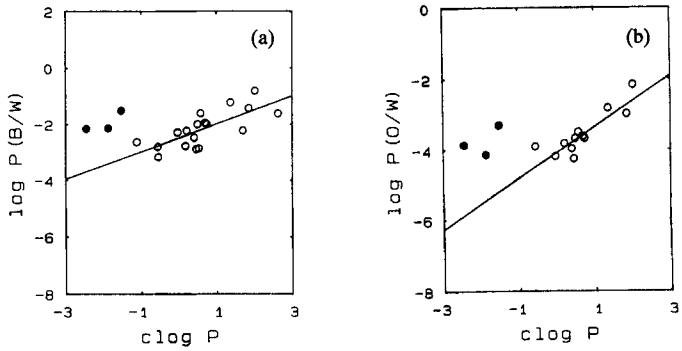

Fig. 2. A correlation of measured log P values (a) in n-butanol/water (b) n-octanol/water with clog P. The chelates GdL (where L = DTPA-BMA, DO3A and DO3MA and plotted by solid points) do not fall on the line.

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Table III. HPLC Capacity Factors (k') in the Buffered Mobile Phase (2 and 4% ACN And 98 and 96% 10 mM EDTA and 50 mM tris acetate, respectively at pH 7.4).

GdL	k'(2% ACN)	k'4%(ACN)	GdL	k'(2% ACN)	k'4%(ACN)
EDTA	0.000	0.000	PG-DO3A	1.35	0.90
DTPA	0.09	0.000	HM-DO3A	3.67	1.75
DTPA-BMA	1.47	0.670	HD-DO3A	a	a
DO3A	1.35	0.76	HH-DO3A	a	a
Me-DO3A	1.88	0.94	NP-DO3A	a	3.86
HP-DO3A	3.09	1.77	HO-DO3A	1.21	0.65
MA-DO3A	0.89	0.57	HAA-DO3A	9.84	3.07
PA-DO3A	a	5.977	DOTMA	13.96	5.30
CE-DO3A	1.32	0.81	DO3MA	a	7.85
OX-DO3A	0.61	0.49	DOTA	0.71	0.44
BZ-DO3A	a	a			

[a]did not elute within 30 min.

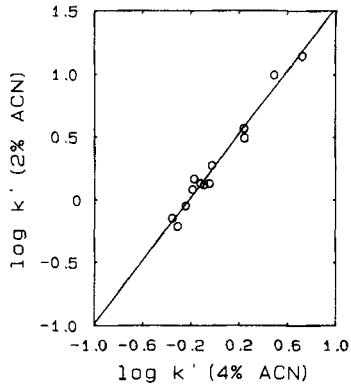

Fig. 3. A Plot of HPLC Capacity Factor log k' in 2% vs. log k' in 4% Acetonitrile.

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GdL or ^{153}GdL and eq. 2. The retention times of Gd(EDTA)$^-$ and GdL were either determined separately or a sample of GdL was spiked with a known amount of free Gd^{3+} and the mixture was injected onto a Nucleosil C_{18} reversed-phase column. The rate of the reaction of Gd^{3+} with the protonated form of EDTA (eq. 7) is rapid [25]; under the HPLC conditions the reaction of Gd^{3+} will be complete in $<10^{-6}$ s. As expected from the reverse-phase chromatography, the HPLC

$$Gd^{3+} + H(EDTA)^- \text{ <====> } Gd(EDTA)^- + H^+ \qquad (7)$$

capacity factor (k') in 4% acetonitrile (ACN) was always smaller than the one obtained in 2% ACN. When the capacity factor values (log k') at 2% acetonitrile (y-axis) and 4% (x-axis) ACN were plotted, an excellent linear correlation resulted (eq. 8, Fig. 3) with a slope of 1.26 ± 0.06 and an intercept of 0.26 ± 0.02 with r= 0.99.

$$\log k' (2\%) = (1.26 \pm 0.06) \log k' (4\%) + (0.26 \pm 0.02) \qquad r = 0.99 \qquad (8)$$

Correlation Between Log P Values and HPLC Capacity Factors

Plots of log k' vs. log P values were attempted (Fig. 4). Only results for log k' vs. log P (B/W) are shown. Linear least squares fits of the plots of log k' vs. log P values in n-butanol/water and n-octanol/water gave the following results.

2% ACN: $\log k' = (0.5 \pm 0.1) \log P(B/W) + (1.8 \pm 0.3)$ r=0.77 (9)

$\log k' = (0.8 \pm 0.2) \log P(O/W) + (3.3 \pm 0.8)$ r=0.83 (10)

4% ACN: $\log k;' = (0.7 \pm 0.1) \log P (B/W) + (1.6 \pm 0.2)$ r =0.89 (11)

$\log k;' = (0.8 \pm 0.1) \log P (O/W) + (3.2 \pm 0.4)$ r =0.91 (12)

Some anomalies exist. For example, $Gd(DTPA)^{2-}$ is more hydrophilic than Gd(EDTA)$^-$, however, the k' value for the later is smaller than the former. Probably the presence of additional

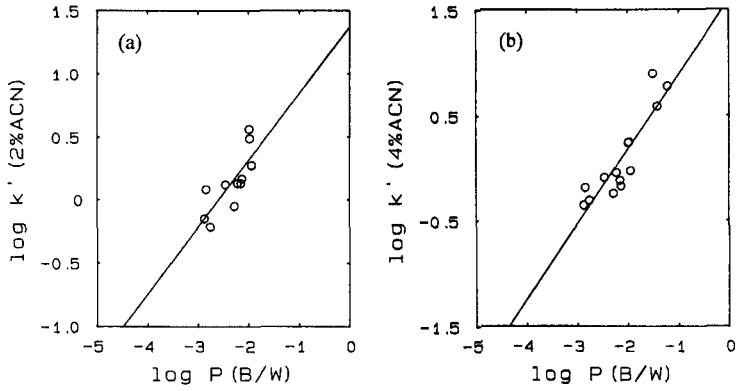

Fig. 4. Plot of log k' (a) in 2% and (b) 4 % acetonitrile vs. log P in n-butanol/water.

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negative charge on $Gd(DTPA)^{2-}$ encourages interaction with silanol groups of the column. Coordinated carboxylate groups in lanthanide polyamino carboxylate complexes are also more labile than coordinated amines and may dissociate briefly and interact with the silanol groups [22]. A similar rationalization can be made for the complexes of HAA-DO3A and DOTMA. Either alcoholic groups on HAA-DO3A or carboxylate groups on DOTMA interact with the stationary phase of the column.

SUMMARY

We conclude that with some exceptions, the log P values of Gd(III) chelates can be predicted from the calculated log P of the free ligand and that the log P in n-butanol/water and n-octanol/water can be calculated from the HPLC capacity factors. These data will be useful in designing future MRI contrast agents, the physical and biological properties of which are influenced by log P values.

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