reversible modulation of T_c. Therefore, we can infer that electrochemically induced alterations in the superconductor lattice oxygen content[21] are not responsible for the effects observed here.

We speculate that modulation of superconductivity is the result of the occurrence of a superconducting proximity effect[22,23] within the composite assembly. If a proximity effect is indeed operative in our hybrid structures, there is an intriguing possibility that superconductivity may also be induced within conductive polymer structures that are in intimate contact with a superconductor. Studies are now in progress to search for such an unprecedented effect. Irrespective of the explanation, a new method for controlling the flow of electrical current in superconductor structures now has been demonstrated.

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Cholesterol-Induced Nearest-Neighbor Recognition in a Fluid Phospholipid Membrane[1]

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One of the most significant challenges presently facing chemists and biologists is to define the suprastructure of biological membranes.[2] In particular, the specific time-averaged lateral distribution of the lipids and proteins that make up these biological enclosures remains to be clarified. We have recently devised a chemical method for probing membrane suprastructure in simple model systems.[3,4] Unlike most other approaches that have previously been taken, ours is directly applicable to the physiologically-relevant fluid phase. The essence of our technique may be summarized as follows: a 1:1 molar mixture of two phospholipid homodimers (AA and BB) is equilibrated via a thiolate-disulfide interchange reaction.[5] In order to ensure that an equilibrium state has been reached, a similar equilibration reaction is carried out starting with the corresponding heterodimer AB (Figure 1). The extent to which the ratio of AA/AB/BB deviates from a molar ratio of 1/2/1 (a random distribution) reflects the thermodynamic preference for one phospholipid to become a covalently-attached nearest neighbor of another, i.e., it defines the ability of an equilibrating phospholipid monomer to "recognize" a nearest neighbor. When dimer distributions are found to be purely statistical, this fact, in and of itself, proves that the lipid components are randomly distributed throughout the membrane at the molecular level as well as at the supramolecular level. It establishes that there is no thermodynamic driving force for nearest-neighbor recognition and domain formation. For those cases in which nearest-neighbor recognition is observed, the existence of domains is inferred. This inference rests on the assumption that the packing forces that govern nearest-neighbor recognition are the same as (or very similar to) those that govern domain formation. Although such bilayers are not identical to those that are derived from single phospholipid molecules (the dominant component of natural biomembranes), they do provide us with a means for exploring membrane composition–suprastructure relationships in ways that have not, heretofore, been possible.

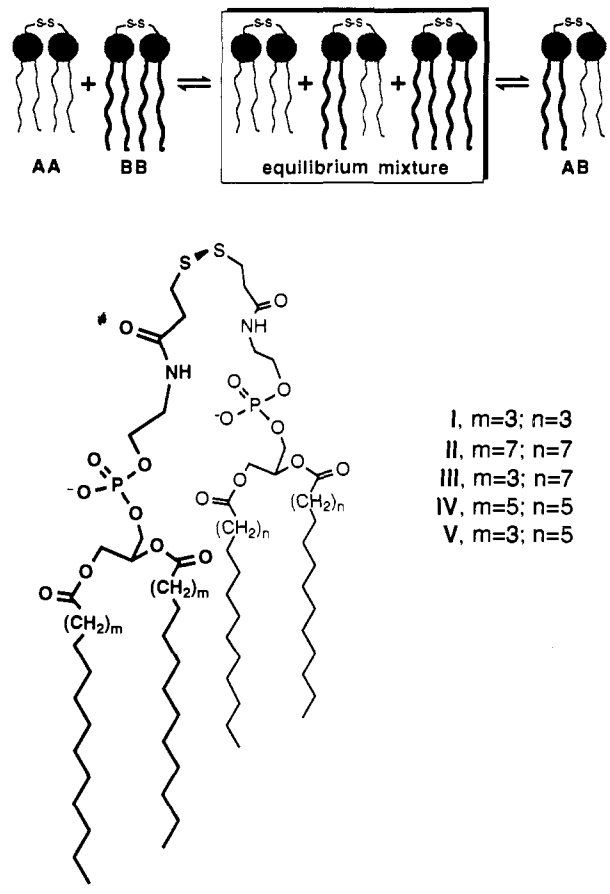

Figure 1. Stylized illustration of an equilibration reaction involving two phospholipid homodimers and one heterodimer. The specific dimers used in this study are I-V.

In the present study, we have examined the influence of cholesterol on nearest-neighbor recognition in fluid bilayers. The fact that mammalian cells are rich in cholesterol makes this particularly relevant from a biological standpoint. The specific phospholipid dimers that have been selected for this work are shown in Figure 1. On the basis of their fatty acid composition and their melting properties, lipids **I**, **II**, and **IV** may be viewed as dimeric analogs of 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC), 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC), and 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC), respectively; lipids **III** and **V** represent the corresponding heterodimers. The gel-to-liquid crystalline-phase transition temperatures for **I**, **II**, and **IV** are 22.7, 55.4, and 41.9 °C, respectively; for DMPC, DSPC, and DPPC, they are 23.9, 54.3, and 41.5 °C, respectively.[4,6]

In Figure 2 we show that equilibration of cholesterol-rich (40 mol %) membranes, which are comprised of phospholipid dimers **I**, **II**, and **III**, is essentially complete after 50 min at 60 °C.[7] Here, the equilibrium molar ratio of **I**/**III**/**II** is $1/(1.55 \pm 0.04)/1$; the error represents two standard deviations from the mean of eight

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(7) The experimental protocol that we have used to form large unilamellar vesicles (1000-Å diameter) and to promote thiolate–disulfide interchange has previously been described.[4]

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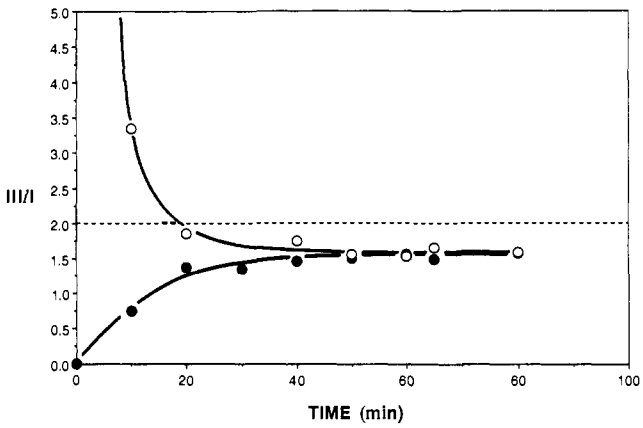

Figure 2. Plot of molar ratio of III/I as a function of equilibration time for vesicles prepared from III plus 40 mol % of cholesterol (○) and a 1/1 mixture of I/II plus 40 mol % of cholesterol (●); the equilibration temperature was maintained at 60 ± 1 °C. In all cases, equal molar ratios of symmetrical dimers were produced (±5%). The percentage of cholesterol is based on phospholipid monomer content.

independent experiments. This level of nearest-neighbor recognition corresponds to a thermodynamic preference for forming homodimers of $\Delta G = 0.17 \pm 0.02$ kcal/mol. Similar equilibration experiments, carried out in the presence of 30 mol % of cholesterol, afforded a molar ratio of I/III/II equaling $1/(1.68 \pm 0.07)/1$ ($\Delta G = 0.12 \pm 0.03$ kcal/mol). In the absence of (or in the presence of 10 mol % of) cholesterol, a completely random distribution of lipid dimers was observed; i.e., the ratio of I/III/II was $1/(2.01 \pm 0.06)/1$ in the absence of cholesterol and $1/(1.98 \pm 0.06)/1$ with 10 mol% of cholesterol. In contrast, equilibrium mixtures that were produced from dimeric analogs of DMPC and DPPC (i.e., I, IV, and V) were not influenced by the presence of 10, 30, or 40 mol % of cholesterol in the fluid phase (53 °C); the ratio of I/IV/V was 1/2/1, within the limits of error in each case.

Why does cholesterol induce nearest-neighbor recognition in fluid bilayers made from DMPC/DSPC analogs but not in those made from DMPC/DPPC analogs? The answer, we believe, lies in the known condensing effect that cholesterol has on the liquid-crystalline phase and in the greater difference in chain length that exists between the monomeric components of I and II, as compared with those of I and IV.[8,9] We have previously shown that I-III favor homodimer formation in the gel-fluid coexistence region, where solid-like domains that are rich in II exist in a fluid "sea" that is rich in I, i.e., two distinct endotherms (23 and 48 °C) are observed by high-sensitivity differential scanning calorimetry.[4] Thus, the thermodynamic preference of the higher melting homodimer II to self-associate in this mixed phase not only drives phase separation but it also leads to nearest-neighbor recognition and domain formation. An analogous situation is likely to exist for cholesterol-rich membranes made from I-III. By increasing the compactness of the bilayer, cholesterol "moves" the liquid-crystalline phase closer toward the gel-fluid coexistence state, where van der Waals forces are greater and where nearest neighbors can be recognized. The inability of cholesterol to alter the dimer distribution of fluid bilayers made from DMPC/DPPC analogs is fully consistent with this interpretation since these lipids favor a random distribution in the gel-fluid coexistence region, i.e., the difference in chain length between the equilibrating monomers is too small to be recognized.[4]

The ability of cholesterol to induce nearest-neighbor recognition in fluid bilayers infers the existence of phospholipid domains. This result further suggests that sterols may influence the suprastructure of biological membranes in ways that have not previously been realized.

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DNA Interstrand Cross-Linking by Reductively Activated FR900482 and FR66979

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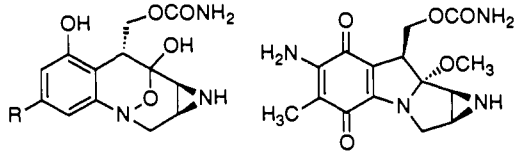
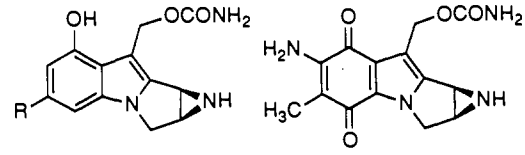
Several hypotheses[1-3] have been offered to account for the in vivo DNA alkylating activity of the antitumor antibiotic substances FR900482[4] (**1**) and FR66979[5] (**2**). We report herein that the DNA interstrand cross-linking reactions of **1** and **2** share in common with mitomycin C (**3**) greatly enhanced efficiency in a reducing medium and selectivity for dG-to-dG cross-linking at 5′-d(CG) with the participation of both dG exocyclic amino groups. We also provide preliminary evidence favoring mitosene-like structures **7** and **8** for these cross-links, analogous to lesion **9** previously derived from mitomycin C.[6] These observations support the hypothesis of reductive activation of **1** and **2** to form mitosene-like, reactive intermediates (e.g., **4**, **5**)[1] which are responsible for interstrand cross-linking.



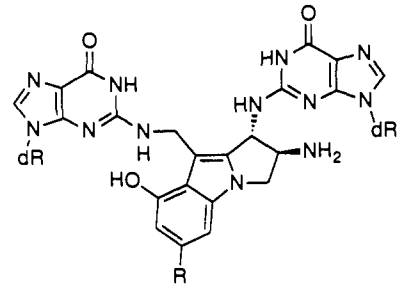
1 R = CHO, FR900482
2 R = CH_2OH, FR66979

3 mitomycin C

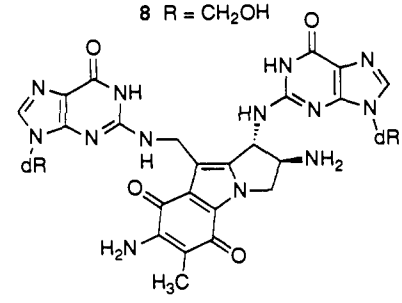


4 R = CHO
5 R = CH_2OH

6



7 R = CHO
8 R = CH_2OH



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