RADIOCHEMISTRY AND RADIOPHARMACEUTICALS

Relationship Between Lipophilicity and Brain Extraction of C-11-Labeled Radiopharmaceuticals

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The brain extraction of fifteen C-11-labeled compounds during a single capillary transit was studied in adult baboons by external detection of these tracers after injection into the internal carotid artery. The log P_{oct} (partition coefficient for octanol/water) values of these compounds range from −0.7 to greater than 4.0. A parabolic relationship was found between the log P_{oct} value of the C-11-labeled compounds and the fraction of the radiopharmaceutical entering the brain. Compounds with log P_{oct} values between 0.9 and 2.5 were found to pass freely across the blood-brain barrier at a cerebral blood flow of 100 ml·min^{-1}·hg^{-1}. An apparently decreased extraction of very lipophilic compounds was shown to be related to binding of the tracer to blood components and macromolecules (red blood cells, albumin, etc.). These data suggest that a radiopharmaceutical designed to measure blood flow should have a log P_{oct} value of between 0.9 and 2.5.

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The potential of lipophilic tracers to map both blood flow and myelin in vivo has been demonstrated by Cohen and co-workers, who studied the autoradiographic distribution of C-14-labeled anesthetics in squirrel-monkey brain (*1*). Recently Frey and co-workers have reported their efforts to label myelin in monkeys with I-123-labeled iodobenzene (*2*).

We have been searching for a positron-emitting radiopharmaceutical suitable for imaging myelin in patients (*3,4*). Such an agent would be useful in following the course of a demyelinating disease such as multiple sclerosis. In addition, such an agent, if freely permeable, would be useful in the measurement of cerebral blood flow (CBF). The critical property of an agent designed to image myelin is its lipid solubility. The ability of a compound to be freely permeable across the blood-brain barrier (BBB) is related to its lipid solubility (*5–8*), extent of protein binding (*9,10*), molecular size (*11*), and charge (*12*). An agent designed to measure blood flow should be free to diffuse across the blood-brain barrier at all flow rates (*13*). In an effort to determine the maximum value of the octanol/water partition coefficient [log P(oct)] at which compounds are still free to diffuse across the BBB, we studied the relationship between the lipophilicity of a compound and its extraction by the brain during a single transit. Such a study should also be useful in determining the characteristics necessary for uncharged tracers labeled with radionuclides such as Tc-99m (*9*) and Ga-68 (*14*) designed to measure cerebral blood flow. If the compound is trapped in tissue, flow can be measured; if it redistributes, myelin content may also be determined (*15*).

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METHODS AND MATERIALS

Materials were obtained commercially and used without purification: dimethyl sulfoxide (DMSO), potassium hydroxide (KOH), benzyl chloride, 1-bromobutane, 1-bromopentane, 1-bromohexane, 2.0 *M* phenyl lithium (70% cyclohexane/30% diethyl ether), lithium

TABLE 1. RETENTION TIMES OF CARBON-11-LABELED COMPOUNDS ON THE PARTISIL 5-ODS-3 HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY C-18 RAC COLUMN WITH AN AQUEOUS ETHANOL ELUANT

C-11-compound	% Ethanol*	Retention time (min)
Methyl butyl ether	56	7
Methyl pentyl ether	56	10
Methyl hexyl ether	60	11
Benzyl methyl ether	53	7
Benzyl hexyl ether	75	10
Diphenylmethanol	45–62†	9
Benzophenone	45–62†	11
Triphenylmethanol	45–62†	16
Diphenylmethane	73	6
Triphenylmethane	73	10
1-butanol	30	9
1-hexanol	53	7
1-octanol	70	6
Benzyl alcohol	50	4

* = flow rate of 3.0 ml/min.
† = linear gradient elution program complete in 12 min with a flow rate of 3.2 ml/min.

aluminum hydride (LAH)/diethyl ether, n-propyl magnesium bromide, n-pentyl magnesium bromide, n-heptyl magnesium bromide, and 1.0 *M* LAH/ethoxyethyl ether (LAH/EEE).

Chromatography supplies used in this study were: C-18 reverse-phase liquid chromatography SEP-PAK cartridges* and C-18 reverse-phase liquid chromatography 5 ODS-3 RAC column†. The conditions for separation of the compounds used are given in Table I.

Design of the reaction vessel used in C-11-labeling procedures. All labeling procedures except the preparation of C-11-labeled diphenylmethanol were performed in reaction vessels constructed from glassware and tapered pyrex test tubes with screw tops and connections.‡ Typical reaction vessels were mounted on a motor-driven support to permit easy tilting to any desired angle, providing for transfer of reaction solutions from one vessel to another. The vessels were capped with Teflon-silicon discs through which disposable needles have been placed. These discs form a tight seal around the needle and provide a convenient means to introduce C-11-labeled carbon dioxide into the vessel, maintain a positive pressure in the vessel, and finally prevent spillage of the reaction mixture during transfer from one compartment to the other.

C-11-labeled diphenylmethanol was prepared in a three-neck flask. Two necks have screw tops that can be capped with Teflon-silicon disks and allow for entry or exit of materials from the reaction vessel. The other neck is attached to a special manifold that supports the reaction vessel in a vertical position and serves to connect the vessel to the exhaust exit.

Design of remote-controlled SEP-PAK filtering system. A remote-controlled SEP-PAK filtering system (Fig. 1) was designed and built to aid in the initial purification of the C-11-labeled compounds before purification by high-performance liquid chromatography (HPLC). The apparatus consists of three pneumatic pinch valves, a pneumatic plunger attached to a 12-ml sterile syringe, and an electric three-way valve (V6). One pneumatic pinch valve interrupts the flow of N_2 carrier gas in a section of sterile disposable tubing extending from the stainless steel coils used to initially trap the $^{11}CO_2$ to the reaction vessel. The other two pneumatic pinch valves are operated in sequence to ensure the unidirectional flow of solvent through the two previously unused and freshly activated SEP-PAK cartridges located immediately before and after the 12-ml sterile syringe. Finally, a solenoid three-way valve is used to direct the liquid flow to either the waste or product-collection vial.

General procedure for the synthesis of C-11-labeled methyl ethers. Recent publications have described the synthetic utility of generating alkoxide anions from alcohols in DMSO containing powdered potassium hydroxide (*16,17*). Modification of these procedures has enabled us to develop a general method for the synthesis of C-11-labeled ethers.

C-11-labeled carbon dioxide was produced by the $^{14}N(p,\alpha)^{11}C$ reaction. The gas was trapped in a stainless steel coil immersed in liquid N_2. The coil was removed from the liquid nitrogen and warmed by applying an AC through the coil. A mixture of C-11-labeled carbon dioxide and nitrogen carrier gas was slowly bubbled (6–10 ml/min) into 0.15 ml of 1.0 *M* LAH/EEE. (This procedure of trapping and subsequent bubbling of $^{11}CO_2$

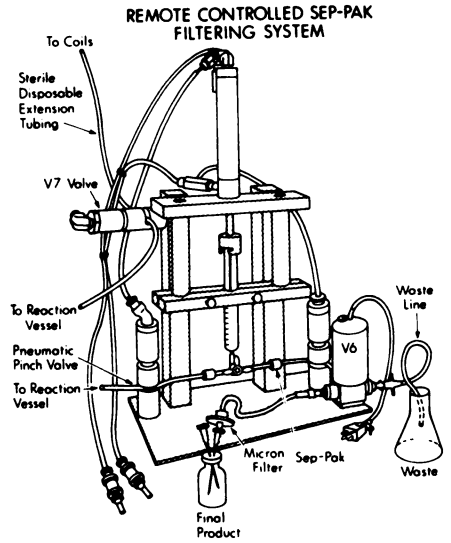

FIG. 1. Diagram of remote-controlled SEP-PAK filtering system used in initial purification of C-11-labeled compounds.

into suitable reactants was used in all of the C-11 preparations in this work). After stopping the gas flow, 0.2 ml of distilled water was added to decompose the lithium complex and form C-11-labeled methanol. Fifty microliters of the appropriate alkyl or benzyl chloride and 2.0 ml of DMSO were added to the reaction vessel, which was then rotated to allow the reaction mixture to flow into the second vessel containing 0.40 g of freshly powdered potassium hydroxide. After 8 to 10 min of stirring, 10 ml of 0.1 *N* HCl were added.

The reaction mixture was then drawn through two SEP-PAK cartridges placed in series (Fig. 1), where all the lipophilic compounds are retained. Following a rinse with 20 ml of H_2O to remove unreacted C-11-labeled methanol and other hydrophilic species, the lipophilic C-11-labeled ether was eluted from the SEP-PAK cartridges with 4.0 ml of 40% EtOH. The solution was filtered (0.22 μm, Millipore§) and purified by HPLC. A diagram of the total labeling procedure is shown in Fig. 2.

General synthesis of C-11-labeled alcohols. The method used to prepare C-11-labeled alcohols is similar to that reported in the literature (*5,18*). The C-11 CO_2 was bubbled (4 ml/min) through 2.0 ml of a 0.1 *M* solution of the appropriate Grignard reagent in diethyl ether, followed by addition of 0.2 ml of LAH/EEE. The solvent was evaporated and 6.0 ml of 1 *N* HCl added to decompose the lithium complex. The solution was then drawn through two SEP-PAK cartridges placed in series, the cartridges rinsed with 20 ml of H_2O, and the C-11-labeled alcohol then eluted using 2.0 ml of 95% EtOH. Isolation and purification were done by HPLC.

Synthesis of C-11-labeled benzyl hexyl ether. The preparation of C-11-labeled benzyl hexyl ether required the synthesis of C-11-labeled hexanoic acid, followed by the subsequent reduction of the C-11-labeled acid to a C-11-labeled alcohol using LAH.

The [1-^{11}C]hexanol was prepared by the general procedure for the carbon-11-labeled alcohols, except that after the acidic decomposition of the lithium salt, the alcohol was extracted into 5 ml of diethyl ether. This ether phase was transferred to a second reaction vessel containing 0.5 g of powdered potassium hydroxide, and the ether evaporated. Two milliliters of DMSO and 50 μl of benzyl bromide were added, and the mixture stirred for 10 min. The product was isolated by retention on SEP-PAK cartridges and elution with 3.5 ml of 95% ethanol, as previously described for the methyl ethers. Purification was by HPLC.

Synthesis of C-11-labeled benzophenone and triphenylmethanol. The C-11 CO_2 was bubbled into 2.0 ml of 0.2 *M* phenyl lithium (70% cyclohexane/30% diethyl ether). Two milliliters of H_2O and 4.0 ml of diethyl ether were added, and the mixture stirred for 3 min. The ether layer containing C-11-labeled benzophenone and C-11-labeled triphenylmethanol was transferred to a second vessel and the solvent evaporated. Ten ml of 30% EtOH were added to the vessel, and the mixture drawn through a SEP-PAK cartridge, which was rinsed with 20 ml of H_2O; the C-11-labeled products were then eluted with 2.5 ml of 95% EtOH. The ethanol eluant was diluted with 2.5 ml H_2O and the products isolated by HPLC.

Synthesis of C-11-labeled diphenylmethanol. Following the reaction of the C-11-carbon dioxide with 1.5 ml of phenyl lithium (70% cyclohexane/30% diethyl ether), 1.0 ml of 1 *N* LAH/diethyl ether was added, and the vessel shaken using a vortex mixer. The solvent was evaporated, 15 ml of 1 *N* HCl quickly added, and the vessel again shaken until all the lithium salts dissolved. The reaction mixture was drawn through two SEP-PAK cartridges, which were rinsed with 30 ml to 40 ml of H_2O, and the product then eluted with 2.5 ml of 95% ethanol. Following dilution with 2.5 ml of H_2O, the product was purified by HPLC. A diagram of the apparatus is shown in Fig. 3.

ANIMAL STUDIES

The fraction of the labeled test substances (C-11-labeled 1-butanol, 1-hexanol, 1-octanol, benzyl alcohol, benzyl methyl ether, butyl methyl ether, pentyl methyl ether, hexyl methyl ether, benzyl hexyl ether, diphenylmethanol, benzophenone and triphenylmethanol) extracted by the brain during a single capillary transit was determined in adult baboons. A 0.2 ml solution containing each test substance in an ethanol-saline mixture

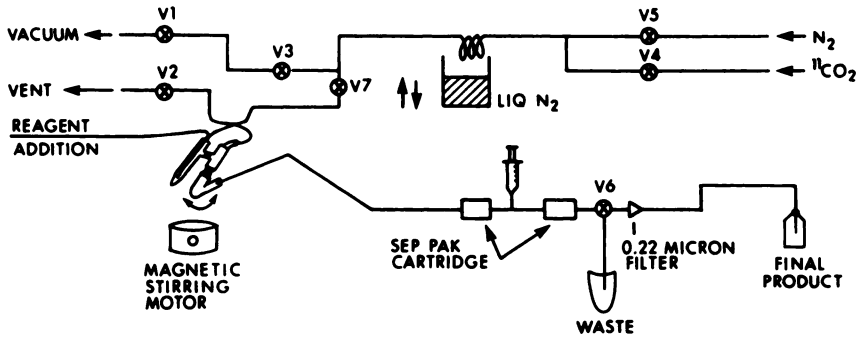

FIG. 2. Diagram of synthesis of C-11-labeled alcohols, ethers, and ketones.

was injected as a bolus into the internal carotid artery. At least two studies were carried out for each compound. A measurement of cerebral blood flow (CBF) accompanied each measurement of the extraction (E) of the test substance by utilizing residue detection of a bolus of 0-15-labeled water injected into the carotid artery (*5*).

Each experimental run consisted of the sequential injection of 0-15-labeled water and a C-11-labeled compound. This permitted the determination of the extraction (E) of the C-11-labeled compound for each run, as well as the cerebral blood flow (*5*). For each of the C-11-labeled compounds whose E was less than one, the E and CBF were measured at several different levels of arterial carbon dioxide tension (PCO_2). The pCO_2 was lowered by passive ventilation and raised by ventilation with a gas mixture of 90% oxygen and 10% carbon dioxide. A period of at least 15 min was allowed for the establishment of a steady state at each level of pCO_2.

To evaluate the effect of nonspecific binding of the C-11-labeled tracer to blood macromolecules (hemoglobin, albumin, etc.), a 0.1-ml sample of C-11-labeled 1-hexanol in 50% ethanol, a 0.1 ml sample of C-11-labeled diphenylmethanol in 55% ethanol, and 0.1 ml of C-11-labeled triphenylmethanol in 60% ethanol (obtained from the maximum of the radioactivity peak during HPLC purification of the reaction mixture) were each thoroughly mixed with 1.0 ml of whole blood from the baboon. The blood sample was then injected into the baboon as described above.

To evaluate the effect of the ethanol concentration in the injectate, a series of studies was conducted where the extraction of C-11-labeled triphenylmethanol was studied as a function of the percentage of ethanol in the injectate. Studies were conducted at 20% and 60% ethanol.

Partition coefficients. Whenever possible, partition coefficients reported in the literature were used in this study. In those few instances where no values were available, we calculated these values by the method of Hansch and co-workers (*19–21*). These calculations are greatly simplified, since none of the compounds studied is ionized at physiological pH, nor does any have a log P(oct) value dependent on pH. Many of the compounds studied belong to a homologous series, and the value for the contribution of the additional methylene substituent was taken to be 0.5 units.

Measurements and calculations. The fraction of labeled test substance extracted by the brain during a single capillary transit (E) was determined by a single-injection, external-registration technique developed by us for use in vivo with cyclotron-produced positron emitters (*12,22,23*). E is measured by graphically extrapolating the relatively slow clearance of the labeled test substance from brain tissue (B) back to the maximum of the perfusion peak (A) and computing the ratio

$$E = B/A \quad (1)$$

The cerebral blood flow was determined by utilizing the height/area residue detection (*24*) of a bolus of labeled water injected into the internal carotid artery. The time-activity curve for the washout of 0-15-labeled water from the brain was used to calculate the mean transit time of water $\bar{t}_{H_2O}$, which is defined as

$$\bar{t} = \frac{q(t)dt}{q_o}, \quad (2)$$

where q(t) is the radioactivity level in the region under study as a function of time, and q_0 is the dose of radioactivity in the injected bolus. The computed value of $\bar{t}_{H_2O}$ was combined with the central-volume principle (*24,25*)

$$\bar{t} = V/F, \quad (3)$$

where F is the volumetric flow rate of vascular fluid, and V is the volume of distribution of the tracer. The mean equilibrium brain-blood partition coefficient of water (λ_{H_2O}) is then used to yield the cerebral blood flow in milliliters per 100 g per min:

$$CBF = \frac{\lambda_{H_2O} \times 100}{\bar{t}}. \quad (4)$$

A value of 0.95 ml/g was used for λ_{H_2O}.

The extraction (E) of the C-11-labeled compounds was related to blood flow in terms of the model for the

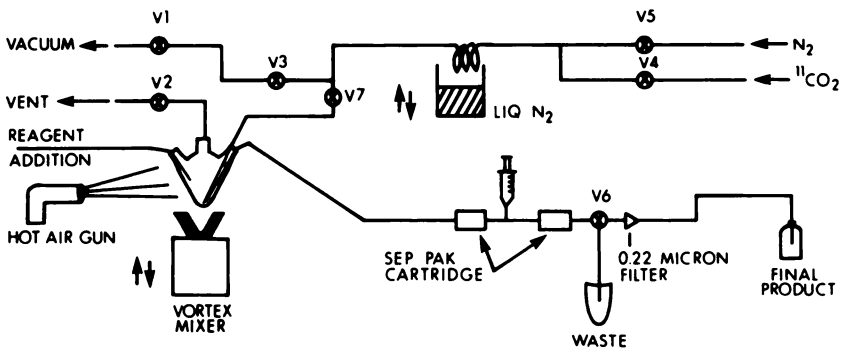

FIG. 3. Diagram of synthesis of C-11-labeled diphenylmethanol.

loss of diffusible substances from a single capillary, as proposed by Renkin (*26*) and Crone (*27*) and later developed for these studies in our laboratory (*5,21,23*). This model relates E to flow by

$$E = 1 - e^{-PS/F}, \quad (5)$$

where P is the permeability of the substance and S the surface area of the capillary bed. In the present application an *apparent* PS product was computed from the experimental data for each C-11-labeled compound, because the true P·S could not be obtained for compounds partially bound to plasma constituents. Using this *apparent* PS, we estimated the E for flows of 60 and 100 ml/(min·100 g) so that comparisons among the compounds could be made.

RESULTS

The data on C-11-labeled methanol, ethanol, and isopropanol have been reported by Raichle and coworkers (*5*).

Radiochemical yields (decay corrected), and the synthesis and purification times of the C-11-labeled compounds are given in Table 2. The reaction of C-11-labeled alcohols and alkyl or benzyl chlorides in the DMSO/KOH system is a general method for the preparation of C-11-labeled ethers, and although we have attempted to maximize yields, impurities were not identified but simply separated from the desired product. However, the DMSO/KOH system can tolerate only small amounts of water without a reduction in the radiochemical yields of the C-11-labeled ethers. The reaction of C-11-labeled CO_2 and phenyl lithium results in the production of a C-11-labeled dilithium salt intermediate [$C_6H_5{}^{11}C(OLi)_2C_6H_5$]. This intermediate can then be reduced directly to C-11-labeled diphenylmethanol via LAH, or alternatively the C-11-labeled intermediate can be hydrolyzed to liberate C-11-labeled benzophenone, which can then react with the excess phenyl lithium, resulting in the concurrent production of C-11-labeled triphenylmethanol.

The extraction data from the primate studies are given in Table 3, and in Table 4 are shown the log P(oct) values and calculated E_{60} and E_{100} values for the C-11-labeled compounds. Table 4 presents the calculated E_{60} and E_{100} values for C-11-labeled 1-hexanol, diphenylmethanol, and triphenylmethanol when mixed with blood before injection, or when injected in a 20% aqueous ethanol solution.

The extraction of C-11-labeled triphenylmethanol was shown to be independent of the percentage of ethanol in the injectate, which varied from 20% to 60%. The calculated E_{100} for C-11-labeled triphenylmethanol in 20% ethanol was 0.55 (n = 4). The calculated E_{100} for C-11-labeled triphenylmethanol in 60% ethanol was 0.51 (n = 3).

TABLE 2. ANALYSIS OF THE RADIOCHEMICAL LABELING OF C-11-LABELED ETHERS, ALCOHOLS, AND KETONES

C-11-labeled compound	Radiochemical yield % (decay corrected)	Synthesis and purification time (min)
Methyl butyl ether	17	40
Methyl pentyl ether	17	40
Methyl hexyl ether	13	40
Methyl benzyl ether	43	40
Hexyl benzyl ether	23	47
Diphenylmethanol	71	38
Benzophenone	21	40
Triphenylmethanol	31	45
1-Butanol, 1-hexanol, 1-octanol, benzyl alcohol	70–92	25–30

Figure 4 illustrates the parabolic relationship between the log P(oct) values and the calculated extraction of the C-11-labeled compounds by the brain at flows of 100 $ml \cdot min^{-1} \cdot hg^{-1}$. This flow rate was chosen as it is higher than any likely to be encountered in human studies.

DISCUSSION

A discussion about the experimental assumptions and conditions of this experimental model has been reported previously (*5*).

There exists a parabolic relationship between the log P(oct) of a C-11-labeled compound and its extraction by the brain. The low extraction of hydrophilic compounds by the brain has been attributed to the inability of the tracer to cross the lipid membrane of the blood-

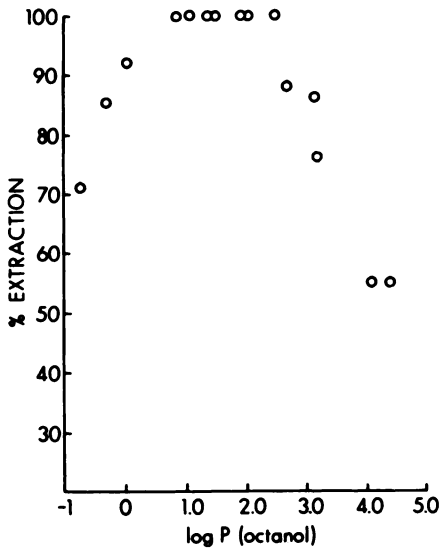

FIG. 4. Calculated extraction of the C-11-labeled compounds plotted against log P (octanol) of compound at CBF of 100 $ml \cdot min^{-1} \cdot hg^{-1}$.

brain barrier, but one would not expect this lipid membrane to be a barrier to lipophilic tracers (*5*). Instead, it is possible that the C-11-labeled tracer is in a form unsuitable for extraction by the brain (if bound to blood components or macromolecules such as red blood cells, albumin, etc.) during the time the compound circulates through the microcirculation of the brain. In our animal model, some mixing of the C-11-labeled compound and blood must occur as the tracer leaves the catheter in the common carotid artery and circulates through the brain. Laux and Raichle estimate this mixing to be 50% (*28*). We believe that if binding of the C-11-labeled compound to macromolecules is responsible for decreased extraction of highly lipophilic compounds, then mixing the C-11-labeled compound with blood before injection serves to maximize this amount of binding to macromolecules and results in further decreased extraction. The mixing of C-11-labeled hexanol (log P = 2.0) and C-11-labeled diphenylmethanol (log P = 2.7) with whole blood before injection did not change their extraction by the brain, indicating that no additional binding to blood macromolecules had resulted from the premixing. However, our results with C-11-labeled triphenylmethanol (log P = 4.4) demonstrate a significant decrease (25%) in the extraction of C-11-labeled triphenylmethanol when this compound was mixed with whole blood before injection.

For these results to be consistent with the argument that very lipophilic compounds are unable to cross the BBB as a result of binding to macromolecules, there must exist a linear relationship between the log P(oct) of a compound and its ability to bind to blood macromolecules, and that such binding of compounds begins to alter penetration of compounds across the BBB when the log P(oct) value of the compound is between 2.7 and 4.4. Support for this argument can be found from the work of Hansch and co-workers, who have reported that the binding of a wide variety of nonionic organic compounds of miscellaneous structure to both bovine serum albumin and bovine hemoglobin appears to depend almost entirely on hydrophobic bonding, and is linearly related to their octanol-water partition coefficients (*29*).

A parabolic relationship between the log P(oct) values of a compound and an observed biological response has been reported by Hansch and co-workers, who studied the structure-activity relationships of alcohols, ethers, barbiturates, ureas, and other miscellaneous compounds (*30–32*). They found that within a family of compounds the relationship between the value for log of the partition coefficient of the compound under study and the log of the observed biological response (log 1/C) for that compound, could best be described by the equation:

$$\log 1/C = -k(\log P)^2 + k' \log P + k''.$$

After obtaining the values of k, k′, and k″ by the method of least squares, they were able to calculate the value for

TABLE 3 EXTRACTION DATA FROM PRIMATE STUDIES. F_{H_2O} IS THE FLOW MEASURED USING $H_2{}^{15}O$, WHILE E_{CMPD} AND PS_{CMPD} ARE THE EXTRACTION AND PS PRODUCTS OF THE ^{11}C-LABELED COMPOUND

C-11-labeled compound	F_{H_2O}	E_{CMPD}	PS_{CMPD}
n-Butyl alcohol	100	1.00	—
	133	1.00	—
	151	1.00	—
	169	1.00	—
Benzyl alcohol	54	1.00	—
	65	1.00	—
Benzyl methyl ether	79	1.00	—
	101	1.00	—
	106	1.00	—
Butyl methyl ether	75	1.00	—
	117	1.00	—
1-Hexanol	60	1.00	—
	75	1.00	—
	86	1.00	—
	95	1.00	—
Pentyl methyl ether	52	1.00	—
	88	1.00	—
Hexyl methyl ether	96	1.00	—
	120	1.00	—
Diphenylmethanol	46	1.00	—
	57	1.00	—
	69	0.94	194
	72	0.90	166
	95	0.92	240
	126	0.88	267
	131	0.84	242
Benzophenone	45	0.96	145
	66	0.90	151
	67	0.87	136
	91	0.80	144
1-Octanol	66	0.88	140
	75	0.86	147
	93	0.93	247
	100	0.92	253
	104	0.91	250
Benzyl hexyl ether	58	0.76	83
	59	0.76	84
	91	0.51	65
	108	0.57	91
Triphenylmethanol	49	0.80	79
	65	0.62	63
	97	0.59	86
	132	0.42	77
	133	0.48	89

F_{H_2O} = Cerebral blood flow obtained from analysis of an extraction study with 0-15-labeled-water.
E_{CMPD} = Extraction of carbon-11-labeled compound.
PS_{CMPD} = Product of permeability of the carbon-11-labeled compound times surface area of capillary.

TABLE 4. CALCULATED EXTRACTION OF C-11-LABELED COMPOUNDS BY THE BRAIN AT CEREBRAL BLOOD FLOWS OF 60 AND 100 ml·min^{-1}·hg^{-1}

C-11 Compound	log $P_{(oct)}$	E_{100}†	E_{60}†
Methanol	−0.74	0.71 (±0.09)	0.87 (±0.06)
Ethanol	−0.32	0.85 (±0.03)	0.96 (±0.01)
Isopropanol	0.05	0.92 (±0.04)	0.98 (±0.02)
1-butanol	0.88	1.00	1.00
Benzyl alcohol	1.1	1.00	1.00
Benzyl methyl ether	1.4*	1.00	1.00
Butyl methyl ether	1.5*	1.00	1.00
1-hexanol	2.0	1.00	1.00
Pentyl methyl ether	2.0*	1.00	1.00
Hexyl methyl ether	2.5*	1.00	1.00
Diphenylmethanol	2.7	0.88 (±0.05)	0.97 (±0.02)
Benzophenone	3.2	0.76 (0.74–0.78)	0.91 (0.90–0.92)
1-octanol	3.2	0.86 (±0.09)	0.95 (±0.04)
Benzyl hexyl ether	4.1*	0.55 (0.48–0.60)	0.74 (0.68–0.78)
Triphenylmethanol	4.4*	0.55 (±0.05)	0.73 (±0.05)

* Calculated log P(oct) values.

† The mean and standard deviation were based on a minimum of five determinations of PS_{CMPD}; for benzophenone and benzyl hexyl ether, ranges are given.

the apex of the parabola by setting the derivative [d log (1/C)]/d log P = 0, and solving the resulting equation for log P. The value obtained, log P_o, represents the ideal lipophilic character for a series of compounds under specific test conditions. Hansch and co-workers have reported a log P_o value of 1.98 ± 0.35 from the study of the structure-activity relationship of 16 sets of hypnotics, eight of which were different sets of barbiturates, and eight were other hypnotics (*30,31,32*). Thus, Hansch and co-workers have stated that the ideal lipophilicity of neutral molecules for passive penetration into the central nervous system is log P_o = 2.0 ± 0.3 (*30–32*).

Support for Hansch's ideal lipophilicity can be found in the work of Soloway and co-workers, who measured the rate at which members of a set of benzeneboronic acids localized in mouse brain tissue following i.p. injection (*33*). In this study, brain concentrations of the benzeneboronic acids were determined by chemical analysis. Hansch has analyzed Soloway's data, and calculated a log P_o = 2.32 for the penetration of benzeneboronic acids into the brain. Our work indicates that nonionized C-11-labeled compounds with log P(oct) values ranging from 0.9 to 2.5 are completely extracted by the blood-brain barrier, and may therefore serve as

TABLE 5. CALCULATED EXTRACTION OF C-11-LABELED COMPOUNDS BY THE BRAIN WHEN MIXED WITH BLOOD OR AQUEOUS ETHANOL BEFORE INJECTION

C-11 compound	Injectate	E_{100}*	E_{60}*
1-hexanol	aq EtOH	1.00	1.00
1-hexanol	blood	1.00	1.00
Diphenylmethanol	aq EtOH	0.88 ± 0.05	0.97 ± 0.02
Diphenylmethanol	blood	0.90 ± 0.03	0.98 ± 0.01
Triphenylmethanol	aq EtOH	0.55 ± 0.05	0.73 ± 0.05
Triphenylmethanol	blood	0.41 ± 0.03	0.58 ± 0.03

* The mean and standard deviation were based on a minimum of five studies.

CBF agents.

The observation that very lipophilic compounds do not freely enter the brain will have a direct effect on the design of a myelin-imaging agent. Our data suggest that an ideal agent will have a log P(oct) value of approximately 2.5–2.7: in this range the lipophilicity is maximized but the tracer is still freely permeable across the BBB. Such a tracer will concentrate with time in the white matter as a result of its lipophilicity, and simultaneously serve as a CBF agent due to its free permeability across the BBB.

Loberg and co-workers (*9*), using the Oldendorf model, observed an increase in the brain permeability of certain Tc-99m complexes by increasing the percentage of methanol in the injectate. Our data did not reveal any alteration in the brain extraction of C-11-labeled triphenylmethanol when the percentage of ethanol in the injectate was varied from 20% to 60%. However, in the Oldendorf model the injectate has enough volume to displace the blood in the common carotid artery, and therefore enters the brain as a bolus nearly identical to that injected; whereas, in our model, the small volume injected (0.2 ml) must partially mix with the blood before entering the brain.

There has recently been great interest in the development of Tc-99m and Ga-68 complexes to serve as CBF agents (*9,10,13,34*). Our studies indicate that neutral complexes having log P(oct) values greater than 0.9 and lacking significant binding by blood macromolecules (similar to that of 1-hexanol) have the potential to be agents for the measurement of cerebral blood flow.

FOOTNOTES

* Waters Associates (Milford, Massachusetts).
† Whatman (Clifton, New Jersey).
‡ Wheaton Scientific (Millville, New Jersey).
§ Millipore Corporation (Bedford, Massachusetts).

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