a mechanism has much of the advantage of specific-acid catalysis but retains the essential feature of general-acid catalysis of being able to localize the proton. Complete proton transfer in the transition state has the advantage of full polarization of the carbonyl bond.[8] These results are much like the recent proposal[9] of late transition states for protonation in the concerted enzymatic general-acid-general-base catalysis of carbon acid enolization.

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Registry No. NADH, 58-68-4; NAD^+, 53-84-9; D-glyceraldehyde-3-phosphate dehydrogenase, 9028-92-6; lactate dehydrogenase, 9001-60-9; dihydrofolate reductase, 9002-03-3.

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Synthetic Sapphyrin-Cytosine Conjugates: Carriers for Selective Nucleotide Transport at Neutral pH

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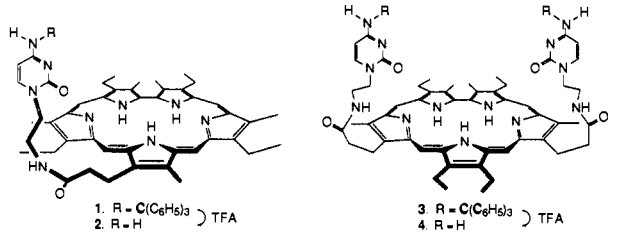
Anionic phosphorylated entities are ubiquitous in biology. They play a critical role in a variety of fundamental processes ranging from gene replication to energy transduction.[1] In addition, certain phosphate-bearing nucleotide analogues, such as, for example, 9-(β-D-*xylo*-furanosyl)guanine 5′-monophosphate (Xylo-GMP), are known to display antiviral activity in vitro.[2] Not surprisingly, therefore, in recent years, increasing effort has been devoted to the problem of phosphate recognition, and a number of elegant phosphate-binding receptors are now known.[3] In spite of this, we are unaware of any artificial entity that is capable of effecting the selective through-membrane transport of guanosine-derived mononucleotides (e.g., guanosine 5′-monophosphate, GMP) at neutral pH or making organic soluble these normally organic insoluble entities. We now wish to report the synthesis of a new cytosine-sapphyrin conjugate, **2**, that acts as a selective carrier for the through-membrane transport of GMP at neutral pH in an Aq I-CH_2Cl_2-Aq II (Aq = aqueous) model membrane system. We also wish to report the preparation of a related doubly substituted analogue **4**.[4]



In prior work, we reported that organic-solubilized, 2′,3′,5′-tris(triisopropylsilyl)-substituted nucleosides would enhance the through-CH_2Cl_2 transport of the corresponding Watson-Crick complementary phosphate-free nucleoside in a standard three-phase Aq I-CH_2Cl_2-Aq II liquid membrane cell.[5] We also reported that the diprotonated form of sapphyrin, a pentapyrrolic "expanded porphyrin",[6] acts as an efficient but nonselective carrier for nucleotide monophosphates at pH < 4.[7] More recently,[8] we have found that a combination of rubyrin, a hexapyrrolic homologue of sapphyrin that is more difficult to prepare,[9] and 2′,3′,5′-tris(triisopropylsilyl)-substituted cytidine (C-Tips) in large (ca. 100-fold) excess was able to effect the selective through-transport of GMP at neutral pH. However, sapphyrin, which remains monoprotonated in the ca. 3.5 ≤ pH ≤ 10 regime,[7,8] was itself found to be ineffective as a GMP carrier at pH 7, even in the presence of a large excess of C-Tips.[8] Thus, it was thought that if sapphyrin-based systems were to be made effective as neutral regime carriers for GMP, it would require the construction of polytopic receptor systems, such as **2** and **4**, in which cytosine-like recognition units are "appended" directly onto the phosphate-chelating expanded porphyrin core.

Receptors **2** and **4** were prepared by trifluoroacetic acid (TFA) induced detritylation of the protected conjugates **1** and **3**. These, in turn, were prepared by coupling 1-(2-aminoethyl)-4-[(triphenylmethyl)amino]pyrimidin-2-one[10] with the appropriate sapphyrin mono- or diacid chlorides.[11] Transport studies were then carried out using a standard[12] Aq I-CH_2Cl_2-Aq II liquid membrane cell.[13]

As can be seen from Table I, both **2** and **4** are able to effect the selective through-membrane transport of GMP at, or near, neutral pH.[14] Interestingly, in all cases, receptor **2** displays a higher selectivity for GMP (by a factor of 8-100 relative to either

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(13) Transport experiments were performed in a manner similar to that detailed in refs 5 and 7.

(14) Using our standard (ref 7) detection system, a quantitative analysis of uridine 5′-monophosphate (UMP) in Aq II could not be made. It has, therefore, been excluded from the present study. In qualitative control experiments, it was confirmed that carrier **2** caused no apparent increase in the rate of through-membrane UMP transport at pH 6.7.

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Table I. Initial Nucleotide Transport Rates (k_T) for Carriers **2** and **4**

carrier[a]	Aq I pH[b]	Aq II	(10^{-9} mol/cm^2·h)[c] k_T(CMP)	k_T(GMP)	k_T(AMP)	k_G/k_A	k_G/k_C
2	6.15	H_2O	0.12	12.0	1.57	7.6	100
2	7.05	H_2O	0.0005	0.011	0.001	11	22
2	6.70	10 mM NaOH	0.30	12.3	2.82	4.4	41
2	7.05	10 mM NaOH	0.16	7.08	0.74	9.6	44
4	6.15	H_2O	0.16	1.01	0.73	1.4	6.3
4	7.05	10 mM NaOH	0.049	1.15	0.36	3.2	24
none	6.15	H_2O	$<10^{-4}$	$<10^{-4}$	$<10^{-4}$	*d*	*d*
sap.[e]	7.0	10 mM NaOH	$<10^{-4}$	$<10^{-4}$	0.004		

[a] 0.1 mM in dichloromethane. [b] The source phase, Aq I, contained a 1:1:1 ratio of AMP, CMP, and GMP at a 10 mM concentration in each. The initial pH was adjusted by the careful addition of NaOH(aq). [c] Transport experiments were performed in a manner similar to those reported in refs 5 and 7. Values reported are the average of three independent measurements; estimated error <5%. [d] Not determined. [e] Control experiment using 3,8,12,13,17,22-hexaethyl-2,7,18,23-tetramethylsapphyrin (0.1 mM) as the putative carrier.

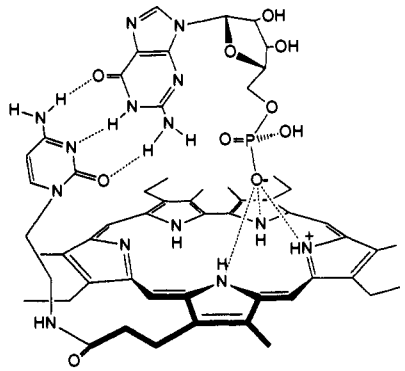

Figure 1. Possible structure for the proposed supramolecular complex formed between conjugate **2** and monobasic GMP.

AMP or CMP[14]) than its congener **4**. Further, better through-transport efficiency is always observed when the receiving phase (Aq II) is kept highly basic. Finally, a significant drop-off in efficiency, for both **2** and **4**, is observed as the initial pH of Aq I is increased from 6.15 to 7.05.

The above results are considered consistent with a model wherein complexation between the monoprotonated form of receptor **2** and the monobasic ($[ROPO_3H]^-$) form of GMP takes place at the Aq I–CH_2Cl_2 interface to produce a neutral, organic-soluble, supramolecular complex such as that depicted in Figure 1. This model, which is in accord with recent X-ray diffraction data,[15] provides a simple rationale for the experimental findings: First, decreased selectivity would be expected upon the introduction of "extra" cytosine-chelating subunits (as in, for example, **4**) since this would result in an increase in the number of possible hydrogen-bonding interactions and an incumbent loss in required substrate specificity. Second, higher through-transport rates would be observed in those cases where the receiving phase is kept basic since sapphyrin deprotonation and facilitated product release at the CH_2Cl_2–Aq II interface would necessarily be favored. Finally, a decrease in the through-transport rate is predicted since a lower concentration of the putative substrate, monobasic GMP (the $[ROPO_3H]^-$ form) in Aq I, would be expected as the second phosphate-centered ionization constant of GMP (pK_a = ca. 6.7[16]) is first approached and then surpassed.[17] That some transport occurs even at pH 7.05 is thus considered a reflection of the fact that, under the conditions of the experiment, binding of monobasic GMP is enhanced relative to that of the dibasic ($[ROPO_3]^{2-}$) form and that this binding enhancement, in turn, serves to augment the effective concentration of this monanionic (and hence readily neutralizable) species in the organic membrane phase.[17]

Although the model of Figure 1 is by no means proved, it is clear from the present study that the transport of a normally organic-insoluble species, namely GMP, can be effected by preparing and using an appropriate nucleobase-expanded porphyrin conjugate. This leads us to suggest that a similar designed receptor approach could be used to achieve the into-cell delivery of Xylo-GMP and other nucleotide drugs in vivo. We are currently exploring this possibility.

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Supplementary Material Available: Listings of synthetic experimental data and time plots for nucleotide transport studies (13 pages). Ordering information is given on any current masthead page.

(15) The 2:1 complex formed between monobasic phenyl phosphate and diprotonated sapphyrin has been analyzed in the solid state by X-ray diffraction. One phenyl phosphate is bound on the "top" face of the macrocycle to each of three pyrroles, while the other phosphate is bound to two pyrroles on the "bottom" side. Furuta, H.; Sessler, J. L.; Lynch, V. Unpublished results.

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(17) Charge neutralization as a requirement for efficient carrier-mediated transport is known as Fick's first law. See ref 12, p 78.

1,5- and 1,9-Hydrogen Atom Abstractions. Photochemical Strategies for Radical Cyclizations

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The use of radical reactions in organic synthesis is now well established.[1] Current topics of research in radical chemistry include the development of nonreductive radical cyclization reactions,[2] the study of acyclic stereochemical control in radical reactions,[3] and the development of new methods for the generation of radicals.[4] Although the reaction of halides or selenides with tributylstannyl radicals is still the predominantly used method for generating radicals, the expense, toxicity, and operational difficulties associated with the organotin reagents have prompted the evaluation of alternate methods. Photochemistry has long been used to generate biradical intermediates; however, few of these reactive biradicals are useful in the generation of new radicals. Notable exceptions include the biradicals derived from benzophenones and certain quinones, which undergo efficient intermolecular hydrogen atom abstraction reactions.[5] The trapping of 1,4-biradicals (whose short lifetimes necessitate intramolecular

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