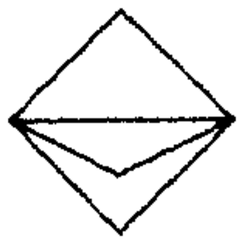
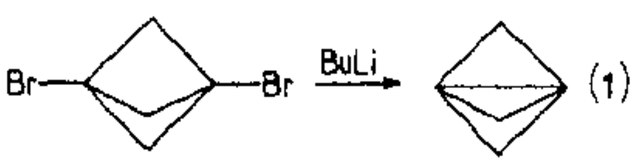


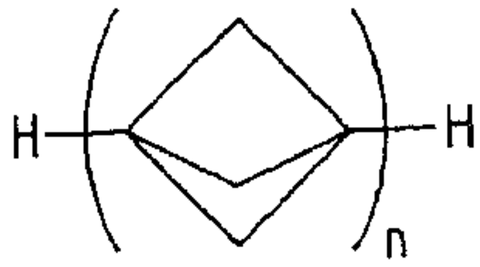
6

The surprise of the decade is the seemingly impossible [1.1.1]propellane, **6**. The molecule has two pyramidal tetracoordinate carbon atoms. Students of organic chemistry are expected to instinctively recognize the instability associated with such structures. However, Wiberg calculated a relatively (compared to other propellanes that had been made) small strain energy for this molecule. He believed in his computations sufficiently to make an attempt at synthesis of **6**. The shockingly simple procedure shown below worked[13]!



(1)

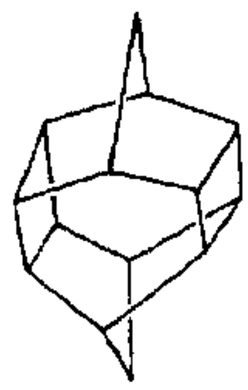
In a further interesting development, the propellane **6** was easily converted to a series of oligomers in a perfectly controlled fashion[14]. Many mind-boggling applications ('molecular-size civil engineering', 'nanotechnology') are being visualized[15] for this class of molecules, called the staffanes (**7**).



n = 2, ..6

7

I shall conclude with a molecule made in India: **8**, bishomohexaprismane,



8

the symmetrical, face-to-face dimer of norbornadiene. Mehta was successful[16] not only in synthesizing the molecule for the first time, but also in contributing a name with an Indian flavour, garudane, to the chemical literature.

1. Sekine, Y. and Boekelheide, V., *J. Am. Chem. Soc.*, 1981, **103**, 1777.
2. Paquette, L. A. and Balogh, D. W., *J. Am. Chem. Soc.*, 1982, **104**, 774.
3. Paquette, L. A., Ternansky, R. J., Balogh, D. W. and Taylor, W. J., *J. Am. Chem. Soc.*, 1983, **105**, 5441.
4. Paquette, L. A., Ternansky, R. J., Balogh, D. W. and Kentgen, G., *J. Am. Chem. Soc.*, 1983, **105**, 5446.
5. Paquette, L. A., Miyahari, Y. and Doecke, G. W., *J. Am. Chem. Soc.*, 1986, **108**, 1716.
6. Fessner, W.-D. *et al.*, *Angew. Chem. Intl. Ed. (Engl.)*, 1987, **26**, 452.
7. Prinzbach, H. *et al.*, *Angew. Chem. Intl. Ed. (Engl.)*, 1987, **26**, 457.
8. Bremer, M., Schleyer, P. V. R., Schotz, K., Kausch, M. and Schindler, M., *Angew. Chem. Intl. Ed. (Engl.)*, 1987, **26**, 761.
9. Kroto, H. W., Heath, J. R., O'Brien, C., Curl, R. F. and Smalley, R. E., *Nature (London)*, 1985, **318**, 162.
10. Iijima, S., *J. Phys. Chem.*, 1987, **91**, 3466.
11. Diederich, F. *et al.*, *Science*, 1989, **245**, 1088.
12. Rubin, Y. and Diederich, F., *J. Am. Chem. Soc.*, 1989, **111**, 6870.
13. Wiberg, K. B. and Walker, F. H., *J. Am. Chem. Soc.*, 1982, **104**, 5239.
14. Murthy, G. S., Hassenruck, K., Lynch, V. M. and Michl, J., *J. Am. Chem. Soc.*, 1989, **111**, 7262.
15. Hameroff, S. R., in *Ultimte Computing, Biomolecular Consciousness and Nano-Technology*, North Holland, Amsterdam, 1987, chapter 10.
16. Mehta, G. and Padma, S., *J. Am. Chem. Soc.*, 1987, **109**, 7230.

J. Chandrasekhar is in the Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012

Does fatty acyl CoA have a role in cellular transport possibly through protein modification?

Amitabha Chaudhuri

THOUGH most proteins are synthesized in the cytoplasmic milieu, internal structural signals dictate functional sequestration and compartmentalization in the cell. The transport machinery that recognizes these signals sorts distinct proteins to the cell surface and to the organelles present in the eukaryotic cell. These signals arise from distinct post-translational modifications that occur in the cell. Besides targeting proteins to respective locations, post-translational modifications like phosphorylation and dephosphorylation, ADP-ribosylation, etc., modulate the function of many proteins. Attachment of lipid molecules to proteins is one such modification, the importance of which has been realized lately. Proteins whose functions are modulated by attachment of lipid molecules have been defined as amphitropic proteins[1].

The nature of the modification of proteins by lipids is, without exception, covalent. Three kinds of modifications are reported. Myristylation involves the attachment of myristic acid to the *N*-terminal glycine through an amide linkage. Palmitic acid is linked through thio-ester and oxy-ester linkages and lastly complex phospholipid tail may be attached to many proteins[2]. The signal for palmitoylation has been apparently identified as a consensus Cys-A-A-X box present at the carboxy terminus of many palmitoylated proteins, in which A represents any aliphatic amino acid[3]. The donor of the lipid moiety in palmitoylation is the CoA derivative of the fatty acid[4].

The true functional significance of this modification is still debatable, barring few exceptions. An obvious consequence of acylation of soluble proteins is its membrane attachment. However, all membrane-bound proteins are not always acylated. In a few instances, membrane attachment has been correlated to distinct functional significance as in the *ras* protein. *Ras* protein is the functional product of *ras* gene, associated with neoplastic development. This protein from various sources has been shown to bind guanine

nucleotides, have GTPase activity and is associated with the plasma membrane[5]. *Ras* proteins become functional after binding to the membrane and palmitoylation of this protein is a pre-requisite for membrane attachment. Lastly, it has been shown in many instances that the action of phospholipases on complex phospholipid tails results in the generation of active molecules such as diacylglycerol, inositol phosphate—known elements in signal transduction in eukaryotes[6]. The functional significance of lipid modification broadens with the publication of a paper in *Cell* by Rothman's group[7]. Their results indicate the requirement of CoA activated palmitic acid in the transport of proteins across the Golgi compartments.

Post-translational targeting of proteins to plasma membrane, lysosomes and secretory granules requires the participation of two organelles, the endoplasmic reticulum (ER) and the Golgi apparatus. The movement of proteins between the membrane-bound compartments is mediated by budding and fusion of transport vesicles. The protein destined to be transported to any one of the three locations mentioned, enter the ER co-translationally and is vectorially transported from the ER to the Golgi, across the Golgi, from *cis* to medial to *trans*-compartments, and on to the various locations in an energy-dependent manner (Figure 1). The sorting of proteins destined to lysosomes and secretory storage vesicles occurs in the *trans* Golgi compartment in a signal-dependent manner. Transit to the cell membrane occurs by default and is referred to as the 'bulk flow'. The bulk flow of proteins is mediated by non-clathrin-coated vesicles but the signal mediated diversion from the bulk flow is accomplished by clathrin-coated vesicles[8].

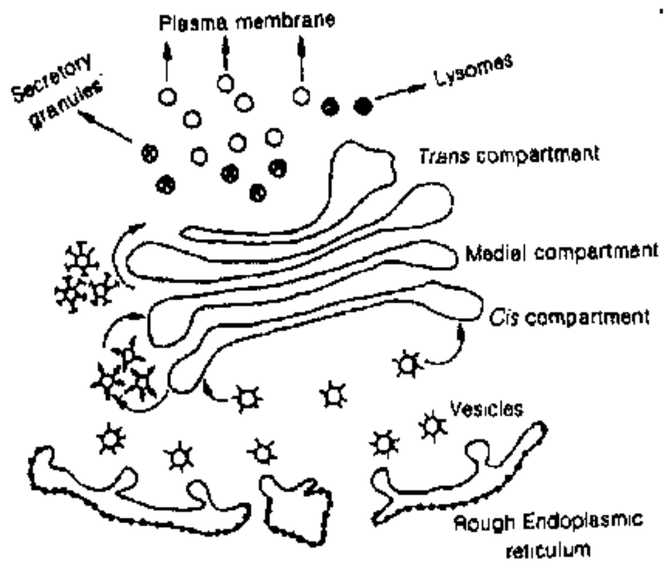


Figure 1. Vectorial transport of proteins into and across the Golgi compartments. The transport is mediated by vesicles. Vesicles are addressed to specific locations with distinct tags. The path is rigorously defined: ER→*cis*→medial→*trans*. The sorting of proteins takes place at the *trans* compartment.

The signals, that allows the transport machinery to sort and address proteins to different locations in the cell, are still not known. However, a protein entering the ER, is tagged with a complex oligosaccharide which is further processed by groups of enzymes residing in specific compartments. Processing in each compartment is the rate-limiting step in the transport. Given this situation, a protein will fail to be transported if a key processing enzyme is nonfunctional. The end result then, is the accumulation of the protein in the compartment containing the defective enzyme. The protein can be rescued by supplementing the defective enzyme with a functional protein during *in vivo* complementation experiments. Such complementation studies have been standardized *in vitro* with the G protein of vesicular stomatitis virus[9–11].

In a paper published in *Nature*, Glick and Rothman[12] reported an *N*-ethylmaleimide (NEM) sensitive cytosolic factor (NSF) that requires fatty acyl CoA as a cofactor and is essential for intra-Golgi transport[12]. The present paper[7] in *Cell* attempts to delineate the probable role fatty acyl CoA plays in vesicular transport.

The fact that acyl CoA hydrolysis is essential for transport was shown by determining the effect of a nonhydrolysable analog of palmitoyl CoA. The analog inhibited transport effectively, competitively, suggestive of the involvement of acyl transferases in transport. The removal of palmitoyl CoA from the membrane system with mild detergents effectively inhibited transport indicating that the membrane compartments have a pool of activated fatty acids. This inhibition is also reversed with the external addition of palmitoyl CoA. Since it is known that the turnover of activated fatty acid is very high in the cell, functional requirement of ATP-dependent acyl CoA synthetase is a prerequisite in maintaining the cellular pool of fatty acyl CoA. The use of a potent competitive inhibitor triascin, inhibited transport as expected. This inhibition could not be reversed by adding palmitoyl CoA or separately adding palmitic acid and CoA-SH indicating the specific requirement of activated fatty acid like palmitic acid with CoA in intracellular transport. To answer, at what step fatty acyl-CoA is required in the complex transport pathway, the authors carried out electron microscopic studies. These studies indicated that palmitoyl CoA promotes the budding of vesicles from the Golgi cisternae. Since transport across the Golgi compartments is mediated by vesicular fusion, activated fatty acids may have an important regulatory functions in this vesicular trafficking. What role does the acyl CoA play? The authors seem to favour the modification of an essential protein by the acyl moiety catalysed by the transferase. The modified protein will assume a membrane-bound position and trigger vesicle formation. The fusion of the vesicle can be achieved by deacylation of the protein. The specificity of fusion can then be controlled by having specific deacylating enzymes in the acceptor compartments. How this essential lipoprotein induces vesicle formation is an open question. In this connection, genetic studies may be very useful since temperature-sensitive mutant strains of yeast blocked at various stages in protein transport are available[13]. Lastly, can covalent modification of proteins by lipids be a general mode of regulation in all intracellular vesicularization especially during cell division[4]?

1. Burn, P., *Trends Biochem. Sci.*, 1987, **13**, 79.
2. Sefton, B. M. and Buss, J. E., *J. Cell. Biol.*, 1987, **104**, 1449.
3. Magee, T. and Hanley, M., *Nature*, 1988, **335**, 114.
4. Berger, M. and Schmidt, M. F. G., *J. Biol. Chem.*, 1984, **259**, 7245.
5. Barbacid, M., *Annu. Rev. Biochem.*, 1987, **56**, 779.
6. Berridge, M. J., *Annu. Rev. Biochem.*, 1987, **56**, 159.
7. Pfanner, N. *et al.*, *Cell*, 1989, **59**, 95.
8. Pfeffer, S. R. and Rothman, J. E., *Annu. Rev. Biochem.*, 1987, **56**, 829.
9. Balch, W. E., Dunphy, W. G., Braell, W. A. and Rothman, J. E., *Cell*, 1984a, **39**, 405.
10. Balch, W. E., Glick, B. S. and Rothman, J. E., *Cell*, 1984b, **39**, 525.
11. Fries, E. and Rothman, J. E., *Proc. Natl. Acad. Sci. USA*, 1980, **77**, 3870.
12. Glick, B. S. and Rothman, J. E., *Nature*, 1987, **326**, 309.
13. Novick, P., Field, C. and Schekman, R., *Cell*, 1980, **21**, 205.
14. Tuomikoski, T., Felix, M., Doree, M. and Gruenberg, J., *Nature*, 1989, **342**, 942.

Amitabha Chaudhuri is in the Department of Biochemistry, Indian Institute of Science, Bangalore 560 012