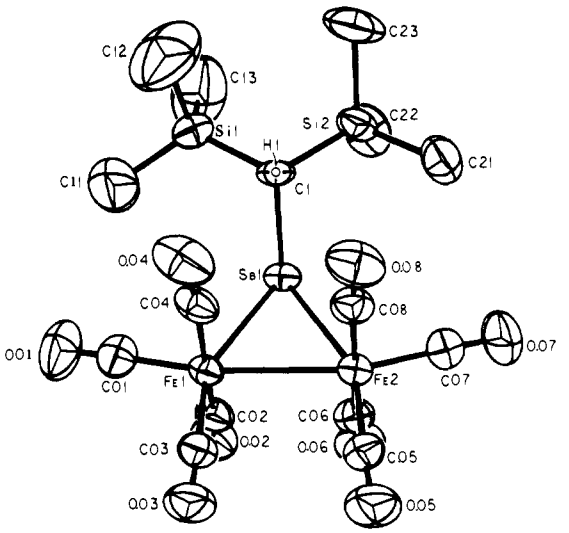

Figure 1. ORTEP view of $[Fe_2(\mu\text{-}SbCH(SiMe_3)_2)(CO)_8]$. Pertinent metric parameters: Fe(1)–Sb(1) = 2.663 (1), Fe(2)–Sb(1) = 2.641 (1), Fe(1)–Fe(2) = 2.801 (1) Å, Fe(1)–Sb(1)–C(1) = 110.81 (9)°, Fe(2)–Sb(1)–C(1) = 112.1 (1)°, Fe(1)–Sb(1)–Fe(2) = 64.15 (2)°.

727.9246. The structure of **3** was established by X-ray crystallography.[7] The Sb–Sb bond length (2.774 (1) Å) indicates that, as in the case of other η^2-bonded trans RE=ER complexes,[8] the bond order is ~1.5. Treatment of **3** (1.61 g, 2.1 mmol) with $Fe_2(CO)_9$ (0.80 g, 2.1 mmol) in 20 mL of *n*-hexane at 25 °C, followed by chromatography (silica gel, *n*-hexane), resulted in a 26% yield of **4** (mp 84–86 °C): HRMS calcd 615.8354, found 615.8333. The structure of **4** was determined by X-ray crystallography (Figure 1).[7] The existence of a "closed" structure is established by the pyramidality at the Sb atom (sum of bond angles = 287.1 (1)°), since in the "open" form the Sb geometry would be trigonal planar. Although the Fe–Fe distance (2.801 (1) Å) exceeds the usual single-bond range of 2.50–2.65 Å, it is clear that the Fe atoms are weakly bonded. Significant differences in the reactivities of the "open" and "closed" complexes are observed. Thus while complexes of type **1** are Lewis acidic at the E center, we find that **4** acts as a Lewis base. For example, **4** reacts readily with $HBF_4{\cdot}OEt_2$ to afford the (unstable) cation, $[(Me_3Si)_2CHSb(H)\{Fe(CO)_4\}_2]^+$.

Interestingly, a minor (labile) fraction is eluted from the column prior to **4**. However, the crystals that are deposited from this solution are identical with **4** in all respects. We speculate that this solution initially contains the "open" form of **4**. The reason for M–M bond formation in **4** is not completely clear. When compared to previous "inidene" complexes, $RE(ML_n)_2$ (ML_n = $Cr(CO)_5$, $Mo(CO)_5$, $W(CO)_5$, $(C_5H_5)Mn(CO)_2$),[1-4] the iron system is less sterically congested when the Fe–Fe bond is present. However, Fe–Fe bonding is also expected on electronic grounds.

The isolobal relationships RSb ↔ CH_2 ↔ $Fe(CO)_4$ reveal parallels between **3**, **4**, cyclopropane, and $Fe_3(CO)_{12}$. (Note, however, that the "open" form of **4** is analogous to the allyl anion.) There is also an interesting analogy between **4** and bridging methylene compounds.[9]

(7) Complex **3**: $C_{18}H_{38}FeO_4Sb_2Si_4$, M_r 730.18; monoclinic, $P2_1/n$; a = 19.958 (4) Å, b = 6.635 (1) Å, c = 24.408 (6) Å, β = 103.51 (2)°; V = 3143 (2) Å^3; Z = 4; D(calcd) = 1.543 g cm^{-3}. Complex **4**: $C_{15}H_{19}Fe_2O_8SbSi_2$; M_r 616.92; triclinic, $P\bar{1}$; a = 7.065 (5) Å, b = 9.179 (2) Å, c = 19.814 (7) Å, α = 86.86 (3)°, β = 85.23 (5)°, γ = 70.04 (4)°; V = 1203 (1) Å^3, Z = 2; D(calcd) = 1.702 g cm^{-3}. Intensity data: Enraf-Nonius CAD4-F diffractometer, ω–2θ scan mode in the range $2.0 \le 2\theta \le 50.0$; 5844 and 3859 unique reflections for **3** and **4**, respectively. The structures of **3** and **4** were solved (Patterson and difference Fourier) and refined (full matrix, least squares) by use of 3884 and 3283 data, respectively. Final residuals were as follows: **3**, R = 0.036, R_w = 0.060; **4**, R = 0.031, R_w = 0.039.

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Registry No. 3, 92315-34-9; **4**, 92345-49-8; $(Me_3Si)_2CHSbCl_2$, 86509-03-7; $Na_2[Fe(CO)_4]$, 14878-31-0; $Fe_2(CO)_9$, 15321-51-4; Sb, 7440-36-0.

Supplementary Material Available: Tables of bond lengths, bond angles, atomic coordinates, thermal parameters, and structure factors for **3** and **4** (53 pages). Ordering information is given on any current masthead page.

A Synthetic Amphiphilic β-Strand Tridecapeptide: A Model for Apolipoprotein B

David Osterman,[†] René Mora,[‡] F. J. Kézdy,[‡] E. T. Kaiser,*[†] and Stephen C. Meredith*[§]

Departments of Biochemistry and Pathology
The University of Chicago, Chicago, Illinois 60637
The Laboratory of Bioorganic Chemistry
and Biochemistry, The Rockefeller University
New York, New York 10021-6399

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The biological activity of many proteins and peptides acting in amphiphilic environments depends on the ability of the polypeptide to assume amphiphilic secondary structures. Previous studies have mainly concerned model amphiphilic α-helices, but it is probable that any possible secondary structure would occur in the amphiphilic form.[1,2] Indeed, indirect evidence suggests that apolipoprotein B, the major protein component of plasma low-density lipoproteins, exists in a predominant β-strand at the surface of the lipoprotein.[3] In order to explore the general properties of amphiphilic β-strands, and to have at our disposal an apolipoprotein B (apoB) model, we designed peptide I, a tridecapeptide with the following amino acid sequence:

NH_2-Val-Glu-Val-Orn-Val-Glu-Val-Orn-Val-Glu-Val-Orn-Val-COOH

We decided upon a tridecapeptide in order to assure that the peptide would be long enough to assume a stable secondary structure and yet short enough to be water soluble. Peptide I contains three different amino acids, valine, glutamate, and ornithine, arranged so that alternating amino acids are hydrophilic and lipophilic and so that alternating hydrophilic amino acids have acidic and basic side chains, conducive to staggering the electric charges upon self-association. Valine is the amino acid with the highest β-forming potential[4] and forms soluble β-sheets in copolymers such as poly(Val-Lys).[5a,b] Although glutamic acid has a low β-forming potential, poly(Glu) and copolymers such as poly(Glu-Val) and poly(Glu-Ala) may under certain conditions be induced to form β-structures.[6,7] We chose ornithine to maximize side chain interactions, and we chose ornithine over lysine because the former can serve as a chemical marker since apoB does not contain ornithine. Thus the use of this amino acid assures that the peptide will have little chemical homology with natural apoB. Peptide I was synthesized by the solid-phase method

[†] Rockefeller University.
[‡] Department of Biochemistry, The University of Chicago.
[§] Department of Pathology, The University of Chicago.

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as previously described,[8] using the trifluoroacetyl group for protecting the δ-amino group of ornithine. The trifluoroacetyl groups were removed by incubating the peptide in 1 M piperidine for 3 h at 37 °C. The peptide was purified by reverse-phase HPLC of either the fully deprotected peptide or the peptide with TFA groups protecting the δ-amino groups and the N-terminal derivatized with a phthaloyl group. The phthaloyl derivative was prepared and subsequently deblocked by the method of Pechère and Bertrand.[9] Both methods yielded pure peptides as assessed by amino acid analysis.[10]

In aqueous solutions, the peptide (2.5×10^{-4} M) showed the typical circular dichroic spectrum of a β-strand with a minimum at 218 nm. Analysis according to the method of Greenfield and Fasman[11] indicated that the peptide contained 55% β-strand and 45% random coil distilled water, and 66% β-strand and 34% random coil in 0.16 M KCl. By evaporating the aqueous solution on a CaF_2 plate, peptide I yielded a film, the infrared spectrum of which also was consistent with an antiparallel β-sheet structure characterized by a strong absorption band centered at 1628 cm^{-1}, and a weak one at 1690 cm^{-1}. Analytical gel permeation chromatography of an aqueous solution of the peptide (6.25×10^{-5} M) was performed using a Toyo Soda G2000SW HPLC column. The chromatogram showed the high tendency of the peptide to self-associate; peaks corresponding to monomeric, dimeric, tetrameric, and octameric forms were predominant.

The amphiphilic properties of the peptide were demonstrated at a variety of interfaces. At the air–water interface the peptide readily formed monolayers of great stability. On a subphase of relatively low ionic strength, 0.16 M KCl, the monolayer behaved as an ideal gas at $\pi \leq 1$ dyn/cm, characterized by an exclusion area of 16 $Å^2$/amino acid, but highly self-associated, with $\bar{M}_n = 2.0 \times 10^4$. The monolayer could be compressed up to 44 dyn/cm without any sign of collapse. In contrast, on a subphase of high ionic strength (4.0 M NaCl) the monolayer at $\pi \leq 1$ dyn/cm was characterized by $\bar{M}_n = 2.3 \times 10^3$. A monolayer of human apoB spread on a subphase of low ionic strength yielded the parameters exclusion area = 17 $Å^2$/amino acid and collapse pressure = 38 dyn/cm, indicating that these surface properties of peptide I are the same as those of apoB.

The affinity of peptide I toward water hydrophobe interfaces was assessed by using low-density lipoproteins from *M. mulatta* made hyperlipemic by a diet rich in peanut oil and cholesterol.[12] The hyperlipemic LDL (h-LDL) at 5.0×10^{-7} M was incubated for 2 h with peptide I at a variety of concentrations ranging from 2.5×10^{-8} to 5.0×10^{-5} M, at 21 °C, in the presence of 3.8 M CsCl. After the incubation, the mixture was centrifuged in a Beckman air-driven ultracentrifuge at 160000*g* for 5 min, yielding a gradient in the LDL concentration. Amino acid analyses of the top and bottom halves of the centrifuge tubes were performed, from which the concentration of peptide I and of apoB in each fraction was calculated. We observed that whereas the peptide in the absence of LDL was equally distributed in the top and bottom halves of the centrifuge tube, in the presence of LDL the top half was enriched in peptide with respect to the bottom half. From these results we conclude that the excess peptide in the top half must be peptide bound to LDL and that the bound peptide was distributed into the two halves in proportion to the distribution of apoB, and hence, of LDL. Since this method of separating free and bound peptide I entailed concentrating the LDL, though only slightly and very briefly, we wished to ascertain that in the time needed to carry out the centrifugation reequilibration of the mixture had not occurred. Indeed, a rapid chromatographic separation of free and bound peptide using the Toyo Soda HPLC G2000SW column, which tends to dilute the LDL, gave essentially the same results as the centrifugation method. We found that

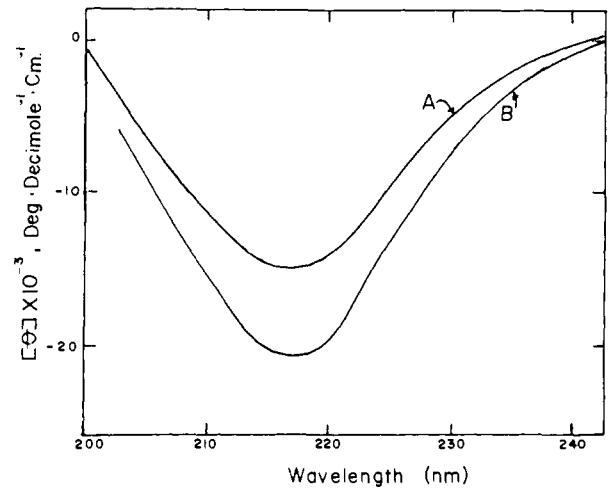

Figure 1. Circular dichroic spectra of peptide I in solution (A) and as part of a peptide–lipid complex (B), both at a peptide concentration of 1.0×10^{-5} M.

peptide I within this concentration range binds to these hyperlipemic LDL with a Langmuir isotherm, with $K_d = 1.45 \times 10^{-7}$ M and 88 sites per LDL. Thus, the peptide, unlike even most apolipoproteins, is able to bind to LDL, underlining the great similarity of the properties of this peptide with those of apoB. From the size and composition of LDL, we calculate that normal and hyperlipemic LDL contain apoB at surface densities of 16 and 18 $Å^2$/amino acid, respectively, and that the binding of 88 peptide molecules per h-LDL would change the surface packing of protein in these h-LDL to 16 $Å^2$/amino acid. Indeed, we find that under conditions in which h-LDL binds 41.3 mol of peptide I/mol of LDL, normal LDL only binds 4.8 mol/mol. These observations suggest that hyperlipemic LDL is surface protein deficient and possesses a surface that is larger and more hydrophobic than that of normal LDL. In our experiments we also observed that peptide I is able to displace from the surface of LDL a minor protein component which upon analysis by SDS-PAGE appears to be apolipoprotein E.

In order to test further the similarity between apoB and peptide I, we showed that the latter is able to associate with synthetic lipids to form a particle of the radius of LDL. Solutions of egg phosphatidyl choline (Avanti Polar Lipids, Inc.), cholesteryl oleate, cholesterol, and triolein (Serdary Research Laboratories, Inc.), all in chloroform/methanol (2/1, v/v), were mixed to a weight ratio of 22/37/8/11, which matches the ratio in normal human LDL of phospholipid, cholesteryl esters, cholesterol, and triglycerides, respectively.[12] An aqueous solution of peptide I was added to a film of these lipids to give a lipid/protein weight ratio of 79/21, again matching that of normal human LDL.[13] Upon mild sonication the suspension lost most of its initial turbidity, and analytical gel permeation chromatography showed that the majority of the peptide coeluted with a particle $M_r = 2.8 \times 10^6$, corresponding to that of LDL. The particle consisted of peptide, cholesterol, cholesteryl oleate, triolein, and egg lecithin with a lipid to protein weight ratio of 78/22 and the following weight ratio of lipids: 25/35/8/10, respectively. Finally, the circular dichroic spectrum of the lipid–peptide complexes is quite similar to that of apolipoprotein B in intact LDL particles[3] and indicates that the peptide has a predominant β-strand structure at this amphiphilic surface as it does in solution. Furthermore, as shown in Figure 1, the mean residue ellipticity of the peptide bound to lipid surfaces is greater than that in solution, clearly indicating that the surface stabilizes β-strand more than the solution does.

From these experiments we conclude that a tridecapeptide designed to form an amphiphilic β-strand structure at amphiphilic interfaces mimics all the salient physical properties of apoB, namely, formation of a stable monolayer at the air–water interface,

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preferential stabilization of lipoprotein particles of about 200-Å diameter, CD spectra consistent with β-strand structure both in solution and at interfaces, a high tendency to self-associate in aqueous media, and an very high affinity for lipid surfaces. For these reasons we feel our model peptide will provide us with an excellent tool to investigate the specific lipid–protein interactions that occur in low-density lipoproteins.

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Registry No. NH_2ValGluValOrnValGluValOrnValGluValQrnVa-lCO2H, 92269-72-2.

Chemical Modification of Nucleic Acid Components: Conversion of Guanosine by Methyl *N*-Cyanomethanimidate to a Tricyclic, Fluorescent Analogue of Adenosine

Nelson J. Leonard,* Ramachandra S. Hosmane,[1] Yankanagouda S. Agasimundin, Linda J. Kostuba, and Fred T. Oakes

Roger Adams Laboratory, School of Chemical Sciences University of Illinois, Urbana, Illinois 61801

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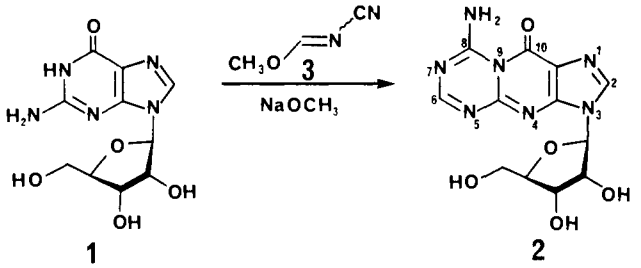
We have accomplished the goal of converting a natural *N*-ribonucleoside into an entity whose structure more closely resembles, in the periphery, that of a different natural *N*-ribonucleoside, for example, guanosine (**1**) into a product that bears a peripheral resemblance to adenosine, as in **2**. Best results were



obtained with methyl *N*-cyanomethanimidate (**3**)[2-6] in the presence of sodium methoxide. The structure of the fluorescent product from **1** and **3** was established by spectroscopic means as 8-amino-9,10-dihydro-10-oxo-3-β-D-ribofuranosyl-3*H*-1,3,5-triazino[1,2-*a*]purine (**2**), or IA′-metamorphosine.[7]

Compound **2**, which possesses an imidazole ring, ribosyl moiety, and the major hydrogen-bonding functionalities generally considered important for the expression of the biological activity of the purine ribonucleosides and ribonucleotides,[8,9] is a laterally extended adenosine analogue in which the terminal rings are

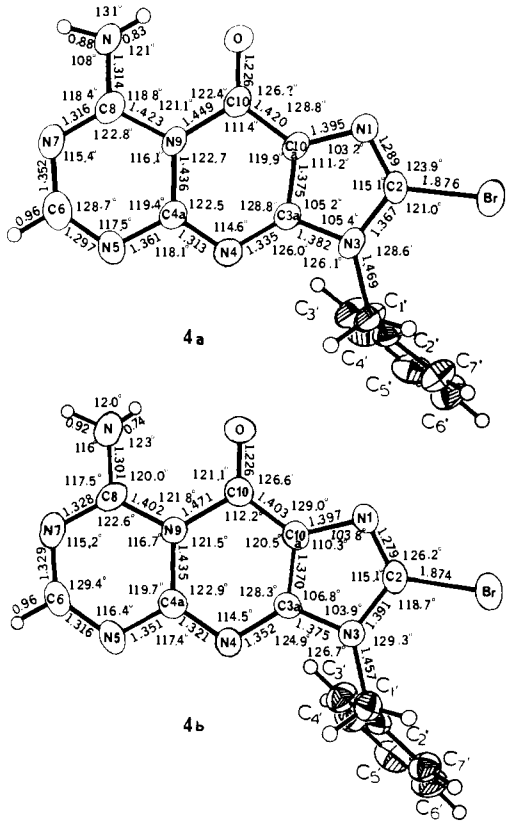


Figure 1. Single-perspective ORTEP drawings simplified.

displaced by approximately 2.4 Å relative to adenosine. As such, it bears resemblance to lin-benzoadenosine,[10,11] with related potential for application in enzyme studies. Conversion of N-bicyclic to N-tricyclic ribonucleosides by simple reagents has already provided interesting results and useful applications.[12-18]

Methyl *N*-cyanomethanimidate (**3**) (7 equiv)[2-6] was introduced through a hypodermic syringe into guanosine (**1**) and sodium methoxide (2 equiv) in methanol, and the mixture was stirred at 20 °C for 24 h. Purification was effected by partial evaporation, filtration, and pressure chromatography on Woelm silica gel using acetone as eluant. Evaporation gave a colorless solid, mp 247–249 °C dec, $C_{12}H_{13}N_7O_5$,[19] in 39% yield (66% based on unrecovered guanosine). The same product, characterized spectroscopically by ^{13}C and ^1H NMR in $(CD_3)_2SO$, was obtainable from guanosine, NaH, and **3** in DMF at 60 °C for 6 h in about the same yield. We could differentiate between the ^1H NMR chemical shifts for the 2-H (δ 8.3) and 6-H (δ 8.03) in the assigned formula **2** by synthesis of the isotopically labeled analogues (a) from **3** and [8-^{2}H]guanosine, made by heating guanosine in D_2O under reflux for 7 h, and (b) from **1** and methyl [1-^{2}H]-*N*-cyanomethanimidate, made from trimethyl [1-^{2}H]orthoformate[6] and cyanamide in cyclohexane at reflux. The D_2O-exchangeable N–H's were

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