Since all the ligands were as conformationally flexible as thyroxine, I can not claim to have determined the relative orientation of the two aromatic rings for the ligand as it lies in the site. In general, if the data set is limited in range of binding energies, conformational differences, and chemical structural differences, then necessarily the outcome of this method must be a limited picture of the site. As more information is added, even in the relatively obscure form of structure and binding energy, our image of the binding site must come into focus.

Acknowledgment. Preparation of Figure 2 was made possible by the generous help of Drs. Peter Kollman, Edgar Meyer, Jeff Blainey, and especially Stan Swanson.

Notes

Synthetic Enterobactin Analogues.[1] Carboxamido-2,3-dihydroxyterephthalate Conjugates of Spermine and Spermidine

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Two examples of a new class of synthetic polycatecholate ligands, the carboxamido-2,3-dihydroxyterephthalate conjugates of spermine (**8**) and of spermidine (**10**), have been synthesized via the generally useful synthon methyl-2,3-dimethoxyterephthaloyl chloride (**6**). Initial biological evaluation reveals tetrameric terephthalate (**8**) to be an extremely effective agent for sequestering and removing plutonium from mice; a single 25-μmol/kg (ip) dose of **8** removed 73% of the plutonium citrate previously injected (iv, 1 h earlier). Under the same conditions, trimeric terephthalate (**10**) excreted only 49% of injected plutonium. In vitro kinetic experiments have shown that **10** rapidly and quantitatively removed Fe from human transferrin. These results are discussed in relation to the design of metal-ion specific sequestering agents.

We have previously described two related research programs for the design and synthesis of specific sequestering agents for iron(III)[3,4] and actinide(IV) metal ions.[4-8] In the case of iron, since the body lacks any mechanism for removing excess amounts of this essential element, it can be an acute or chronic poison. A major program is underway for the development of iron chelating agents to be used in treating Cooley's anemia, a genetic disease which results in chronic iron overload.[9] Our ferric-ion chelating agents are modeled after the siderophores, a class of low-molecular-weight iron sequestering and transport agents that are produced by microbes. The most powerful natural iron chelator known is enterobactin.[10] Since this siderophore incorporates catechol chelating agents (in the form of 2,3-dihydroxybenzoyl groups, DHB), our initial approach has been the incorporation of several substituted DHB groups into multidentate chelate molecules.

Of the radioactive isotopes produced as byproducts of the nuclear fuel cycle, the major long-term radiation hazard is posed by the transuranium actinides. Of the actinides, plutonium is a particularly dangerous biological hazard because of the chemical and biological similarities of Pu(IV) and Fe(III).[11-14] Incorporated plutonium is bound by transferrin, the mammalian iron-transport protein, at the same site that normally binds Fe(III) and is then concentrated in iron storage sites, where most of it remains indefinitely. In order to prepare specific sequestering agents for Pu(IV) and other actinide ions, we have explicitly recognized this similarity of Pu(IV) and Fe(III) in using as chemical models the microbial chelating agents which are so specific for Fe(III).

As direct analogues of the siderophores such as enterobactin[10] and a threonine conjugate of spermidine isolated by Tait,[15] we have prepared tetrameric[5] and trimeric[16] 2,3-dihydroxybenzoyl conjugates incorporating certain linear, cyclic, and platform amines. Direct sulfonation of these compounds produced the 5-sulfonato-2,3-di-

(1) This is paper number 5 in the series "Ferric Ion Sequestering Agents", and also number 5 in the series "Specific Sequestering Agents for the Actinides". For previous papers in these series see ref 3 and 6, respectively.
(2) (a) Materials and Molecular Research Division, Lawrence Berkeley Laboratory. (b) Address correspondence to this author at the Department of Chemistry, University of California, Berkeley. (c) Biology and Medicine Division, Lawrence Berkeley Laboratory.
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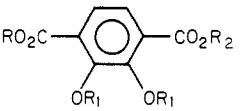
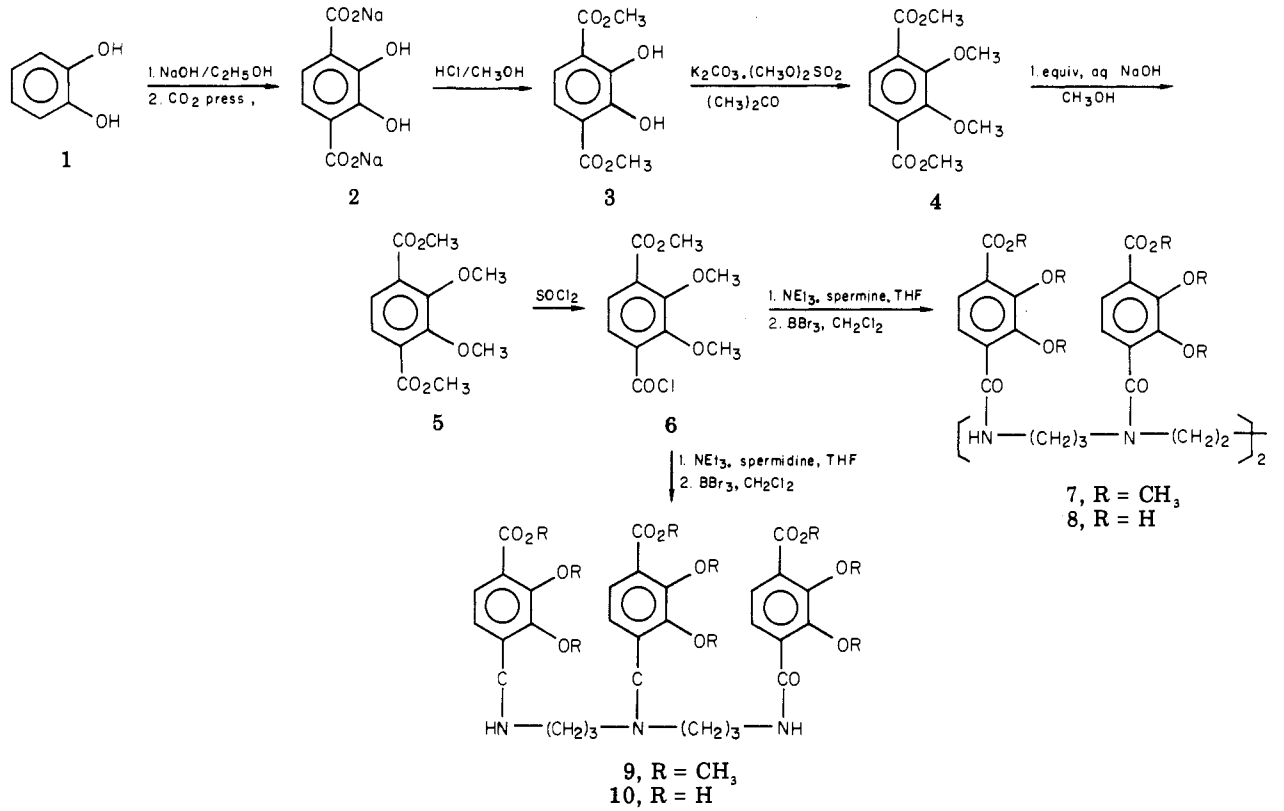
Table I. Monomeric 2,3-Dihydroxyterephthalic Acid Derivatives



no.	R	R_1	R_2	mp or bp (mm), °C	% yield	recrystn solvent	emp formula[a]
2	Na	H	Na	>300	24	H_2O	$C_8H_4O_6Na_2$
2a	H	H	H	289-290 dec[b]	35		$C_8H_6O_6$
3	CH_3	H	CH_3	141-143[c]	82	CH_3OH	$C_{10}H_{10}O_6$
4	CH_3	CH_3	CH_3	130 (0.4)[d]	68		$C_{12}H_{14}O_6$
5	CH_3	CH_3	Na	205-207	68	CH_3OH/acetone/ether	$C_{11}H_{11}O_6Na$
6	CH_3	CH_3	Cl	e	100	CCl_4	$C_{11}H_{11}O_6Cl$

[a] Analyses for C, H, and Na are within 0.4% of theoretical values. [b] Lit. mp 293 °C; see ref 20. [c] Lit. mp 145-146 °C; see ref 21. [d] Lit. bp 165 °C (0.5 mm) see ref 21. [e] Used as a crude, dry, crystalline solid without further purification; see Experimental Section.

Scheme I



hydroxybenzamide analogues.[3,17] These are potent sequestering agents for plutonium in vivo[6] and iron in vitro.[18] The sulfonated derivatives show high water solubility at any pH, improved resistance toward oxidation, and increased phenolic acidity; these properties make them better ligands under physiological conditions.

A most important property of any sequestering agent to be used in chelation therapy over long time periods is that it be orally active. Of the compounds tested to date, none of the effective sequestering agents for iron or the actinides have achieved this goal. Some promise was shown by the simple monomeric catechol derivative 2,3-dihydroxybenzoic acid, and it has undergone clinical tests in man.[19] The oral activity of this compound may be due to its dual acid–anion functionality. In addition, the ortho carboxylate group gives two possible modes of metal binding (catecholate or salicylate type) and these are pH dependent.[10]

Thus, the introduction of the 4-carboylate group might be expected to improve substantially the usefulness of the catechol sequestering agents. We now report the synthesis of the title compounds. These are the first examples of 4-carboxylate-catechoyl amides. As before, the tetrameric catecholate (8) was designed to satisfy the eight-coordinate geometry of a single Pu(IV) ion (the predominant in vivo oxidation state[11]) through the four pairs of phenolic oxygens. The related trimer (10) is potentially a six-coordinate catecholate ligand for Fe(III).

General Procedure. To achieve good water solubility in the catecholate ligands via the carboxylate moiety, the symmetrical 2,3-dihydroxyterephthalic acid was chosen as the monomeric unit. Thus, the dry disodium salt of catechol (1) was carboxylated according to a modified procedure of Cason and Dyke.[20] The dry disodium carboxylate derivative (2) provided crystalline dimethyl ester (3) upon refluxing with HCl/CH_3OH. Permethylation to ligand (4) was achieved with K_2CO_3/dimethyl sulfate in

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refluxing acetone. When a hot CH_3OH solution of **4** was treated with 1 equiv of 6 M NaOH overnight, a 70% yield of the monosodium salt (**5**) resulted. Neat $SOCl_2$ at 50 °C converted this compound directly to acid chloride (**6**), the necessary synthon for preparation of permethyl tetraamide **7** and permethyl triamide **9**. Demethylation with excess BBr_3 at room temperature provided the spermine (**8**) and spermidine (**10**) derivatives. Both were purified by acid–base precipitation and were dried over P_2O_5 under vacuum.

Experimental Section

Melting points were taken on a Buchi apparatus in open capillaries and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 283 instrument. Proton NMR spectra were recorded on a Varian A-60 instrument using Me_4Si or 3-(trimethylsilyl)-1-propanesulfonic acid, sodium salt, hydrate as internal standard. Evaporations were accomplished under vacuum (oil pump) with a Buchi Rotovapor-RE at ≤55 °C. Thin-layer chromatography (TLC) was performed on precoated 60F-254 silica gel sheets, developed in tetrahydrofuran/C_6H_{12}/H_2O (93:7:5) and visualized with UV, I_2 vapor, or Fe^{3+}/H_2O/EtOH spray. Column chromatography was performed using 60–200 mesh silica gel in a 35 × 2.5 cm o.d. column, and fractions were monitored by TLC. Microanalyses and mass spectra (*m/e*, 70 eV) were performed by Analytical Services, Chemistry Department, University of California, Berkeley. Both spermine (the amine component of **7** and **8**) and spermidine (the amine component of **9** and **10**) were purchased from Ames Laboratories, Inc., Milford, Conn. The BBr_3 used was a product of the Alfa Division of Ventron Corp., Danvers, Mass. All chemical analyses were within 0.4% of calculated values. Those elements analyzed appear after each empirical formula.

Disodium 2,3-Dihydroxyterephthalate (2). The procedure of Cason and Dyke[20] has been modified as follows: To catechol, **1** (33 g, 300 mmol), dissolved in 300 mL of CH_3OH (under argon atmosphere) was added at once NaOH pellets (24 g, 600 mmol). The resulting solution was allowed to sit overnight and was then evaporated in vacuo (105 °C, 48 h) to a light tan, dry powder, which was further treated with excess CO_2 (1100 psi) at 175–200 °C (48 h) in a static, stainless-steel bomb. The light tan solid product was acidified with hot aqueous 6 N HCl, filtered, and washed with hot H_2O. The solid product was dissolved in hot aqueous NaOH, (pH 9), treated twice with charcoal, and then cooled in an ice bath to obtain nearly white, crystalline **2** (17.6 g, 24%): mp >300 °C; ^{1}H NMR (D_2O) δ 7.45 (s, 2 H, Ar H). The remaining (basic) solution was acidified with aqueous HCl, to obtain nearly white **2a** (20.8 g, 35%): mp 289–90 °C;[20] ^{1}H NMR (Me_2SO) δ 7.42 (s, 2 H, Ar H). Anal. (**2**) ($C_8H_4O_6Na_2$) Na.

Dimethyl 2,3-Dihydroxyterephthalate (3). To a slurry of **2** (12.1 g, 58 mmol) in 150 mL of CH_3OH was added excess HCl via a gas-diffusion tube. After 60 h under reflux, the hot reaction mixture was filtered to remove NaCl. Ice-bath cooling provided white needles of **3** (10.7 g, 82%): mp 141–143 °C;[21] ^{1}H NMR (Me_2SO) δ 4.13 (s, 6 H, $-CO_2CH_3$), 7.36 (s, 2 H, Ar H).

Dimethyl 2,3-Dimethoxyterephthalate (4). The following materials were combined and kept at reflux (under argon) for 48 h: **3** (13.6 g, 60 mmol), K_2CO_3 (16.6 g, 120 mmol), dimethyl sulfate (11.4 mL, 120 mmol), and acetone (150 mL). Filtration while hot to remove salts, followed by distillation in vacuo, gave **4** (10.3 g, 68%): bp 130 °C (0.5 mm);[15] n^{22}_D 1.5156; ^{1}H NMR (CCl_4) δ 3.8–4.0 (2 s, 12 H, OCH_3 + CO_2CH_3), 7.49 (s, 2 H, Ar H).

Sodium Methyl 2,3-Dimethoxyterephthalate (5). To **4** (10.1 g, 40 mmol) in CH_3OH (200 mL) solution was added NaOH (1.6 g, 40 mmol) and H_2O (5 mL). The resulting solution was refluxed overnight and then concentrated in vacuo to about one-fourth volume. Addition of acetone (several volumes) to precipitate a small amount of disodium byproduct, followed by filtration, gave a clear colorless solution. Addition of ethyl ether (1–2 volumes) with scratching gave white microcrystalline **5** (7.1 g, 68%), which was dried at 75 °C (<1 mm): mp 205–207 °C; ^{1}H NMR (D_2O) δ 3.9–4.0 (2 s, 9 H, OCH_3 + CO_2CH_3), 7.30 (d, 1 H, J_{AB} = 9 Hz, Ar H), 7.70 (d, 1 H, J_{AB} = 9 Hz, Ar H). Anal. ($C_{11}H_{11}O_6Na$) C, H, Na.

Methyl 2,3-dimethoxyterephthaloyl Chloride (6). Compound **5** (6.5 g, 25 mmol) was added in portions to $SOCl_2$ (25 mL) with the evolution of SO_2 and heat. After the mixture was stirred overnight under a Drierite tube, an equal volume of CCl_4 was added and the mixture was filtered to remove NaCl. Coevaporation of this solution in vacuo with CCl_4 (3 × 30 mL) gave white, crystalline CCl_4-soluble **6** (~100%), which was satisfactory for immediate use in the synthesis of **7** and **9**.

***N,N′,N″,N‴*-Tetrakis[2,3-dimethoxy-4-(carbomethoxy)benzoyl]-1,5,10,14-tetraazatetradecane (7).** To crude, dry **6** (25 mmol) was added tetrahydrofuran (THF; 50 mL), spermine (1.2 g, 6.0 mmol), and NEt_3 (3.5 mL, 25 mmol). An immediate white precipitate formed, and the evolution of heat was evident. The reaction was allowed to stir overnight at ambient temperature in a stoppered flask. Filtration, THF wash, and then oven drying provided NEt_3·HCl (3.2 g, 97%). Evaporation of the THF solution in vacuo gave a viscous oil; this was dissolved in a small amount of $CHCl_3$ and then eluted from a silica gel column (initially with $CHCl_3$). The product was eluted with 2–4% CH_3OH in $CHCl_3$ (v/v): TLC R_f 0.63. Coevaporation (in vacuo) with CCl_4 (3 × 50 mL) gave a glassy solid, which when dried at 56 °C (5 μm), for 20 h gave **7**·$^2/_3CCl_4$ (6.2 g, 86%): IR (neat, NaCl) 3380 (CO*NH*), 2940 (CH), 1730 (*CO*$_2$CH$_3$), 1665–1625 (*CO*NR), 1520, 1455, 1400, 1305–1235, 1020, 755 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.2–2.2 (br m, 8 H, NCH$_2$*CH*$_2$), 3.0–4.1 (br m, 12 H, NC*H*$_2$CH$_2$), 2.8–4.2 (br s, 36 H, OC*H*$_3$ + CO$_2$C*H*$_3$), 6.8–7.9 (br m, 8 H, Ar H). Anal. ($C_{54}H_{66}N_4O_{20}$·$^2/_3CCl_4$) C, H, N.

***N,N′,N″*-Tris[2,3-dimethoxy-4-(carbomethoxy)benzoyl]-1,5,10-triazadecane (9).** Using the same procedure as for **7**, the following ingredients were combined: **6** (25 mmol), THF (50 mL), spermidine (1.2 g, 8 mmol), and NEt_3 (3.5 mL, 25 mmol). This resulted, after purification as before, in CCl_4-soluble **9**: TLC R_f 0.71. Coevaporation (in vacuo) with CCl_4 (3 × 50 mL) gave a glassy solid, which when dried (56 °C, 5 μm, 20 h) gave **9**·0.5 CCl_4 (6.5 g, 92%): IR (neat, NaCl) 3380 (CO*NH*), 2950 (CH), 1730 (*CO*$_2$CH$_3$), 1665–1630 (*CO*NR), 1525, 1455, 1400, 1300–1235, 1020, 755 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.2–2.2 (br m, 6 H, NCH$_2$*CH*$_2$), 3.0–4.1 (br m, 8 H, NC*H*$_2$), 3.8–4.2 (br s, 27 H, OC*H*$_3$ + CO$_2$C*H*$_3$), 6.8–8.0 (br m, 6 H, Ar H). Anal. ($C_{40}H_{49}N_3O_{15}$·0.5CCl_4) C, H, N.

***N,N′,N″,N‴*-Tetrakis(2,3-dihydroxy-4-carboxybenzoyl)-1,5,10,14-tetraazatetradecane (8).** Precursor **7** (6.0 g, 5.5 mmol) dissolved in CCl_4 (75 mL) was added dropwise via an addition funnel (under argon) to a CH_2Cl_2 (175 mL) solution of BBr_3 (7 mL, ~70 mmol), which was vigorously stirred (magnetic bar) and immersed in a room-temperature water bath. An immediate yellow precipitate formed with each drop. The reaction mixture was allowed to stir overnight. The dropwise addition of H_2O (75 mL) hydrolyzed the boron compounds. After 3–6 h hydrolysis time, a light tan solid was collected by filtration and washed well with H_2O. The crude product was slurried in H_2O (150 mL) and aqueous NaOH was added to achieve a pH ~7 solution, which was clarified by filtration through Celite. The addition of aqueous HCl gave a flocculent precipitate. This was collected by filtration, washed well with H_2O, and dried over P_2O_5 (in vacuo, room temperature, 48 h). Thus, an amorphous tan powder was obtained **8**·3H_2O (3.6 g, 67%): mp 230–240 °C (glass); IR (KBr) 3600–3300 (OH), 2600–2400 (COOH), 1675 (*CO*OH), 1605 (*CO*NH), 1450, 1320, 1225, 1175, 740 cm^{-1}; ^{1}H NMR (Me_2SO–D_2O) δ 1.5–2.5 (br m, 8 H, NCH$_2$*CH*$_2$), 3.3–4.3 (br m, 12 H, NC*H*$_2$), 7.0–8.0 (br m, 8 H, Ar H). Anal. ($C_{42}H_{42}N_4O_{20}$·3H_2O) C, H, N.

***N,N′,N″*-Tris(2,3-dihydroxy-4-carboxybenzoyl)-1,5,10-triazadecane (10).** Using the same procedure as for **8**, the following ingredients were combined: **9** (6.5 g, 8 mmol) dissolved in CCl_4 (75 mL) and BBr_3 (8 mL, 80 mmol) dissolved in CH_2Cl_2 (175 mL). Hydrolysis of the boron compounds, filtration, water wash, acid–base precipitation, and drying over P_2O_5 (as before) gave an amorphous tan powder, **10**·2.5H_2O (4.1 g, 71%): mp 235–45 °C dec; IR (KBr) 3600–3200 (OH), 2600–2400 (*CO*OH), 1680 (*CO*OH), 1610 (*CO*NR), 1455, 1325, 1230, 1180, 745 cm^{-1}; ^{1}H NMR (Me_2SO–D_2O) δ 1.2–2.2 (br m, 6 H, NCH$_2$*CH*$_2$), 3.1–4.2 (br m, 8 H, NC*H*$_2$), 7.1–7.7 (br m, 6 H, Ar H). Anal. ($C_{31}H_{31}N_3O_{15}$·2.5H_2O) C, H, N.

Biological Results and Discussion

The general procedures used have been described in detail elsewhere.[6] All solutions tested were isotonic in

(21) Dallacker, F.; Korb, W. *Liebigs Ann. Chem.* **1966**, *694*, 98–109.

saline at pH 7. Animal experiments were carried out on groups of five adult female mice (35 g), injected first with ^{238}Pu citrate (about 1.5 μCi/kg, iv), followed 1 h later by a single 20 to 30 μmol/kg of body weight (ip) dose of test compound. Radioactivity measurements (whole body counts) were made at injection and 24 h later. One group of mice received compound 8, another compound 10, and a control group isotonic saline. The counts showed 27, 51, and 94% retention of plutonium, respectively. Continued administration of ten daily injections of compound 8 for 14 days produced no grossly observable signs of toxicity.

These initial animal experiments indicate that the 4-carboxylate tetramer 8 is even more effective in promoting plutonium excretion than the corresponding 5-sulfonate derivative[17] (35% retention), which was previously tested and reported as the most effective compound to date.[6] There is also a strong correlation of the Pu removal capability and the number of substituted DHB groups in the molecule: the monomeric catechol carboxylate is ineffective as a Pu removal agent, a dimer has not been tested, and the trimer removes 49% and the tetramer removes 73%. These single-dose results are consistent with the hypothesis that a chelate able to provide an eight-coordinate metal ion environment will be most effective as a Pu(IV) removal agent.

It is also pertinent that the 4-CO_2^- substituent not only increases the solubility of these compounds but is potentially a ligating group as well, which is not true of the 5-SO_3^- groups of the previous compounds. Finally, a 0.2 mM solution of trimeric 10 removes Fe(III) from iron-saturated human transferrin with an apparent first-order rate constant of 2.1×10^{-3} min^{-1}, which is essentially the same rate as with enterobactin.[18] This shows that these carboxylate-substituted compounds are both kinetically and thermodynamically capable of removing iron from this iron-transport protein.

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Comparison of Solution Conformational Preferences for the Hallucinogens Bufotenin and Psilocin Using 360-MHz Proton NMR Spectroscopy

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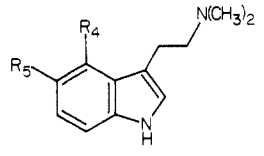
The 360-MHz ^1H NMR spectra of bufotenin and psilocin were obtained, both as the free bases in $CDCl_3$ and as protonated salts in D_2O. Coupling constants for the side-chain methylenes were derived using the LAOCN3 program. These time-averaged coupling constants indicate that the trans and gauche rotamers of both compounds have about equal energy in D_2O. There is a slight excess of the trans rotamer of bufotenin in $CDCl_3$. For psilocin, in contrast, the gauche form is highly favored in $CDCl_3$. The magnitude of this stabilization was estimated at about 1 kcal/mol using rotamer populations and free energy of transfer from published partitioning studies. It is suggested that this could result from a very weak hydrogen bond. On the other hand, the difference in partitioning between bufotenin and psilocin, which seems to be a major determinant of biological activity, is largely due to a difference in the basicity of the two compounds. The pK_a values for the amino group of psilocin and bufotenin were determined to be 8.47 and 9.67, respectively.

Bufotenin (I) and psilocin (II) are isomeric compounds



I, R_4 = H; R_5 = OH
II, R_4 = OH; R_5 = H

which are classified as hallucinogens. This classification seems unequivocal for psilocin.[1] Whether or not bufotenin is hallucinogenic is still a source of some dispute.[2] In any case, in man an oral dose of 100 mg of bufotenin was without effect, whereas 4–8 mg orally of psilocin elicits quite pronounced hallucinogenic intoxication.[3] The in vivo distribution of these two isomeric compounds also differs markedly. Although psilocin penetrates the CNS readily, Vogel[4] has reported that only small concentrations of bufotenin are detectable in the brain following intravenous administration. However, at the receptor bufotenin may actually possess quite high intrinsic activity. This has been pointed out by Vogel and Evans[5] and is supported by studies by Glennon and Gessner,[6] Lovell and Freedman,[7] Fillion et al.,[8] and others. In vitro serotonin receptor binding assays demonstrate that bufotenin possesses high affinity for the 5-HT receptor and potent serotonin-like activity.

Gessner et al.[9] suggest that the low potency for bufotenin following peripheral administration is due to low lipid solubility and consequent inability to penetrate into the central nervous system. This concept is supported by

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