Indian Journal of Chemistry
Vol. 41B, May 2002, pp. 1064-1067

Removal of some commonly used protecting groups in peptide syntheses by catalytic transfer hydrogenation with formic acid and 10% palladium on carbon

D Channe Gowda*

Department of Studies in Chemistry,
Manasagangotri, University of Mysore, Mysore 570 006, India

It is shown that HCOOH, a good solvent for most peptides, can be conveniently used as a hydrogen donor for catalytic transfer hydrogenation with less expensive 10% Pd on C when compared to palladium black. The protecting groups that are being successively removed include the N^{α}-benzyloxycarbonyl, N^{ε}-2-chlorobenzyloxycarbonyl, *C*-terminal benzyl ester, *O*-benzyl ether of *O*-benzyltyrosine, serine or threonine, nitro of nitroarginine and N^{im}-benzyloxymethyl of histidine.

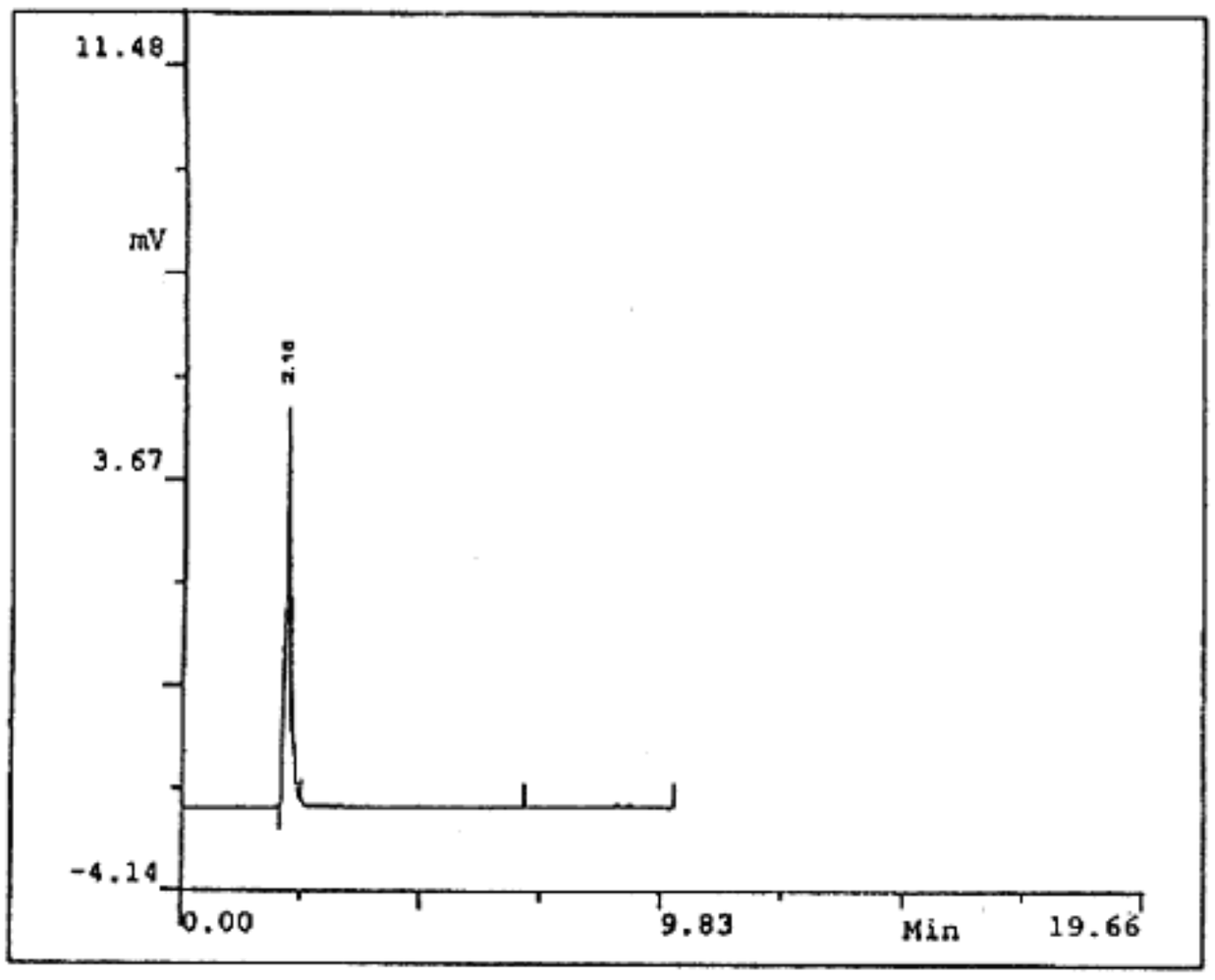
For the removal of some commonly used protecting groups in peptide synthesis, catalytic transfer hydrogenation offers certain advantages over the catalytic hydrogenation procedure, which is generally employed for this purpose. A number of improvements in the area of catalytic transfer hydrogenation have been reported[1-8] which greatly simplify these procedures and some even reduce the operating conditions to standard room temperature and pressure[5-8]. These employed such catalytic transfer hydrogenation agents as cyclohexene[1,2], hydrazine[3], cyclohexadiene[4], formic acid[5,6] and $HCOONH_4$[7,8]. Palladium catalyst has been reported to be most effective for transfer hydrogenation[9]. It was reported that 10% Pd on carbon was effective with cyclohexene, hydrazine, cyclohexadiene and $HCOONH_4$ whereas with HCOOH donor, it requires more reactive and expensive freshly prepared palladium black catalyst, further the deprotection with formic acid is no longer rapid as that with $HCOONH_4$/ 10% palladium on carbon[7].

The present work describes the use of formic acid, a good solvent for most peptides, as a convenient hydrogen donor for catalytic transfer hydrogenation with less expensive 10% Pd on carbon when compared to palladium black. Using methanol as the solvent, a variety of amino acids and peptide derivatives were smoothly deprotected in minute as shown in the **Table I**. The protecting groups that are being successively removed include the N^{α}-benzyloxycarbonyl, N^{ε}-2-chlorobenzyloxycarbonyl, *C*-terminal benzyl ester, *O*-benzyl ether of *O*-benzyl-tyrosine, -serine or -threonine, nitro of nitro-arginine, and N^{im}-benzyloxymethyl of N^{im}-benzyloxymethyl-histidine. Even as a low concentration of formic acid in methanol (50%) results in rapid removal of these protecting groups but which also reduces the possibility of removal of acid labile protecting groups like N^{α}-*tert*-butyloxycarbonyl and *tert*-butyl esters. Under these experimental conditions the *tert*-butyloxycarbonyl group appears to be quite stable as indicated by 90-98% yield of Boc-amino acid and peptide derivatives, which is, supported fairly well by the absence of free amino acids as revealed by the TLC of the crude products. The results given in **Table I** demonstrate the feasibility of using HCOOH/10% Pd-C for the removal of N^{α}-benzyloxycarbonyl, N^{ε} -2-chlorobenzyloxycarbonyl, *C*-terminal benzyl ester, *O*-benzyl ether of *O*-benzyl-tyrosine, -serine or -threonine, nitro of nitro-arginine, and N^{im}-benzyloxymethyl of N^{im}-benzyloxymethyl-histidine protecting groups by this method. All the products were characterized by comparison of their TLC and melting points with authentic samples. It was observed that this method is equally competitive with other methods in deblocking N^{α}-benzyloxycarbonyl group and even more efficient in deblocking *O*-benzyl ethers of *O*-benzyl-tyrosine or -serine or -threonine and *C*-terminal benzyl esters. The advantages of transfer hydrogenation over conventional hydrogenation have been described. Formic acid, however, offers several additional advantages as compared to previously used hydrogen donors, and should be preferred in more cases. Thus, unlike cyclohexene or cyclohexadiene, HCOOH is an excellent solvent for most peptides and peptide derivatives and allows for complete solubilization of reactants and products in the great majority of cases. *tert*-Butyloxycarbonyl group present in the protected peptides has been completely removed along with the other protecting groups by using 98-100% formic acid. The use of 10% Pd-C/ HCOOH makes this a rapid, low-cost alternate to Pd black and reduce the work-up to a simple filtration and extraction operation.

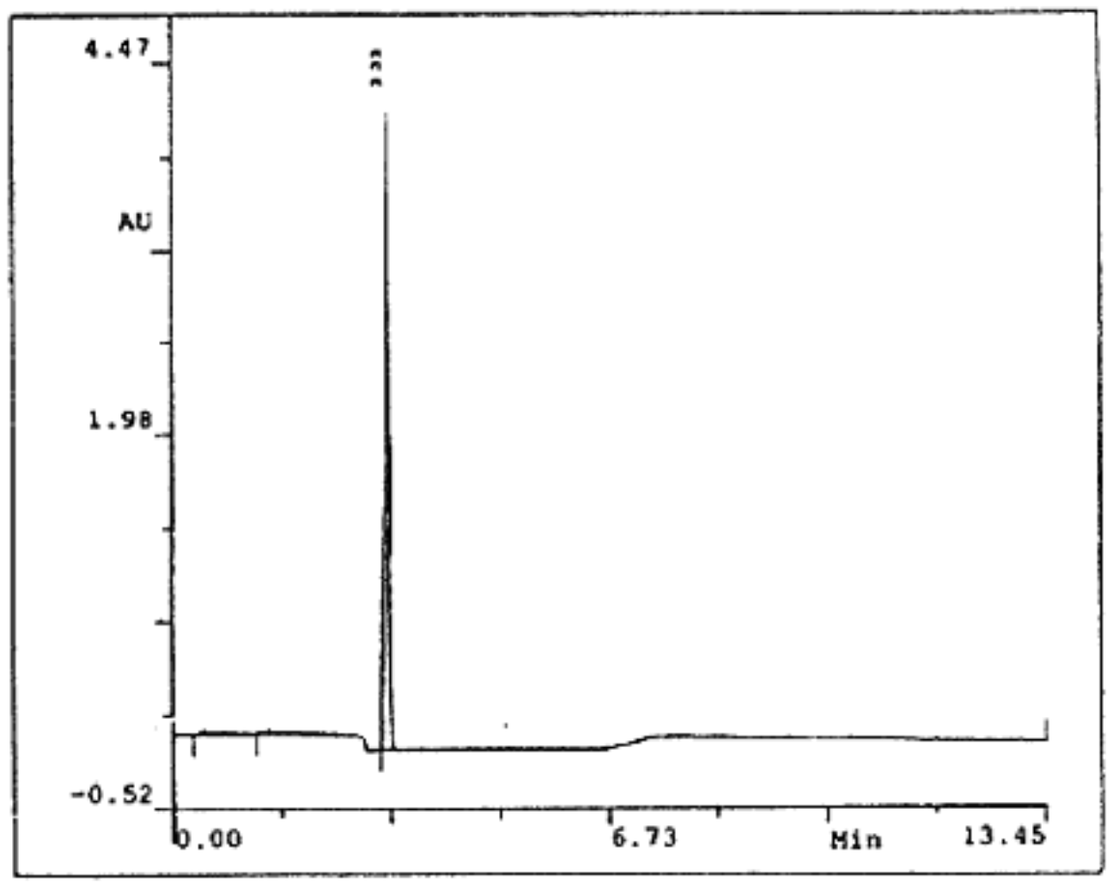
Table I — Catalytic transfer hydrogenolysis of protected amino acids and peptides with formic acid / 10% Pd-C

Substrate[a]	Reaction period (in min)	Product [b]	Yield[c] (%)	mp °C (reported)
Z-Gly	3	Gly-HCOOH	95	n.d.
Z-Lys	3	Lys.2HCOOH	92	186-187 (186-187)[6]
Z-Pro	3	Pro. HCOOH	92	n.d.
Z-Phe	3	Phe. HCOOH	95	n.d.
Z-Ala	3	Ala. HCOOH	95	n.d.
Z-Met	3	Met. HCOOH	89	n.d.
Z-Leu-OC_4H_9-t	5	Leu-OC_4H_9-t.HCOOH	88	Oil (Oil)[7]
Boc-Lys(Z)	3	Lys.2HCOOH[e]	92	186-187 (186-187)[6]
Boc-Lys(2-ClZ)	360	Lys.2HCOOH[e]	92	186-187 (186-187)[6]
Boc-Asp(OBzl)	5	Boc-Asp[d]	95	176-177 (176-177)[10]
Boc-Glu (OBzl)	10	Boc-Glu[d]	90	172-173 (171-172)[10]
Boc-Tyr(Bzl)	8	Boc-Tyr	85	136-137 (136-137)[10]
Boc-Ser (Bzl)	8	Boc-Ser[d]	86	140-141 (140-142)[10]
Boc-Thr (Bzl)	5	Boc-Thr[d]	90	154-155 (154-155)[10]
Boc-His (Bom)	120	Boc-His. HCOOH	84	191-192 (191-192)[11]
Z- Gly-Gly	5	Gly-Gly. HCOOH	90	208-210 (207-211)[6]
Z-Gly-Arg (NO_2)	120	Gly-Arg.2HCOOH	84	114-117 (115-118)[6]
Z-Phe-Met-NH_2	10	Phe-Met-NH_2.HCOOH	82	147-149 (147-149)[5]
Z-Phe-Leu-OC_4H_9 -t	10	Phe-Leu-OC_4H_9-t HCOOH	80	Oil (Oil)[7]
Boc-Ala- Ser (Bzl)-Tyr-OMe[e]	120	Ala-Ser-Tyr-OMe. HCOOH	88	135-137 (134-138)[5]
Boc-Ala-Tyr (Bzl)-Gly-Leu-OEt[e]	120	Ala-Tyr-Gly-Leu-OEt. HCOOH	85	101-108 (101-109)[5]
Boc-Leu Phe- Gly-Gly-Arg (NO_2)-OBzl[e]	180	Leu-Phe-Gly-Gly-Arg.2HCOOH	83	180-184 (181-185)[5]

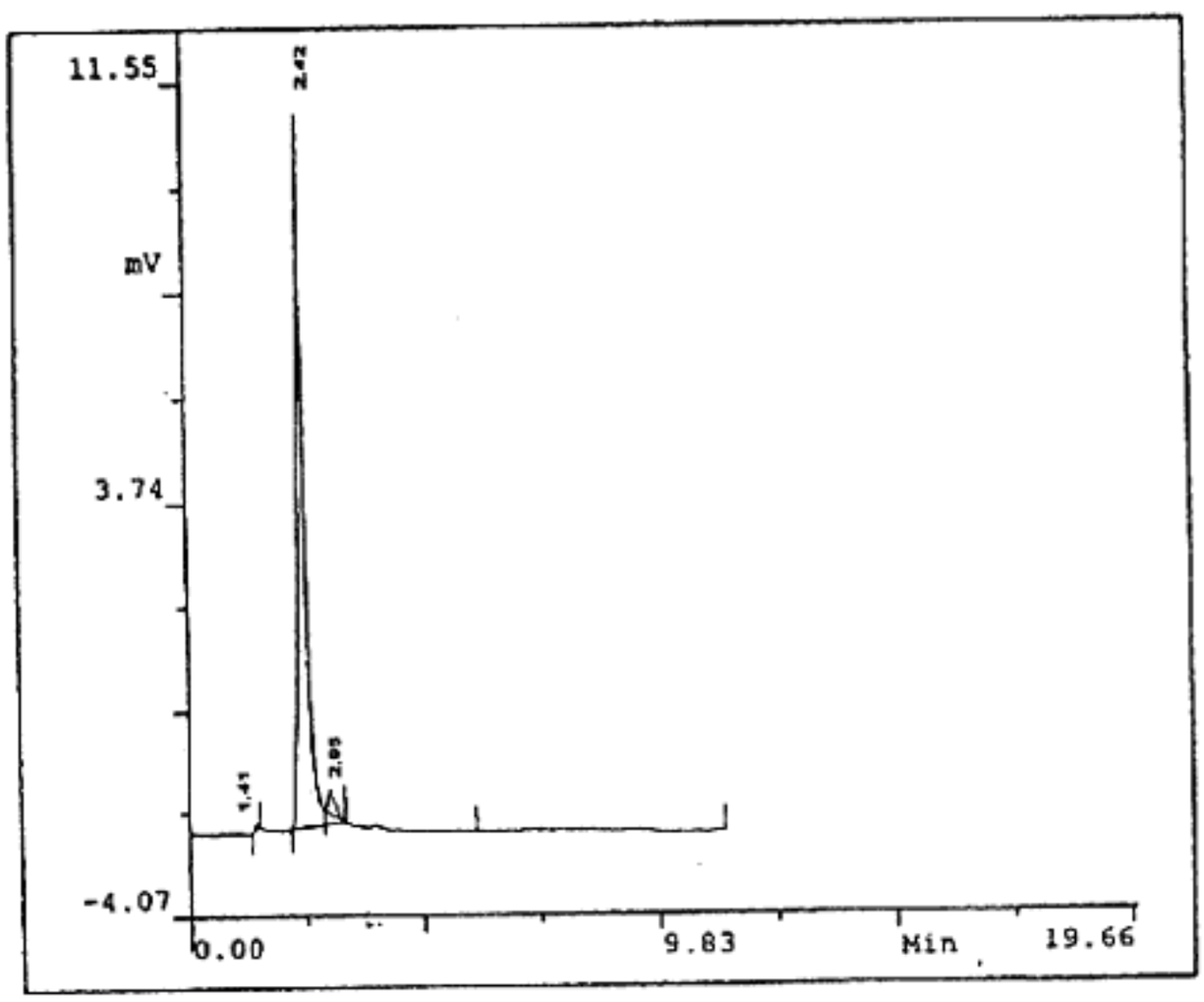
[a] Except for glycine, the amino acids in these peptide have the L-configuration,
[b] Satisfactory elemental analyses have been obtained,
[c] No attempt was made to optimize these yields.
[d] Isolated as dicyclohexylammonium salt
[e] 98-100% formic acid was used.
n.d. Not determined



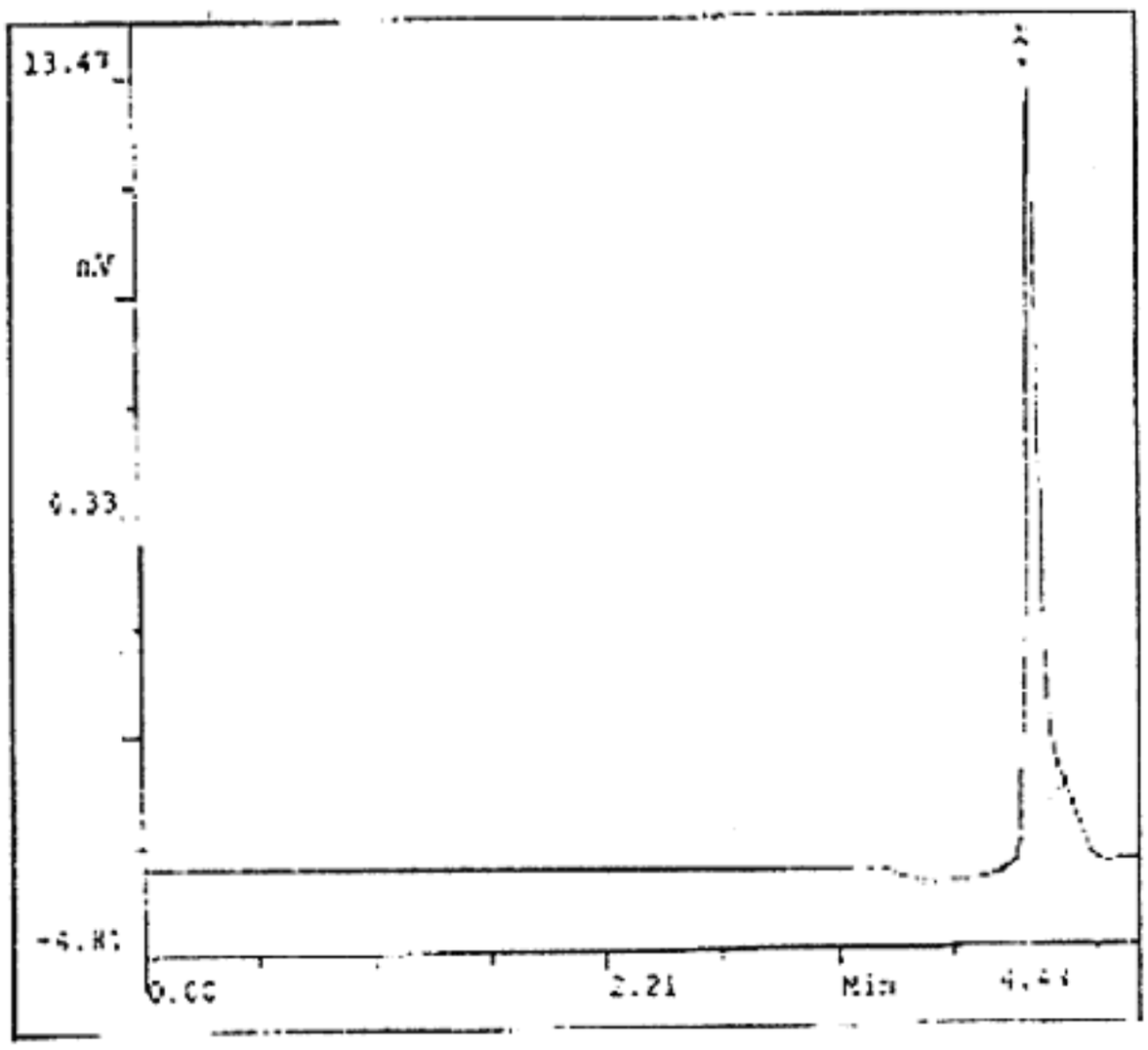
(a)



(b)



(c)



(d)

Figure 1 — HPLC Chromatograms of (a) Boc-Tyr(OBzl) [before deprotection], (b) Boc-Tyr [after deprotection], (c) Boc-Leu-Phe-Gly-Gly-Arg(NO_2)-OBzl [before deprotection], (d) Leu-Phe-Gly-Gly-Arg [after deprotection]

Experimental Section

General procedure for hydrogenolysis using formic acid. To a stirred solution of an appropriate protected amino acid derivative or peptide (200 mg) and 10%Pd-C (50 mg) in methanol (2.5 mL), 90% formic acid (2.5 mL) was added. The resulting reaction mixture (exothermic and effervescent) was stirred at room temperature. After completion of the hydrogenolysis (monitored by TLC), the mixture was filtered through celite and washed with formic acid. The combined washings and filtrate were evaporated, the residue was taken up in methanol and anhydrous ether was added to precipitate amino acid or peptide derivatives. The reaction periods, yields and physical constants are listed in **Table I**. The HPLC chromatograms of an amino acid derivative and a peptide are provided in **Figure 1**.

References

1 Jackson A E & Johnstone R A W, *Synthesis*, **1976**, 685.
2 Anantharamaiah G M & Sivanandaiah K M, *J Chem Soc, Perkin Trans 1*, 5, **1977**, 490.

3 Felix A M, Heimer E P, Lambros T J, Tzougraki C & Meienhofer J, *J Org Chem*, 43, **1978**, 4194.
4 Anwer M K, Khan S A & Sivanandaiah K M, *Synthesis*, **1978**, 75.
5 Sivanandaiah K M & Gurusiddappa S, *J Chem Res (S)*, 7, **1979**, 108.
6 Elamin B, Anantharamaiah G M, Royer G P & Means G E, *J Org Chem*, 44, **1979**, 3442.
7 Anwer M K & Spatola A F, *Synthesis*, **1980**, 929.
8 Channe Gowda D, Rajesh S & Shankare Gowda, *Indian J Chem*, 39B, **2000**, 504.
9 Braude E A, Linstead R P & Woolridge K R H, *J Chem Soc*, **1954**, 3586.
10 Fletcher G A & Jones J H, *Int J Pept Protein Res*, 4, **1972**, 347.
11 Hartford B O, Hylton T A, Wang K & Weinstein B, *J Org Chem*, 33, **1968**, 425.