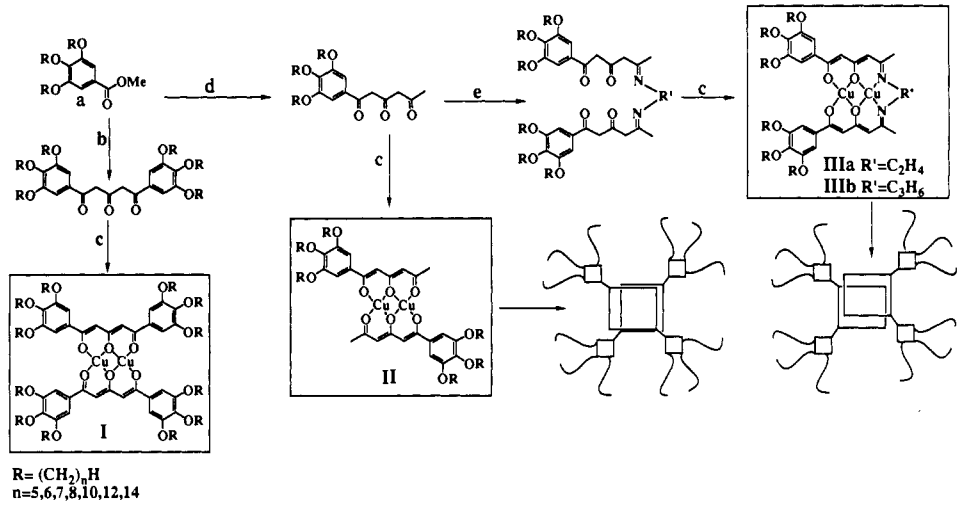
Scheme I[a]



[a] All reactions carried out under N_2; a. 1 eq. Methyl 3,4,5-trihydroxybenzoate, 3.3 eq. RBr, 7 eq. K_2CO_3, acetone reflux 3 days, ≈90%; b. 0.5 eq. acetone, 6 eq. NaH, DME reflux 24 hr., ≈85%; c. 1 e.q. $Cu(OAc)_2(H_2O)$, $CHCl_3$/EtOH (1/4), 70 °C, 1 hr., 95%; d. 1 eq. acetylacetone, 3 eq. NaH, DME reflux 24 hr., ≈75%; e. 0.5 eq. $H_2NC_2H_4NH_2$ or $H_2NC_3H_6NH_2$, EtOH, RT 12 hr., 90%.

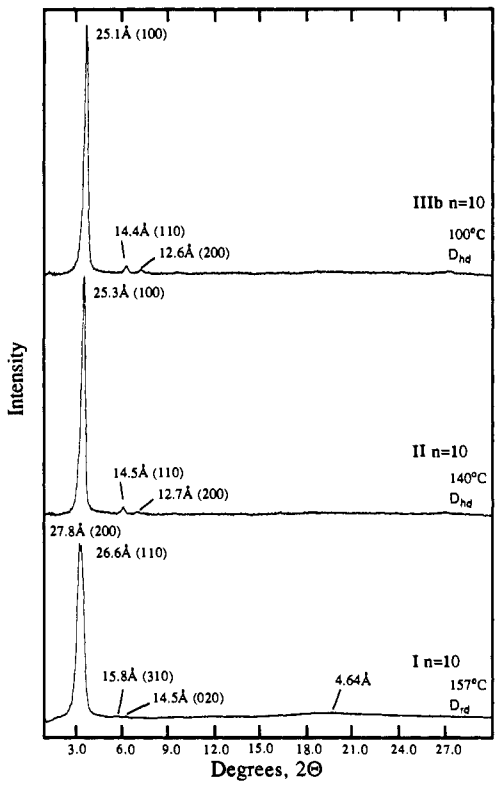


Figure 1. X-ray diffraction data for the liquid crystalline phases of **I**, **II**, and **IIIb** (n = 10).

D_{hd} phases of **II** and **IIIa,b** are the same, their dynamics are different. **II**'s texture shows a considerable reduction in the birefringence with increasing temperature, whereas **IIIa,b**'s textures show essentially constant birefringence. This is likely the result of precessional motion of the phenyl rings in **II**'s D_{hd} phase which is not possible for **IIIa,b** due to a higher density within the columns.

We have discussed our results on the dicopper complexes; however, the ligands reported display extensive coordination chemistry and represent versatile building blocks for the formation of a variety of materials with different transition metals.[5,10] Our future reports will describe related homo- and heteronuclear bimetallic liquid crystalline complexes as well as related trimetallic mesomorphic complexes.

Acknowledgment. We are grateful for funds provided by the National Science Foundation (DMR-9119045) and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their generous support of this work. A.S. is a Ford Foundation Predoctoral Fellow and is appreciative of a Gloria Twine Chisum Fellowship. We thank Professors J. E. Fischer and P. A. Heiney for the use of their X-ray equipment.

Supplementary Material Available: Tables of crystal coordinates, thermal parameters, bond distances, and bond angles and ORTEP diagrams of **IIIb** (n = 6) and graphs of phase transitions and tables of enthalpies of phase changes and elemental analysis data for all compounds reported (26 pages). Ordering information is given on any current masthead page.

(9) A crystal structure determination on **IIIb** (n = 6) has been performed and is included in the supplementary material.

(10) (a) Glick, M. D.; Lintuedt, R. L. *Prog. Inorg. Chem.* (Lippard, S. J., Ed.) **1976**, *21*, 2331 and references therein. (b) Casellato, U.; Vigato, P. A.; Fenton, D. E.; Vidali, M. *Chem. Soc. Rev.* **1979**, *8*, 199 and references therein.

First Hydrogen Abstraction–Rearrangement Model for the Coenzyme B_{12}-Dependent Methylmalonyl-CoA to Succinyl-CoA Carbon Skeleton Rearrangement Reaction

Paul Dowd,* Boguslawa Wilk, and Bogdan K. Wilk

Department of Chemistry, University of Pittsburgh Pittsburgh, Pennsylvania 15260

Received June 1, 1992

Coenzyme B_{12} is an obligatory cofactor in a remarkable series of 12 enzyme-catalyzed rearrangement reactions.[1] Of these, the three-carbon skeleton rearrangements in the series have been particularly intriguing because of the lack of precedent for such transformations among organic reactions.

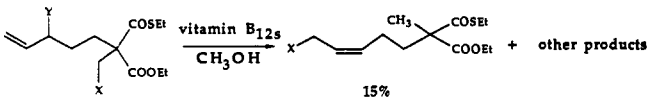
The rearrangements are typified by the interconversion of methylmalonyl-CoA with succinyl-CoA (eq 1), in which the thioester migrates to the methyl carbon following hydrogen abstraction. Rearrangements in this series can be represented more

(1)

(1) Recent review: Dowd, P. In *Selective Hydrocarbon Activation*; Davies, J. A., Watson, P. L., Liebman, J. F., Grunberg, A., Eds.; VCH Publishers, Inc.: New York, 1990; pp 265-303.

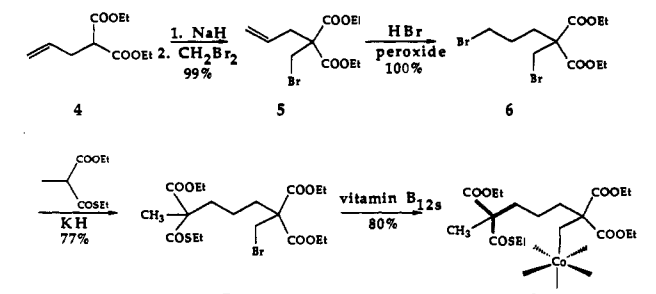
0002-7863/92/1514-7949$03.00/0

Scheme I



1, X = Br, Y = H
1-d, X = H, Y = D and X = D, Y = H
2-h, X = H
2-d, X = D

Scheme II



4 5 6 7 3

generally as an interchange between a hydrogen and a group X, in which X can be COSCoA, acrylate, or glycinate in the carbon skeleton rearrangement series and OH and NH_2 in the diol dehydrase and amino mutase series.[1] For none of the members of the B_{12} series have nonenzymic model reactions been observed in which *both* hydrogen abstraction and group migration occur in the same model.

Recent years have seen the development of many models mimicking the rearrangement step.[2] By contrast, there are no models showing how the hydrogen abstraction steps can be effected nonenzymically and in conjunction with the carbon skeleton rearrangement. Thus, the hydrogen abstraction step may be viewed as one of the least well understood of all biochemical transformations.[3]

In a recent study[4] designed to probe the extent of involvement of free radical intermediates in a vitamin B_{12s}-promoted model for the methylmalonyl-CoA rearrangement, we observed an unusual allylic hydrogen abstraction that, since it led to the *Z* olefin **2-h** (Scheme I), gave the appearance of proceeding through a carbanionic intermediate. This surmise was confirmed by conducting the reaction in CH_3OD, whereupon deuteration in the rearranged olefin occurred exclusively at the allylic position (Scheme I), yielding **2-d** in addition to the reduced product **1-d**. The analogous free radical rearrangement yielded only the *E* isomer.[4]

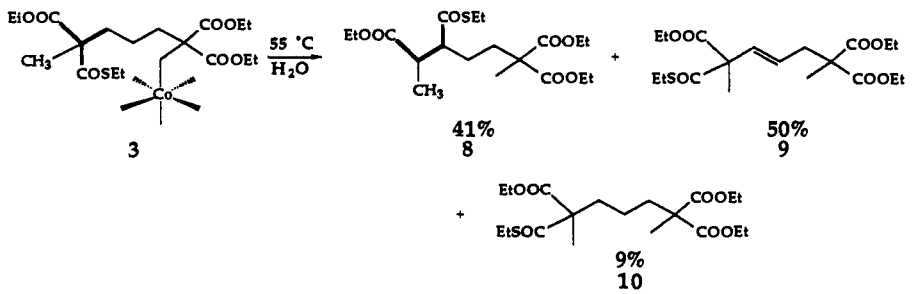
Allylic protons are weakly acidic, with pK_a's in the range 35–43,[5] comparable to protons whose abstraction leads to homoenolate anions.[6] Accordingly, it was attractive to take advantage of the apparent tendency of this system to place a reactive carbanion at a remote site and devise a modified model system which might undergo carbon skeleton rearrangement following creation of the reactive center. The target molecule was the thioester **3**, which has a methylthiomalonate group tethered through a five-carbon chain to a labile carbon–cobalt bond to the vitamin B_{12} nucleus.

Synthesis of **3** was carried out by condensing diethyl allylmalonate **4** with methylene dibromide to obtain the corresponding allyl(bromomethyl)malonate[7a] **5** (Scheme II). Hydrogen bromide was added to the terminal double bond under free radical conditions, yielding **6**.[7a] The final condensation with diethyl methylthiomalonate yielded bromide **7**,[7a] with alkylation occurring exclusively at the non-neopentyl, primary carbon. The bromide **7** was then treated with vitamin B_{12s} (from vitamin B_{12a} treated with Zn and NH_4Br in methanol at room temperature under Ar) to form the desired alkylcobalamin **3**. Although the neopentyl-like carbon–cobalt bond in this series is very sensitive to oxygen, the adduct **3** can be isolated under an inert atmosphere and characterized by UV–vis ($\lambda_{max}^{H_2O}$ (ϵ): 525 (3×10^3), 335 (5.2×10^3), 314 (5.4×10^3)) and FAB MS (*m/e* 1733 ($M^+ + H$), 1755 ($M^+ + Na$)).

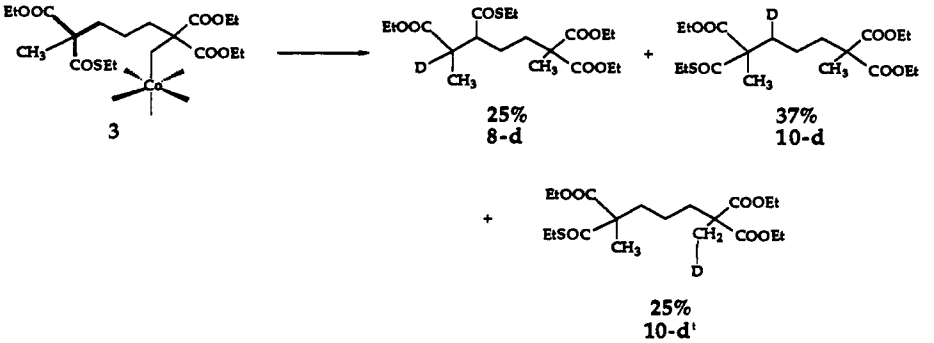
The alkylcobalamin **3** is a versatile model and can be explored in a variety of ways. When the adduct **3** was warmed to 55 °C in water under Ar for 14 h, rearrangement to **8**[7a,b] occurred in 41% yield (Scheme III). *This constitutes the first B_{12} model in which abstraction of hydrogen from unactivated carbon is coupled with group migration, leading to carbon skeleton rearrangement.* The olefin **9**[7a,b] and the reduced product **10**[7a,b] were also isolated. The material balance for the reaction in Scheme III was 93%.

Rearrangement also occurs when the bromide **7** is treated with vitamin B_{12s} in methanol at 55 °C. Again, the remote methylthiomalonate group is converted to thiosuccinate **8** (pair of diastereomers) in 25% yield, triggered by the reaction with vitamin B_{12s}. The remaining material is reduced product **10**.

Scheme III

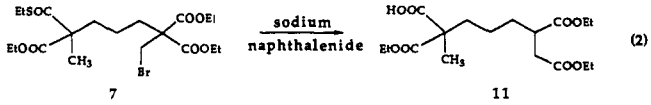


Scheme IV



This model makes it possible to compare the outcome of reactions originating from the carbon–cobalt bonded intermediate with those from free radical initiated ones. Moreover, free radicals in this series can be generated by two independent means. In one approach, the carbon–cobalt bonded adduct **3** was photolyzed at 27 °C in water under Ar yielding mainly the direct reduction product **10** (90%), but the rearrangement product **8** was detected and is present to the extent of 2–4%. In the second method, the starting bromide was treated under high-dilution conditions with tri-*n*-butyltin hydride. Reduction of the bromide to **10** was the major reaction course, but rearrangement product **8** was detected in 11% yield. If a further dilution was effected using syringe pump addition, the yield of rearrangement product **8** was 23%. From these experiments, after generation of the presumed free radical intermediate by two independent means and observation of rearrangement product in both instances, it is safe to suggest that the free radical pathway is a competent mechanism for the thermal rearrangement in Scheme III.

We also explored a carbanion pathway by treating the bromide **7** with sodium naphthalenide (eq 2). The product, formed in about 80% yield, was the ester-migrated product **11**;[7a,b] none of the thioester rearrangement product was detected.



7 11 (2)

If the rearrangement of **3** to **8** is carried out in CH_3OD, deuterium is incorporated into the products **8-d** (100% d_1), **10-d** (80% d_1), and **10-d′** (80% d_1) as shown in Scheme IV. The presence of deuterium in **10-d** suggests that a carbanion could play a role in the latter stages of the rearrangement. Thus, in addition to the radical path, a combination of radical and electron transfer steps leading to a carbanion as the penultimate intermediate can also be considered for the mechanism of the rearrangement in Scheme III.

Acknowledgment. This research was generously supported by the Institute for General Medical Sciences of the National Institutes of Health under Grant GM 19906.

(2) Dowd, P.; Shapiro, M.; Kang, K. *J. Am. Chem. Soc.* **1975**, *97*, 4754. Dowd, P.; Shapiro, M.; Kang, J. *Tetrahedron* **1984**, *40*, 3069. Flohr, H.; Pannhorst, W.; Rêtey, J. *Helv. Chim. Acta* **1978**, *61*, 1565. Dowd, P.; Shapiro, M. *J. Am. Chem. Soc.* **1976**, *98*, 3724. Dowd, P.; Shapiro, M. *Tetrahedron* **1984**, *40*, 3063. Scott, A. I.; Kang, K. *J. Am. Chem. Soc.* **1977**, *99*, 1997. Scott, A. I.; Kang, J.; Dalton, D.; Chung, S. K. *J. Am. Chem. Soc.* **1978**, *100*, 3603. Scott, A. I.; Kang, J.; Dowd, P.; Trivedi, B. K. *Bioorg. Chem.* **1980**, *9*, 227. Dowd, P.; Trivedi, B. K.; Shapiro, M.; Marwaha, L. K. *J. Am. Chem. Soc.* **1976**, *98*, 7875. Dowd, P.; Trivedi, B. K.; Shapiro, M.; Marwaha, L. K. *J. Chem. Soc., Perkin Trans. 2* **1985**, 413. Dowd, P.; Hershline, R. *J. Chem. Soc., Chem. Commun.* **1986**, 1409. Dowd, P.; Hershline, R. *J. Chem. Soc., Perkin Trans. 2* **1988**, 61. Wollowitz, S.; Halpern, J. *J. Am. Chem. Soc.* **1988**, *110*, 3112. Wollowitz, S.; Halpern, J. *J. Am. Chem. Soc.* **1984**, *106*, 8319. Dowd, P.; Choi, S.-C. *J. Am. Chem. Soc.* **1987**, *109*, 3493. Dowd, P.; Choi, S.-C. *Tetrahedron* **1989**, *45*, 77. Grate, J. W.; Schrauzer, G. N. *Z. Naturforsch.* **1984**, *39b*, 821. Grate, J. H.; Grate, J. W.; Schrauzer, G. N. *J. Am. Chem. Soc.* **1982**, *104*, 1588.

(3) For hydrogen abstraction models, see: Breslow, R.; Khanna, P. L. *J. Am. Chem. Soc.* **1976**, *98*, 1297. Breslow, R.; Khanna, P. L. *J. Am. Chem. Soc.* **1976**, *98*, 6765. Müller, P.; Rêtey, J. *J. Chem. Soc., Chem. Commun.* **1983**, 1342. Golding, B. T.; Kemp, T. J.; Sell, C. S.; Sellars, P. J.; Watson, W. P. *J. Chem. Soc., Perkin Trans. 2* **1978**, 839. Golding, B. T.; Sell, C. S.; Sellars, P. J. *J. Chem. Soc., Perkin Trans. 2* **1980**, 961.

(4) Choi, G.; Choi, S.-C.; Galan, A.; Wilk, B.; Dowd, P. *Proc. Natl. Acad. Sci. U.S.A.* **1990**, *87*, 3174.

(5) Cram, D. J. *Fundamentals of Carbanion Chemistry*; Academic Press: New York, 1965; p 19. Boerth, D. W.; Streitwieser, A., Jr. *J. Am. Chem. Soc.* **1981**, *103*, 6443.

(6) Werstiuk, N. H. *Tetrahedron* **1983**, *39*, 205.

(7) (a) The structure of this substance was established by the full range of spectroscopic tools including exact mass determination. (b) The structure of this product was established by direct comparison with an independently synthesized sample.

Isodideoxynucleosides: A Conceptually New Class of Nucleoside Antiviral Agents

Vasu Nair* and Zoraida M. Nuesca

Department of Chemistry, The University of Iowa Iowa City, Iowa 52242

Received April 6, 1992

Among active site directed inhibitors of HIV reverse transcriptase are the "natural" dideoxynucleosides: 2′,3′-dideoxyadenosine (ddA) and its metabolite, 2′,3′-dideoxyinosine (ddI), 2′,3′-dideoxyguanosine (ddG), and 2′,3′-dideoxycytidine (ddC).[1-5] However, dideoxynucleosides, particularly those of the purine family, are inherently unstable with respect to cleavage of the glycosidic bond,[6,7] because of the absence of the –I effect of the OH groups and the involvement in hydrolysis of the proximal ring oxygen. The discovery of therapeutically useful antiviral compounds that would be stable both with respect to glycosidic bond cleavage and enzymatic deamination, would be of considerable value in this area. Although numerous analogs of dideoxynucleosides (Scheme I, structure A) are known (see, for example, references 8–14), the synthesis of optically active regioisomeric structures has received much less attention.[15,16] One such class of compounds involves transposition of the base moiety from the natural 1′- to the 2′-position (using normal nucleoside numbering), while maintaining its cis relationship with the CH_2OH (Scheme I, structure B, *S,S* absolute configuration). We wish to report on the design and synthesis of this new family of stable, optically active compounds as antiviral agents.[17]

The chemistry will be illustrated with the case of 4(*S*)-(6-amino-9*H*-purin-9-yl)tetrahydro-2(*S*)-furanmethanol (**5**). A key step of the synthesis involved "glycosylation" of adenine with an appropriately tailored carbohydrate **4**, which was prepared in 17% overall yield from natural D-xylose, through preparation of **2**[18,19] and its conversion in several steps to **3** (Scheme II) involving deoxygenation (of imidazole thiocarbonyl ester of **2** with AIBN/Bu_3SnH), methyl acetal formation (MeOH, HCl), and demethoxylation (HMDS, TMSCl followed by Et_3SiH, TMS trilfate[20]). Condensation of the tosylate **4** with adenine (K_2CO_3,

(1) Mitsuya, H.; Weindhold, K. J.; Furman, P. A.; St. Clair, M. H.; Lehrman, S. N.; Gallo, R. C.; Bolognesi, D.; Barry, D. W.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1985**, *82*, 7096.

(2) Mitsuya, H.; Yarchoan, R.; Broder, S. *Science* **1990**, *249*, 1533.

(3) De Clercq, E. *Antiviral Res.* **1989**, *12*, 1.

(4) Yarchoan, R.; Mitsuya, H.; Thomas, R. V.; Pluda, J. M.; Hartman, N. R.; Perno, C.-F.; Marczyk, K. S.; Allain, J.-P.; Johns, D. G.; Broder, S. *Science* **1989**, *245*, 412.

(5) Mitsuya, H.; Broder, S. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 1911.

(6) York, J. L. *J. Org. Chem.* **1981**, *46*, 2171.

(7) Nair, V.; Buenger, G. S. *J. Org. Chem.* **1990**, *55*, 3695.

(8) Nair, V.; Buenger, G. S. *J. Am. Chem. Soc.* **1989**, *111*, 8502.

(9) Chu, C. K.; Beach, J. W.; Jeong, L. S.; Choi, B. G.; Comer, F. I.; Alves, A. J.; Schinazi, R. F. *J. Org. Chem.* **1991**, *56*, 6503.

(10) Beach, J. W.; Jeong, L. S.; Alves, A. J.; Pohl, D.; Kim, H. O.; Chang, C.-N.; Doong, S.-L.; Schinazi, R. F.; Cheng, Y.-C.; Chu, C. K. *J. Org. Chem.* **1992**, *57*, 2217.

(11) Marquez, V. E.; Tseng, C. K.-H.; Mitsuya, H.; Aoki, S.; Kelley, J. A.; Ford, H., Jr.; Roth, J. S.; Broder, S.; Johns, D. G.; Driscoll, J. S. *J. Med. Chem.* **1990**, *33*, 978.

(12) Vince. R.; Hua, M.; Brownell, J.; Daluge, S.; Lee, F.; Shannon, W. M.; Lavelle, G. C.; Qualls, J.; Weislow, O. S.; Kiser, R.; Canonico, P. G.; Schultz, R. H.; Narayanan, V. L.; Mayo, J. G.; Shoemaker, R. H.; Boyd, M. R. *Biochem. Biophys. Res. Commun.* **1988**, *156*, 1046.

(13) Nasr, M.; Litterest, C.; McGowan, J. *Antiviral Res.* **1990**, *14*, 125.

(14) Buenger, G. S.; Nair, V. *Synthesis* **1990**, 962.

(15) Huryn, D. M.; Tam, S. Y.; Weigele, M. European Patent No. 0 383 239, 1990.

(16) Terao, Y.; Akamatsu, M.; Achiwa, K. K. *Chem. Pharm. Bull.* **1991**, *39*, 823.

(17) These compounds are novel and have not been previously synthesized. They are isomeric with those reported in ref 15.

(18) Nair, V.; Emanuel, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 1571.

(19) Barton, D. H. R.; Subramanian, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1718.

(20) Bennek, J. A.; Gray, G. R. *J. Org. Chem.* **1987**, *52*, 892.

0002-7863/92/1514-7951$03.00/0