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Paley's watchmaker analogy and prebiotic synthetic chemistry in surfactant assemblies. Formaldehyde scavenging by pyrroles leading to porphyrins as a case study†

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The formation of elaborate molecules is regarded as an essential first step in prebiotic chemistry, but how such transformations could spontaneously occur, particularly in dilute aqueous conditions, remains poorly understood. Here, micromolar concentrations of a 3,4-dialkylpyrrole and excess formaldehyde in aqueous micellar solution (pH 7) at 25 or 50 °C were found to give good yield (up to 40%) of the lipophilic octaalkylporphyrin. The reaction occurs despite a mean occupancy number of ~0.1 pyrrole molecules/micelle, and <1 of 10 000 micelles initially containing the requisite 4 pyrrole molecules to form the porphyrin assuming a (random) Poisson distribution. Yields of up to 13% were observed in large, unilamellar phosphatidylcholine vesicles, wherein there are ~15 000 pyrrole molecules per vesicle membrane. Double-labeling crossover experiments (of 3,4-diethylpyrrole and 3,4-dimethylpyrrole) examined by mass spectrometry revealed facile exchange processes of reactive constituents among both micelle and vesicle surfactant assemblies. Together, the exchange of pyrrolic reactants among micelles and the thermodynamic driving force for tetrapyrrole formation overcome the apparent statistical odds against reaction. The fruitful exchange, accumulation and reaction of minute quantities of reactants in aqueous-surfactant assemblies suggest a general means for formation of prebiotically valuable constituents, even when the statistical odds at the outset are overwhelmingly improbable.

Introduction

Paley's watchmaker analogy,[1,2] which dates to the turn of the 19th century, expresses the statistical improbability of the spontaneous origin of life – in particular, that the formation of valuable constituents and their accumulation to afford an organized functional ensemble are not expected to occur by chance. Concerning the formation of valuable constituents, a large body of work beginning with the Miller–Urey experiment in the 1950s has identified structure-directed reactions that yield plausible prebiotic reactants (amino acids, sugars, surfactants, nucleic acid bases, *etc.*). Considerably less success has been achieved in the formation of organized assemblies of diverse molecules, which is necessary to generate a functional protocell.[3] Regardless, many studies in prebiotic chemistry concern reactions at very high concentrations, yet the concentration of dissolved organic compounds in the ocean of early Earth has been suggested to be <1 mM.[4] Methods of concentration have been proposed,[5] yet experimental implementation appears to be rare.

Our interests in chemical models for the origin of photosynthetic pigments[6–10] have led to examination of reactions in surfactant media, where hydrophobic reactants and products are expected to accumulate. Two recent reports bear on the studies reported herein. First, Cleaves described a host of fruitful reactions of formaldehyde, a plausible prebiotic reactant.[11] Second, Fox and Strasdeit described the formation of numerous alkylpyrroles, albeit in trace quantities, by thermolysis of amino acids in aqueous solution.[12] While the reaction of formaldehyde with a 3,4-dialkylpyrrole is a well-known path to an octaalkylporphyrin (Scheme 1),[13–15] the conditions in the synthesis lab employ strong acids and high concentrations. *meso*-Tetraarylporphyrins have been prepared in aqueous-surfactant media, but again in the presence of strong acids and concentrations of 4 mM (ref. 16) or 10 mM.[17] By contrast, our interest was in examining octaalkylporphyrin formation under neutral conditions with tiny (10s of μM) concentrations of the pyrrole, more representative of what might be expected under prebiotic conditions. Given the lipophilic nature of such porphyrins,[18]

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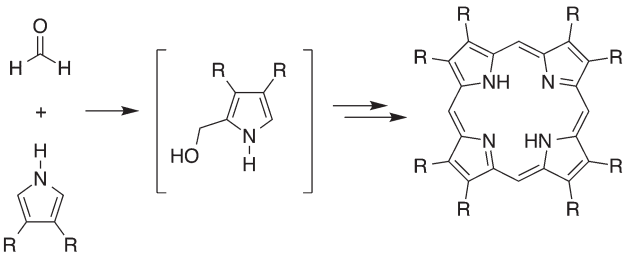


Scheme 1 Formaldehyde scavenging by a 3,4-dialkylpyrrole leads to the porphyrin.

and the fact that extant photosynthetic machinery is localized in membranes, the reactions were carried out in aqueous-surfactant assemblies. Here, we report results concerning formation of octaalkylporphyrins from pyrroles and formaldehyde, and in so doing reveal facile reactant exchange processes among aqueous micelles and vesicles. The facile exchange provides a path for reaction despite the initial odds, which would appear to doom the reaction altogether.

Experimental section

General features

Micellar experiments were conducted with 30 mM cetyltrimethylammonium chloride (CTAC) or sodium dodecyl sulfate (SDS) as the surfactant and 0.3 M potassium phosphate (pH 7) buffer. Stock solutions of 3,4-diethylpyrrole (**1-Et**, in methanol), 3,4-dimethylpyrrole (**1-Me**, in methanol) and formaldehyde (in water) were prepared and used each week. The stock concentrations of the pyrroles varied so that only 25 μL of a stock solution was added to a reaction vial, thereby ensuring that the amount of methanol in each reaction was constant and low. The pyrrole stocks were stored at −15 °C, and the formaldehyde stocks at 4 °C. All materials were obtained from commercial sources.

Representative procedure

The following stock solutions were prepared: (1) **1-Et** in methanol (0.80 mM), (2) formaldehyde in deionized water (80 mM), and (3) CTAC (50 mM) in 0.5 M potassium phosphate buffer (pH 7). A 3 mL reaction vial was charged with 25 μL of the 0.80 mM **1-Et** solution, 1200 μL of the 50 mM CTAC solution, and 750 μL of deionized water. The resulting mixture was stirred for 1 min, and then treated with 25 μL of the 80 mM formaldehyde solution. The total reaction volume was 2000 μL, with corresponding **1-Et** and formaldehyde concentrations of 0.010 mM and 1.0 mM, respectively. The vial was sealed (a syringe needle pierced the cap to ensure no pressure build-up), placed in a heating block held at 25 °C, and stirred for 24 h under aerobic conditions. Any solvent loss was typically <2% of the total. Upon completion of the reaction, the entire contents of the vial were transferred to a 1 cm pathlength cuvette, and the porphyrin yield was obtained *via* absorption spectroscopy as described in the next section. Spreadsheets for sets of analogous reactions are provided in Tables S1 and S2.†

Porphyrin yield determination

Porphyrin yields were determined by absorption spectroscopy from the intensity of the Soret band with manual subtraction of the non-porphyrin background.[19] The net absorption value was used to calculate the porphyrin concentration in the reaction mixture *via* Beer's law, using $\varepsilon_{\text{Soret}} = 159\,000\ \text{M}^{-1}\ \text{cm}^{-1}$ in all cases.[15] The entire reaction mixture was either placed directly in the cuvette for yield determination or diluted if needed to achieve a more suitable concentration. For reactions in micelles, such dilutions were carried out in a larger quantity of the same aqueous buffer-micellar medium. For reactions in vesicles, disruption of the vesicles (to avoid light-scattering) was achieved by addition of excess SDS accompanied by brief sonication (benchtop sonication bath). The amount of added SDS varied across reactions – the typical procedure entailed addition of 200 μL of 300 mM SDS solution followed by sonication, with the process repeated as necessary until an optically clear solution was obtained.

For many porphyrin-forming reactions, an oxidant (*e.g.*, I_2, *p*-chloranil, DDQ, air) is required to convert the porphyrinogen (or other hydroporphyrins) to the porphyrin.[19] Here, the porphyrin formed without added oxidant (indeed, treatment with I_2/ethanol gave no increase in yield), regardless if the reaction was carried out under an inert atmosphere; hence an explicit oxidation step was omitted. In those reactions where the yield of porphyrin was 0%, treatment with I_2/ethanol[6] was performed to insure that any macrocycles were not missed, but again, in no case was porphyrin observed. The porphyrin was further characterized by fluorescence (emission, excitation) spectroscopy and MALDI-MS.

Preparation of lipid vesicles

Large, unilamellar vesicles (diameter ~106 nm) of L-α-phosphatidylcholine (PC) were prepared by extrusion[7,20] to give a 65 mM suspension that was diluted into 0.1 M potassium phosphate buffer (pH 7) to give the desired concentration of vesicles for reactions (see the ESI for a full description and Fig. S1†).

Double-labeling crossover experiment

Four stock solutions were prepared: (1) 4 mM **1-Et** in methanol, (2) 4 mM **1-Me** in methanol, (3) 200 mM formaldehyde in deionized water, and (4) 50 mM SDS in 0.5 M phosphate buffer (pH 7). In a "pre-mixed" control experiment, a vial containing 1500 μL of the SDS solution and 913 μL of deionized water was treated with 14.5 μL of each pyrrole solution, such that the combined concentration of **1-Et** and **1-Me** was 0.046 mM. The contents of the vial were stirred for 5 min, then treated with 58 μL of the formaldehyde stock solution. The resulting mixture was stirred at 25 °C for 24 h. For the double-labeling crossover ("post-mixed") experiment, two separate vials

containing 1500 μL of the SDS solution and 913 μL of deionized water were treated with 29 μL of only one of the pyrrole stocks, such that one vial contained 0.046 mM **1-Me** only and the other contained 0.046 mM **1-Et** only. These two vials were stirred for 5 min, and subsequently mixed 0.5 : 0.5 into a third vial such that the total volume was 2442 μL. This third vial was treated immediately with 58 μL of the formaldehyde stock solution to initiate the reaction, and the mixture was stirred at 25 °C for 24 h. Yield determination was achieved by absorption spectroscopy. For MALDI-MS analysis, a vial was extracted twice with 2 mL of diethyl ether, the ether extract was concentrated with a stream of argon, and the concentrate was spotted on the matrix 1,4-bis(5-phenyloxazol-2-yl)benzene (POPOP).

Calculations concerning micelles and vesicles

The concentration of micelles is given by eqn (1),

$$[\text{micelles}] = ([\text{surfactant}] - \text{cmc})/N_{\text{agg}} \quad (1)$$

where N_{agg} is the surfactant aggregation number and cmc is the critical micelle concentration.[21] For SDS, the cmc is reported to be 8 mM (but can range as low as 1 mM in the presence of high concentrations of ions);[22] N_{agg} ranges from ~55–120 depending on salt concentration.[23,24] For CTAC, the cmc is reported to be 1 mM (but also can be lower); N_{agg} ranges from 70–90 [25] (although higher values have been reported).[26,27] Upper and lower limits of values for N_{agg} (50–100) and the cmc (1–10 mM) were used to bracket the expected range of concentration of micelles. For 30 mM surfactant, the result is 0.20–0.58 mM spherical micelles. This range is employed with the pyrrole concentration to give the mean occupancy number, m. Note that a lower value of N_{agg} gives an increase in number of micelles and hence a lower value for m.

Calculated partition coefficients

Organic-aqueous partitioning coefficients ($\log P$ values) were calculated for various diethyl-substituted saturated species (*e.g.*, pyrrole, pyrrole–carbinol, dipyrromethane–carbinol, porphyrinogen) and unsaturated species (*e.g.*, dipyrrin–carbinol, porphyrin) using ChemBioDraw (version 13.0.2.3020).

Results

Reactions in micelles

The reaction of pyrrole **1-Et** and formaldehyde was carried out in an aqueous micellar solution of CTAC or SDS. Formation of the resulting octaethylporphyrin (**Et_8P**) could be monitored directly without treatment by an added oxidant (formaldehyde may serve as an *in situ* oxidant), thereby facilitating absorption spectrometric yield determination. The porphyrin gave fluorescence spectra[28] (Fig. S2–S5†) nearly identical with that of an authentic sample in a hydrocarbon solvent, as well as characteristic mass spectral data.

The timecourse was examined for reactions at selected concentrations in CTAC or SDS micelles. The results for 0.046 mM pyrrole and 100 equiv. of formaldehyde at 25 or 50 °C are shown in Fig. 1. The yields were substantially higher with SDS than CTAC at both temperatures. The reactions at 50 °C were faster than at 25 °C ($t_{1/2}$ = 1 or 2.5 h *versus* 8 or 19 h, respectively), as expected; regardless, under both conditions the reactions were essentially complete at 24 h. The reaction with 1000 equiv. of formaldehyde was faster than that with 100 equiv., yet the ultimate yield of porphyrin was essentially the same for the two conditions (Fig. S6†). The reaction trajectories mirror those of many aldehyde–pyrrole condensations leading to porphyrins.[29,30]

To assess the robustness of the reaction conditions, a broad range of concentrations was examined. A suitable concentration grid for the reaction of various ratios of 3,4-diethylpyrrole (**1-Et**) to formaldehyde was found to encompass 0.01 mM–1.0 mM of the pyrrole and varying equivalents (1, 10, 100, or 1000) of formaldehyde (points requiring >100 mM formaldehyde were omitted). All reactions were carried out at 25 °C for 24 h. The results are displayed in Fig. 2. The yields at 24 h, while not necessarily the maximum during the overall reaction trajectory in every case, provide a reasonable measure. The significant yield of porphyrin despite the very low concentration of pyrrole is a striking finding. Indeed, the highest yielding reactions occurred with concentrations approximately 100-fold less than that for a comparable porphyrin-forming reaction in an organic solvent.[19] It is noteworthy that the reaction at 0.046 mM **1-Et** affords 15% or 35% yield of porphyrin (CTAC or SDS micelles, respectively), which corresponds to 1.7 or 4.1 μM porphyrin. Given that the concentration of surfactant (30 mM) affords a micelle concentration of 0.20–0.58 mM, a yield of 35% corresponds to ~1 porphyrin per 50–140 micelles. Differences in reaction rates in cationic *versus* anionic micelles are well known and can stem from a variety of factors,[31] the delineation of which is beyond the scope of the present paper.

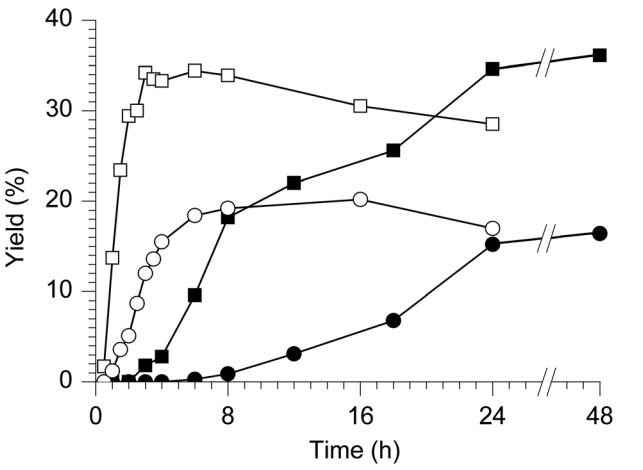


Fig. 1 Yield of porphyrin Et_8P *versus* time for 0.046 mM **1-Et** and 100 equiv. of formaldehyde in aqueous micelles: SDS at 25 °C (solid squares) or 50 °C (open squares); CTAC at 25 °C (solid circles) or 50 °C (open circles).

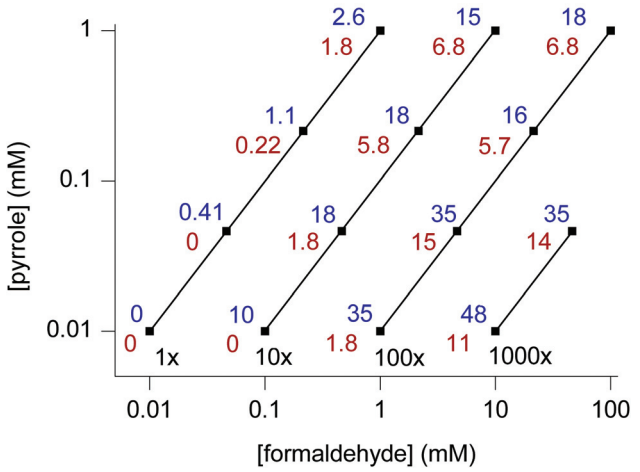
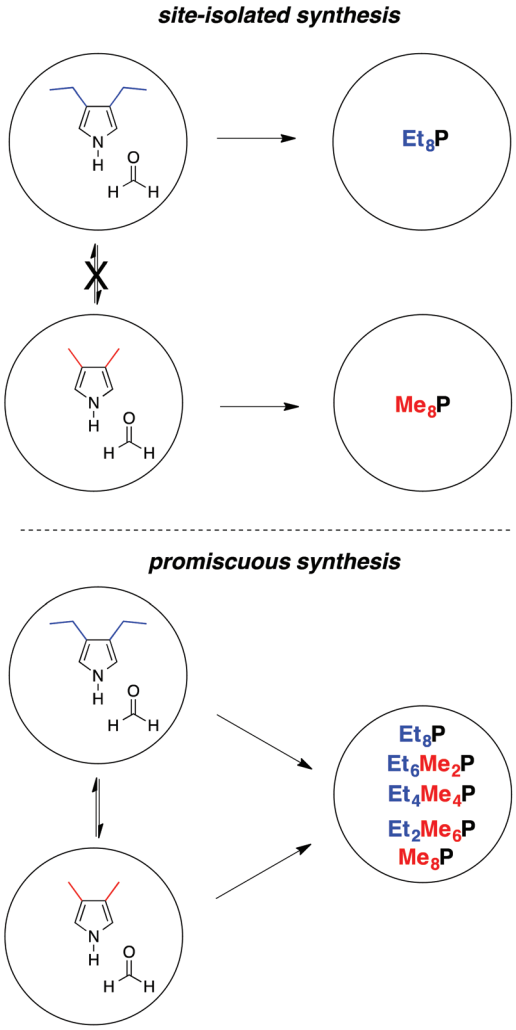


Fig. 2 Yield of porphyrin Et_8P over a 100-fold range of pyrrole **1-Et** concentration with 1–1000 equiv. of formaldehyde at 25 °C in aqueous micelles (pH 7) of CTAC (red, lower numbers) or SDS (blue, upper numbers) after 24 h. The ratio of [pyrrole]/[formaldehyde] is given at the base of each ratio line.

Several additional experiments were carried out to explore the role of micelles. (1) Micelles convert from spherical to rodlike in aqueous media at very high ionic strength.[32,33] While the ionic strength of the 0.3 M phosphate buffer employed herein was far below that for such a change in morphology, we carried out reactions of **1-Et** at even lower ionic strength (no phosphate buffer). Thus, the reaction of **1-Et** (0.046 mM, 24 h, 25 °C) with 100 equiv. of formaldehyde in the presence of 50 mM SDS containing NaCl at 20 or 100 mM gave Et_8P in 43% or 37% yield, respectively. (2) When SDS or CTAC was omitted altogether (25 °C, 24 h) from the reaction, no porphyrin was detected. These results are consistent with reaction occurring in small, spherical micelles.

To assess possible exchange processes among surfactant assemblies, double-labeling crossover experiments were performed. For this study, we first examined the reactivity of 3,4-dimethylpyrrole (**1-Me**). The reaction of **1-Me** at 0.046 mM and 100 equiv. of formaldehyde at 25 °C in SDS micelles gave octamethylporphyrin (Me_8P) in 23% yield. For the crossover experiment, SDS micelles were separately treated with the respective pyrrole (**1-Me** *versus* **1-Et**), then mixed ("post-mixed"), treated with formaldehyde, and allowed to react (Scheme 2). A control ("pre-mixed") experiment entailed adding the two pyrroles together to the surfactant followed by formaldehyde. After 24 h, examination of the pre-mixed reaction mixture in micelles revealed a porphyrin yield of 39%. Mass spectral analysis of the pre-mixed reaction mixture revealed the presence of Et_8P (m/z = 534.3) and Me_8P (422.2) in addition to the products Et_6Me_2P (506.3), Et_4Me_4P (478.3), and Et_2Me_6P (450.3), in agreement with calculated values for the porphyrin cation radicals. The post-mixed reaction mixture gave essentially identical yield (37%) and distribution of species upon MALDI-MS analysis. The mass spectral data for the reaction in SDS micelles are shown in Fig. 3. Similar data were obtained



Scheme 2 Distinct models for reactions in micelles.

upon crossover experiments in CTAC micelles, or in SDS micelles with 20 or 100 mM concentrations of NaCl (Fig. S7–S9†). While quantitative analysis of the mass spectral data is not possible given uncertainty about ionization efficiencies of the porphyrin products of exchange, the data from the double-labeling crossover experiment qualitatively are consistent with promiscuous if not exhaustive exchange of constituents in the micelles on the timescale of the synthesis.

Reactions in vesicles

Reactions in vesicles were examined as a counterpoint to the studies in micelles. Whereas dilution of micelles below the cmc results in disassembly of the micelle, vesicles remain intact upon dilution. Unilamellar PC vesicles (~100 nm diameter) in aqueous solution (pH 7) were diluted to 30, 3, 0.3 and 0.03 mM of PC. On the assumption of $\sim 10^5$ molecules of PC per vesicle,[20] the concentration of vesicles was ~300, ~30, ~3 and ~0.3 nM. Reactions were carried out at 25 °C upon addition of **1-Et** (0.046 mM) and 100 equiv. of formaldehyde.

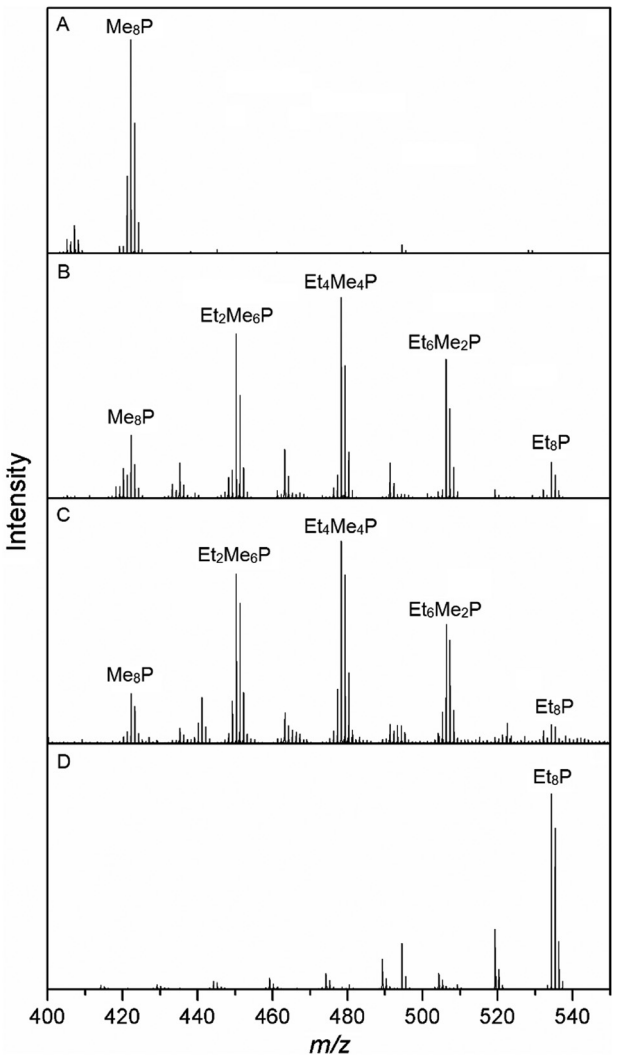


Fig. 3 MALDI-MS spectra for crossover experiment in 30 mM SDS at 25 °C. Panels A, B, C, and D correspond to **1-Me** only (absorption spectroscopic yield = 23%), pre-mix control (39%), post-mix (37%), and **1-Et** only (35%), respectively.

Table 1 Porphyrin formation in PC vesicles[a]

[PC] (mM)	PC/pyrrole (**1-Et**)	Pyrrole/ vesicle	Yield (%)
30	650	150	0
3.0	65	1500	7.0
0.30	6.5	15 000	13
0.030	0.65	150 000	0

[a] Reactions employed 0.046 mM **1-Et** and 4.6 mM formaldehyde at 25 °C for 24 h.

The yields for the reactions after 24 h are given in Table 1. A double-labeling crossover experiment with **1-Et** and **1-Me** in vesicles, analogous to that in micelles, also gave complete exchange (Fig. S10†).

Discussion

There are numerous remarkable features of the results reported herein, including that (1) a 3,4-dialkylpyrrole is an exceptionally potent scavenger of formaldehyde, perhaps more so than many of the proposed prebiotic reactants;[11] (2) the reaction proceeds smoothly at neutral pH and modest temperature; (3) 8 reactant molecules combine, 8 C–C bonds form and a $6e^-/6H^+$ dehydrogenation occurs with overall yield of up to 40%; (4) the reaction proceeds in the presence of cationic or anionic surfactants; and (5) the process occurs with a very low concentration (10–50 μM) of the pyrrole. While each of these features is noteworthy, we focus here on the latter point – in particular, how can the successful formation of a porphyrin at such low concentrations of the pyrrole be understood?

The concentrating effect and rate acceleration of surfactant assemblies on organic constituents is well known.[34–36] Yet, micelles and vesicles are fundamentally different. While each vesicle contains ~10^5 surfactant molecules and a large number of pyrrole molecules is contained in the vesicle membrane, each micelle contains ~50–100 surfactant molecules. Accordingly, there is insufficient pyrrole to fill all of the micelles – indeed, most micelles are empty.

The Poisson equation (eqn (2))[37] can be used to describe the random distribution of molecular species (*e.g.*, pyrrole) in a surfactant assembly, and is relevant here to the reactions in micelles. Thus, m is the mean occupancy number of pyrrole molecules per micelle, and k takes on integer values for the number of pyrroles per micelle (k = 0, 1, 2...).

$$P(x = k) = m^k e^{-m}/k! \quad (2)$$

The mean occupancy number varies depending on the concentration of micelles (0.20–0.58 mM, for surfactant concentrations of 30 mM and a cmc ranging from 1–10 mM) and the concentration of pyrrole employed (0.01–1.0 mM).

The corresponding Poisson distribution of pyrrole per micelles is shown in Fig. 4 for 0.39 mM micelles (for 0.20 and 0.58 mM, see Fig. S11–13†). Porphyrin formation requires four pyrroles to create the macrocycle, thus we are interested in the fraction of micelles that contain 4 pyrroles. For the reaction with 0.046 mM pyrrole and 0.39 mM micelles, the mean occupancy number m = 0.12 pyrrole/micelles. The fraction of micelles with a given value of k pyrroles then is as follows: 0.89 are empty (k = 0), 0.11 contain 1 pyrrole, 0.0063 have 2 pyrroles, 2.5×10^{-4} contain 3 pyrroles, and 7.4×10^{-6} contain the requisite 4 pyrroles. In other words, only 1 of ~130 000 micelles contains four pyrrole molecules, yet the yield of porphyrin at this concentration is 15 or 35% (CTAC or SDS micelles). Note that as the concentration of micelles increases, the mean occupancy number m decreases for a fixed concentration of pyrrole. For the reasonable limit of 0.20 or 0.58 mM micelles, the number containing 4 pyrroles is 9.6×10^{-5} or 1.6×10^{-6}, respectively, which corresponds to only 1 of 10 000 or 630 000 micelles. Indeed, upon complete site-isolation, the yield would be limited to the chemistry that occurs in the

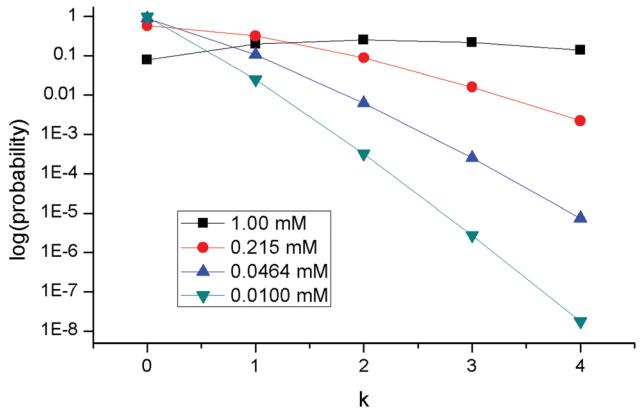


Fig. 4 Poisson distribution of the fraction of micelles having k = 0–4 pyrroles over a 100-fold range of pyrrole concentrations (for 0.39 mM micelles).

fraction of micelles containing four pyrroles (1/10 000 to 1/630 000 micelles depending on N_{agg} and thus [micelle]). This statistical analysis would suggest that almost no porphyrin should form.

The reasonable yield of porphyrin *versus* the statistical distribution of pyrrole among micelles suggests the micelles undergo extensive exchange of their contents during the course of the reaction. The exchange of solutes between micelles has been extensively studied.[21,38–41] Three distinct mechanisms include (1) exit–re-entry of the solute (*i.e.*, exchange *via* water mechanism); (2) micellar collision–exchange–separation (*i.e.*, fusion–fission); and (3) micellar fission–growth. The contribution of each mechanism depends on the surface charge of the micelle, aqueous ionic strength, and polarity of the solute. While discrimination of such mechanisms for the micellar formation of porphyrins is beyond the scope of the present paper, it warrants emphasis that even very hydrophobic substrates such as dodecylpyrene undergo extensive exchange in minutes–hours among SDS micelles.[42]

Alternatives to facile exchange include (1) a non-random distribution of the pyrrole, or (2) reaction largely in the aqueous phase. Clustering of the solute dodecylpyrene has been observed in SDS micelles.[42] In the case of clustering, one would assume that increased concentration of the pyrrole would afford higher yields, yet the lower concentrations of pyrrole generally gave higher yields. Synthesis largely outside the micelles (or in association with non-micellar surfactant) is possible, but the concentrative effect of the micelles is then lost; moreover, control experiments in the absence of surfactants showed no porphyrin. As for the exchange of reactants among micelles, many of the open-chain pyrrolic species appear to be somewhat amphiphilic, which would facilitate exchange, with the overall hydrophobicity increasing (and exchange thereby diminishing) upon oligomer assembly leading to the tetrapyrrole. The calculated organic-aqueous partitioning coefficients (log P values) are consistent with this general qualitative trend (Fig. S14†), but the calculated values for these and related molecules exhibit profound variation across programs,[18] and hence are not reliable for quantitative evaluation.

In summary, the results reported herein are consistent with facile reaction of minute quantities of a 3,4-dialkylpyrrole (10–50 μM) with formaldehyde in the presence of micelles and vesicles. The reaction process results in accumulation of the octaalkylporphyrin in the surfactant assembly. Statistical issues are at the heart of origin-of-life processes. Here, the statistical distribution of pyrrole among micelles – which would suggest little or no reaction – is overcome by (1) an apparent exchange process that is faster than the timescale of reaction, and (2) the thermodynamic driving force for tetrapyrrole macrocycle formation. The competition and transfer of lipid constituents among vesicles has been described previously;[43] here, the constituents transferred (pyrrolic reactants) are far more valuable than lipids alone. The process of transfer and accumulation of reactants in surfactant assemblies may have more general occurrence. Dobson and Tuck and coworkers have proposed that atmospheric aerosols could serve as prebiotic reactors, where organic constituents accumulate in high concentrations in the outer amphiphilic layer of inverted micelles.[44,45] Such assemblies are proposed as sites for chemical reaction[44] and perhaps chemical differentiation *via* selective partitioning of constituents upon aerosol fission,[45] thereby constituting precursors of the first cells. Reactions in inverted micelles might well complement those in normal micelles as reported here, together providing a means for assembly of a variety of functional entities that otherwise appear, like Paley's watch, to be statistically unlikely.

Acknowledgements

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