$N_2$-reducing reaction involving titanium, a Job plot[8] was constructed in which the yield of ammonia was measured as a function of the starting titanium(IV) isopropoxide/sodium naphthalide ratio. The absence of either reagent precluded ammonia formation, while a maximum yield of product was observed with a 1:6 ratio, reflecting the redox relationship required for the over-all conversion of $N_2$ to ammonia. Independently of the Ti/NaNp molar ratio, there was formed approximately 2 mol of ammonia per mol of $N_2$ taken up. Although the maximum ammonia yield observed per run in this system was 60–65%, essentially quantitative yields have been realized with titanium(IV) chloride under higher $N_2$ pressures.[9]

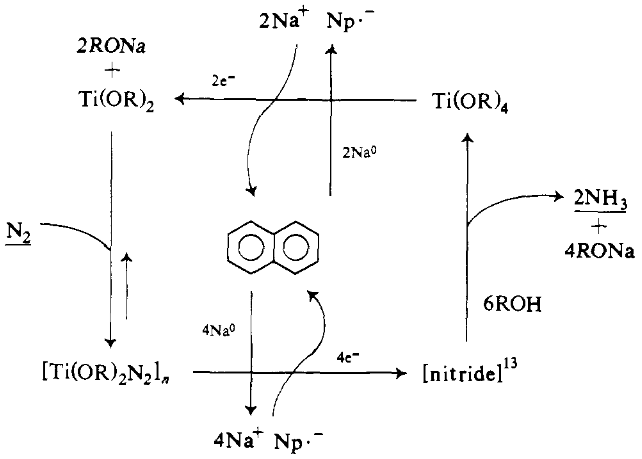
On the basis of early observations made on a slow, over-all aprotic reaction based on titanium(IV) chloride, alkoxide ion, and potassium metal, it was suggested that hydrogen in the product ammonia molecules originated under these conditions in the ethereal solvent used in the fixation–reduction reaction.[1] This claim is now qualitatively confirmed by experiments carried out with perdeuterated solvent, but otherwise in the same fashion as the earlier runs. By employing potassium *t*-butoxide and perdeuteriotetrahydrofuran and sweeping the system periodically with $N_2$ gas over a period of about 4 weeks, there was obtained solvent distillate which contained about 10% deuterium bound to ammonia nitrogen, as indicated by high-resolution mass spectral means. The amount of nitrogen-bound deuterium lost by exchange with water before or during the analytical determination is not known. Neither has the intermediate stage at which hydrogen abstraction takes place been identified; but because of the slower rate of formation and poor yield (about 10%) of ammonia in this reaction modification, it is likely that hydrogen abstraction from solvent does not intervene to any measurable extent in the runs featuring the efficient and rapid naphthalide reduction.[10]

On the basis of the evidence accumulated thus far, we believe the scheme in Chart I represents the titanium-based cycle by which $N_2$ is converted to ammonia in our system. Cyclical operation thus depends on the $N_2$-fixing ability of titanium(II), as well as regenerability of titanium(II) and reduction of the titanium-bound $N_2$, both brought about by NaNp available from a naphthalene pool by periodic reaction with reagent sodium metal. The over-all net process can be expressed as

$$N_2 + 6e^- + 6ROH \rightarrow 2NH_3 + 6RO^-$$

It is evident that this mode of $N_2$ fixation—the first room-temperature, atmospheric pressure process to be operated in an over-all catalytic fashion—differs from the original Vol'pin reaction,[11] wherein transition metal compounds are used in conjunction with alkyl Grignard reagents or metal hydrides as reducing species and hydrogen sources.[12] Finally, this cycle serves as a crude parallel or model for the biological $N_2$-fixation process, which in its simplest form probably involves initial interaction of lower valent transition metal with $N_2$ from the air, reduction of the coordinated $N_2$ species, followed by protonation of the fixed–reduced entity to give ammonia and regenerated lower valent metal.[13]

Chart I



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[8] M. M. Jones, "Elementary Coordination Chemistry," Prentice Hall Inc., Englewood Cliffs, N. J., 1964, p 282.

[9] G. Henrici-Olivé and S. Olivé, *Angew. Chem.*, **79**, 898 (1967); *Angew. Chem. Intern. Ed. Engl.*, **6**, 873 (1967).

[10] The Ti–H bonds postulated on the basis of esr data for the titanocene–naphthalide system [G. Henrici-Olivé and S. Olivé, *Angew. Chem.*, **80**, 398 (1968); *Angew. Chem. Intern. Ed. Engl.*, **7**, 386 (1968)] might be formed by such reactions. However, this phenomenon would probably be unrelated to the normal $N_2$ fixation–reduction process under discussion in that, whereas reaction with $N_2$ by titanium(IV)–naphthalide reagent prepared under $N_2$ is very rapid (~30–80 min), $N_2$ fixation is considerably slower by the titanium–naphthalide reagent prepared in advance under argon. It is clear that some additional reaction is superimposed, possibly hydrogen abstraction from solvent.

[11] (a) M. E. Vol'pin and V. B. Shur, *Nature*, **209**, 1236 (1966); (b) H. Brintzinger, *J. Am. Chem. Soc.*, **88**, 4305, 4307 (1966).

[12] The difference is illustrated by the result, *viz.*, no $N_2$ uptake and no ammonia formation, of treating titanium(IV) isopropoxide with α-naphthylmagnesium bromide, the Grignard counterpart of the naphthalene radical anion.

[13] Our efforts to characterize the nonprotonated fixation–reduction product have been only modestly rewarding. After a purification sequence involving selective organic solvent extractions and precipitations, there could be obtained an unstable, air-sensitive, black, powdery product, apparently a nitride which contained titanium, nitrogen, sodium, and isopropoxide units and which liberated ammonia on reaction with water or alcohols. Reliable evidence on the homogeneity of the intermediate is lacking.

[14] National Institutes of Health Postdoctoral Fellow, 1966–1968.

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[18] Fellowship provided by Swedish Council for Applied Research, 1967–1968.

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# Mechanism of the Titanium-Promoted Deoxygenative Coupling of Allyl and Benzyl Alcohols to Hydrocarbons

*Sir:*

As a convenient method for the synthesis of bibenzyls and 1,5-dienes, the direct reductive coupling of benzyl and allyl alcohols was recently innovated and developed in this laboratory.[1,2] Involving either identical or nonidentical

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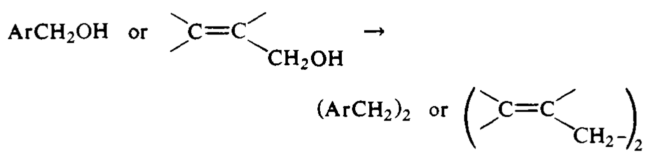
[1] E. E. van Tamelen and M. A. Schwartz, *J. Am. Chem. Soc.* **87**, 3277 (1965).

[2] K. B. Sharpless, R. P. Hanzlik, and E. E. van Tamelen, *ibid.*, **90**, 209 (1968).



alcoholic partners, coupling is effected by treatment of the starting alcohol with controlled amounts of titanium(III) or -(IV) chloride, reduction of the nonisolated titanium alkoxide species with metallic potassium, alkyllithium, or sodium naphthalide (NaNp), and final warming or photolyzing the titanium organic intermediates. We have now accumulated results confirming that all variations of the process involve the production of titanium(II) alloxide or benzoxide, which decomposes easily, providing product by way of a benzyl or allyl radical route.

The following observations point to the crucial role of titanium dialkoxides in the coupling process. In the titanium trichloride–sodium naphthalide system, for example, optimal yields are realized with 1 mole of reducing agent; use of lesser or greater amounts of naphthalide results in a diminished yield of coupled hydrocarbon[3] (Table I). Similarly, use of more than an equivalent amount of methyllithium with titanium trichloride leads to greatly lowered yields of final product.[3] Clearly, titanium(III) intermediates are less effectual in coupling, and reduction below the titanium(II) level is deleterious.

**Table I.** $(C_6H_5CH_2O)_2TiCl$ + *a* Moles of Sodium Naphthalide

| *a* | Total yield of bibenzyl, % | Yield of bibenzyl corrected for recovered $C_6H_5CH_2OH$, % |
|---|---|---|
| 0.5 | 27 | 48 |
| 1.0 | 55 | 57 |
| 1.5 | 15 | 16 |
| 2.0 | <1 | <1 |

In the titanium trichloride–methyllithium modification, there is produced from benzyl alcohol an isolable but impure and highly air-sensitive black, titanian product, mp 58–62°, analysis of which indicated a predominance of titanium(II) benzoxide.[4] On being heated in glyme under conditions which approximate those prevailing in the normal coupling reaction, the black alkoxide generated bibenzyl in >50% yield. Reduction–coupling attempts depending on the use of zirconium, gallium, chromium, manganese, or uranium halides were completely unsuccessful. Limited reaction was observed by means of silicon or vanadium halides, as previously described.[1,2]

That the formation of the new carbon–carbon bond in the coupling reaction requires an extra measure of stabilization in the organic residues was demonstrated by the success in allyl and benzyl cases, and failure in saturated alkyl attempts. The following observations strongly indicate that this stabilization is associated with lower energy radical participation. Coupling of pure *trans*-geraniol gives all possible (five) *cis*, *trans*, primary–primary, and primary–tertiary joined products (recovered alcohol is pure *trans*-geraniol). Nerol and linalool behave the same, except that (1) a slightly different ratio of the isomers is formed in lower yield and (2) in the case of nerol, limonene is apparently also generated. In a cross-coupling experiment conducted by mixing equal amounts of titanium(II) geranoxide and farnesoxide prior to heating, $C_{20}:C_{25}:C_{30}$ products were formed in the statistical ratio 1:2:1. In the reaction of $\gamma,\gamma$-dimethylallyl alcohol, all three possible coupling products (primary–primary, primary–tertiary, and tertiary–tertiary) are generated. The ratio of products formed in the normal titanium(II) coupling reaction (Table II) compares well with ratios observed[5,6] for decomposition which has been shown to involve liberation of allyl-type radicals (no. 9), but is different from those which probably possess carbanionic character (no. 7 and 8).[7,8] In the benzyl alcohol case, benzyl radicals can be intercepted by anthracene, and 9,10-dibenzyldihydroanthracene and dibenzyltetrahydrodianthryl were isolated in good yield; concurrently, the yield of bibenzyl plummets.

Accepting that decomposition of a titanium(II) alkoxide occurs by a radical route, we endeavored to distinguish between the extremes of a stepwise (a) and a concerted (b) expulsion of carbon radicals. Only a trace of bibenzyl was formed when the product, presumed to be $TiO(OCH_2C_6H_5)$, of interaction between 1 equiv of sodium

$$Ti(OCH_2C_6H_5)_2 \rightarrow C_6H_5CH_2\cdot + TiO(OCH_2C_6H_5) \rightarrow TiO_2 + C_6H_5CH_2\cdot \qquad (a)$$

$$Ti(OCH_2C_6H_5)_2 \rightarrow TiO_2 + 2C_6H_5CH_2\cdot \qquad (b)$$

naphthalide and $TiO(OCH_2C_6H_5)Cl$, was heated under customary conditions, and thus no support for possibility a was forthcoming.

In view of the foregoing the most reasonable interpretation of the over-all $TiCl_4$–$K^0$ or sodium naphthalide process can be summarized as

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[3] (a) Insignificant amounts of toluene are formed in this coupling reaction. (b) In the titanium trichloride system, some coupling product is produced even when the reducing agent is omitted from the otherwise normal procedure. Since the appearance of this reaction in its later stages (*e.g.*, development of opaque, black reaction medium) connotes incursion of a titanium(II) species, the over-all process may be promoted by a disproportionation reaction (i), similar to the known thermal conversion of titanium trichloride to a mixture of dichloride and tetrachloride.

$$2(RO)_2Ti\text{-}Cl \rightarrow (RO)_2TiCl_2 + (RO)_2Ti \qquad (i)$$

[4] The titanium benzoxide can be converted to a bipyridyl complex which on thermolysis gives rise to bibenzyl in ~20% yield. The bipyridyl ligand may lower the yield by acting as an "internal" trapping agent for benzyl radicals.

(5) D. B. Denney, R. M. Hoyte, and P. T. MacGregor, *Chem. Commun.*, 1241 (1967).

(6) L. W. Menapace and H. G. Kuivila, *J. Am. Chem. Soc.*, **86**, 3047 (1964).

(7) Because of extensive primary–tertiary bond formation, the linear coupling of substituted allyl halides by the Grignard method has limited synthetic value.

(8) Although the radicals may not be completely free, as indicated by the slightly different isomer distribution obtained from geraniol, nerol, and linalool, the extreme efficiency of anthracene as a radical scavenger indicates that the decomposition of titanium dialkoxide has little cage character. One mole of anthracene per mole of titanium gave only 3% of bibenzyl, in contrast to the decomposition of dibenzylmercury, which in the presence of 1 mole of anthracene/mole of mercury gave 30% bibenzyl (K. C. Bass and P. Nababsing, *J. Chem. Soc.*, 1184 (1966)). However, the decomposition of titanium dibenzoxide in the presence of anthracene gave mainly the thermodynamically unstable isomer of dibenzyltetrahydrodianthryl, mp 227–228°, whereas benzylmagnesium chloride and cobalt chloride gave mainly the more stable isomer, mp 238–240° (R. O. C. Norman and W. A. Waters, *ibid.*, 950 (1957)). Therefore, in the case of titanium dibenzoxide, the decomposition may involve coordinated anthracene.

**Table II**

| No. | Reactions: Starting material | Reactions: Reagents | Product ratios: *trans–trans* | *cis–trans* | *cis–cis* | *trans–tert* | *cis–tert* |
|---|---|---|---|---|---|---|---|
| 1 | Geraniol | $TiCl_3$–MeLi | 1.00 | 0.82 | 0.24 | 0.77 | 0.32 |
| 2 | Nerol | $TiCl_3$–MeLi | 1.00 | 1.23 | 0.44 | 0.72 | 0.43 |
| 3 | Linalool | $TiCl_3$–MeLi | 1.00 | 1.20 | 0.40 | 0.80 | 0.50 |
| 4 | Geraniol | $TiCl_3$–$C_6H_5Li$ | 1.00 | 1.24 | 0.31 | 0.85 | 0.34 |
| 5 | Geraniol | $TiCl_3$–NaNp | 1.00 | 0.90 | 0.23 | 0.75 | 0.33 |
| 6 | Geraniol | $TiCl_3$–MeLi (uv photolysis) | 1.00 | 0.66 | 0.10 | 0.63 | 0.15 |
| 7 | Geranyl chloride | NaNp | 1.00 | 0.04 | None | 1.20 | None |
| 8 | Geranyl chloride | Geranyl MgCl | 1.00 | 0.74 | 0.22 | 2.20 | 0.67 |
| 9 | Geranyl chloride | $(C_6H_5)_3SnH$ (product: $(CH_3)_2C{=}CH(CH_2)_2\underset{\underset{CH_3}{\vert}}{C}{=}CHCH_3)$ | $\frac{cis}{trans} = 0.38\text{–}0.48$; $\frac{tert}{cis + trans} = 0.14\text{–}0.16$ | | | | |

$$RO^- + TiCl_4 \rightarrow \left\{ (RO)_2TiCl_2 \xrightarrow[NaNp]{K^0 \text{ or}} \left[ (RO)_2Ti \right]_n \leftrightharpoons \right.$$

$$\left. n(RO)_2Ti \overset{\Delta}{\rightarrow} (TiO_2)2R\cdot \right\} \rightarrow R{-}R$$

In the case of the aryllithium–titanium trichloride modification, no chlorobenzene was detectable as product when phenyllithium was employed; however, biphenyl and benzene were observed. Since titanium(III) and -(IV) alkyls and aryls are known to generate carbon radicals, the following view of this modification is thought reasonable.

$$TiCl_3 + 2ROH \xrightarrow{2R'Li} \left\{ (RO)_2TiCl \xrightarrow{R'Li} (RO)_2TiR' \xrightarrow{-R'} \right.$$

$$\left. (RO)_2Ti \xrightarrow[\text{(as in a)}]{\Delta} \right\} \underline{R{-}R}$$

The pertinence of this coupling chemistry to the titanium-induced nitrogen fixation–reduction phenomena currently under study in this laboratory is evident (see preceding communication).

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[9] Fellowship provided by Swedish Council for Applied Research, 1967–1968.

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## The Effects of Metal Components and Acids on Racemization in the Synthesis of Peptides by the Oxidation–Reduction Condensation

*Sir:*

In our previous paper[1] we reported that Z-Phe-Gly-OEt can be synthesized without racemization by way of an oxidation–reduction condensation starting from the NPS-amino acid ester (A) or from a free amino acid ester (B), respectively, according to the following equations.

$$(Z\text{-}L\text{-}Phe)_2Cu + 2NPS\text{-}Gly\text{-}OEt + 4Ph_3P \rightarrow 2Z\text{-}L\text{-}Phe\text{-}Gly\text{-}OEt + [Cu(SC_6H_4NO_2)_2\cdot Ph_3P] + 3Ph_3P{=}O \quad \text{(A)}$$

$$Z\text{-}L\text{-}Phe\text{-}OH + H\text{-}Gly\text{-}OEt + HgCl_2 + (o\text{-}O_2NC_6H_4S)_2 + Ph_3P + 2Et_3N \rightarrow Z\text{-}L\text{-}Phe\text{-}Gly\text{-}OEt + Hg(SC_6H_4NO_2)_2 + Ph_3P{=}O + 2Et_3N\cdot HCl \quad \text{(B)}$$

This communication reports the further examination of racemization during peptide bond formation by the more sensitive Young test[2] and its prevention.

In the type A reaction, an unsatisfactory result was obtained with the Young test, probably because of the generation of ethyl glycinate anion as an intermediate.

For example, when copper(II) benzoyl-L-leucinate (5 mmol), N-(*o*-nitrophenylsulfenyl)glycine ethyl ester (10 mmol), and triphenylphosphine (20 mmol) were allowed to react in methylene chloride for 8 hr, Bz-Leu-Gly-OEt was obtained by chromatography on silica gel in 77% yield, mp 148–149°, $[\alpha]^{20}D$ −17.4° (*c* 3.1, EtOH), L isomer[2] 57% [lit.[2] L isomer mp 156–157°, $[\alpha]^{20}D$ −34° (*c* 3.1, EtOH)].

As to the Young test, the racemization intermediate is known to be 4-isobutyl-2-phenyloxazolone whose formation is catalyzed by bases.[3] A base-catalyzed enolization mechanism which involved two possible proton abstraction steps from the amide hydrogen and from the oxazolone hydrogen was also reported by Kemp and his associates.[4]

The effect of acidic additives was studied on the assumption that racemization could be prevented by keeping the reaction medium neutral or acidic. For example, when copper(II) benzoyl-L-leucinate (5 mmol), NPS-glycine ethyl ester (10 mmol), and triphenylphosphine (10 mmol) were allowed to react in the presence of 2,4-dinitrophenol (10 mmol) for 8 hr, Bz-Leu-Gly-OEt was obtained in 81% yield, 77% L isomer.[2]

Of six acidic additives, 2,4-dinitrophenol (81% yield, 77% L isomer), picric acid (48%, 80% L isomer), and N-hydroxysuccinimide[5] (63%, 82% L isomer) proved to be

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[1] T. Mukaiyama, M. Ueki, H. Maruyama, and R. Matsueda, *J. Am. Chem. Soc.*, **90**, 4490 (1968).

[2] M. W. Williams and G. T. Young, *J. Chem. Soc.*, 881 (1963). The per cent of L isomer was calculated from $[\alpha]^{20}D$ − 34° as in Young's report.

[3] M. W. Williams and G. T. Young, *J. Chem. Soc.*, 3701 (1964).

[4] D. S. Kemp and S. W. Chien, *J. Am. Chem. Soc.*, **89**, 2746 (1967).

[5] J. E. Zimmerman and G. W. Anderson, *ibid.*, **89**, 7151 (1967). Favorable results were obtained by adding N-hydroxysuccinimide in the DCCD method but not obtained by pivalic acid. The major reason is reported to be the formation of N-hydroxysuccinimide ester.