Autorecycling System for Reduction of Carbonyl Compounds to Alcohols by 1,5-Dihydro-5-deazaflavins

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Summary An effective recycling system for the reduction of carbonyl compounds to alchohols was constructed for the first time using 5-deazaflavins and formic acid, in such a way that each mol of the compound catalyses the reduction, by formic acid, of up to 25 mol of benzaldehyde.

1,4-DIHYDROPYRIDINE derivatives (NADH analogues) can reduce non-enzymatically only those carbonyl compounds which are highly activated because of the presence of electron-deficient and *ortho*-phenolic groups.[1,2] Ohnishi and Kitami reported that, with the aid of Mg^{2+} ions, benzaldehyde is reduced by 1,4-dihydronicotinamides (10-fold excess) in 2—9% yield.[3]

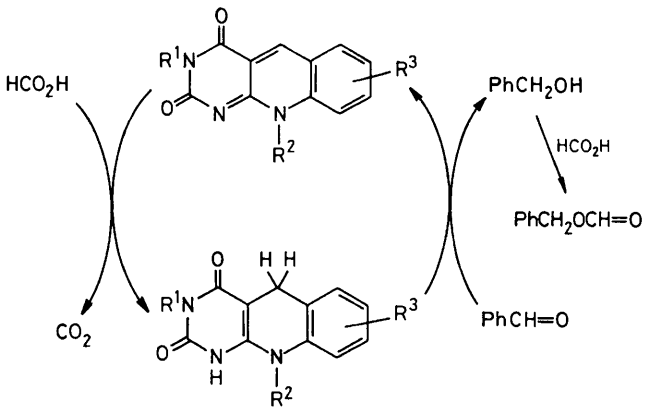
We recently found that 1,5-dihydro-5-deazaflavin (or 5-deazaisoalloxazine; 'NADH in flavin clothing'[4]) is able to reduce carbonyl compounds in stoicheiometric yields in the presence of strong proton sources.[5,6] This was the first example of the reduction of carbonyl substrates which are not activated to the corresponding alcohols by an NADH model. Shinkai *et al.* showed that 3-carbamoyl-*N*-benzyl-1,4-dihydroquinoline is also able to reduce benzaldehyde in 20—30% yield under acidic conditions.[7]

We have now found that the reduction of carbonyl compounds by 1,5-dihydro-5-deazaflavin is automatically recycled in formic acid. This communication describes the first example of an autorecycling system for the reduction of carbonyl compounds to alcohols using 5-deazaflavins and formic acid.

A typical experimental run is as follows: a mixture of a 5-deazaflavin or analogue (0·066 mmol) and benzaldehyde (1·888 mmol) in 98% formic acid† (3 ml) was gently refluxed (oil-bath temperature 120 °C). The reaction mixture was analysed by gas chromatography or high-speed liquid chromatography and the product was identified as

† 80% Formic acid was also effective in the system, giving slightly lower yields however.

benzyl formate. On treatment of the reaction mixture with sodium hydroxide, the benzyl formate was readily converted into benzyl alcohol in quantitative yield (g.l.c.). Under these conditions, the 5-deazaflavin or analogue is initially hydrogenated by formic acid to the corresponding 1,5-dihydro-5-deazaflavin or analogue, which acts as turnover catalyst according to the Scheme. In fact, refluxing of a 5-deazaflavin in formic acid for several hours gave the corresponding 1,5-dihydro-5-deazaflavin in about 60% yield.



SCHEME

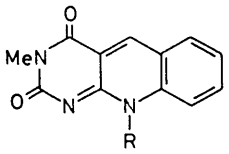
The Table shows the results for the reduction of benzaldehyde by several organic catalysts. In this series, a significant substituent effect was observed; in particular 10-aryl-5-deazaflavins (**5a**—**e**)[8] exhibited a strong reducing ability towards benzaldehyde. In contrast with compounds (**5**), the corresponding flavins (**6a**, **b**)[9] did not show any appreciable reducing ability.

It is interesting that the above reduction proceeds until the aldehyde substrate is almost exhausted: for example, in the system using compound (**5a**), benzaldehyde was converted into benzyl formate in 41·8 and 81·2% yield after 25 and 50 h, respectively. These yields represent conversions of 11·96 and 23·21 mol of benzaldehyde per mol of catatyst (**5a**). No reduction of benzaldehyde by formic acid alone can be detected under the reaction conditions.

TABLE. Reduction of benzaldehyde to benzyl alcohol (identified as benzyl formate) by 5-deazaflavins or analogues and formic acid at 120 °C.

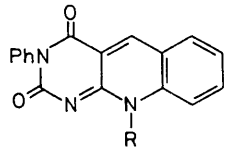
Catalyst	Recycling number of the catalyst	Yield (%)[b] of benzyl formate after 10 h
(**1a**)	1·07	3·7
(**1b**)	1·60	5·6
(**1c**)	1·77	6·2
(**1d**)[a]	0·39	1·4
(**1e**)[a]	0·20	0·7
(**2a**)	<0·20	<0·7
(**2b**)	1·19	4·2
(**2c**)	1·66	5·8
(**2d**)[a]	<0·20	<0·7
(**3**)	<0·10	<0·3
(**4a**)	1·30	4·5
(**4b**)	0·80	2·8
(**4c**)	<0·10	<0·3
(**5a**)	5·98	20·9
(**5b**)	5·63	19·7
(**5c**)	2·87	10·0
(**5d**)	6·76	23·6
(**5e**)	3·10	10·8
(**6a**)	<0·20	<0·7
(**6b**)	<0·20	<0·7
(**7**)	<0·10	<0·3

[a] Compounds (**1d** and **e**) and (**2d**) are new compounds synthesized by the condensation of 6-chloro-5-formyluracils and *N*-alkylanilines (refs. 10, 11); satisfactory analytical and spectral data were obtained for these compounds. [b] Based on benzaldehyde.



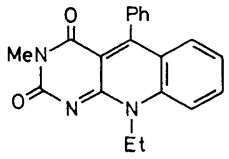
(1)[a]

a; R = Me
b; R = Et
c; R = Bu^n
d; R = n-C_8H_{17}
e; R = n-$C_{12}H_{25}$

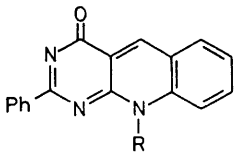


(2)[b]

a; R = Et
b; R = Pr^n
c; R = Bu^n
d; R = n-$C_{12}H_{25}$

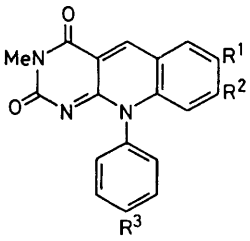


(3)[c]



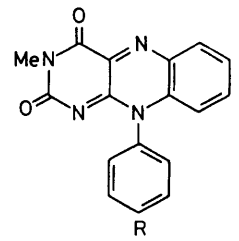
(4)[b]

a; R = Me
b; R = Et
c; R = Bu^n



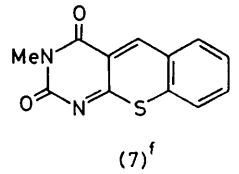
(5)[d]

a; $R^1 = R^2 = R^3 = H$
b; R^1 = Cl, $R^2 = R^3 = H$
c; $R^1 = R^3 = H$, R^2 = Cl
d; $R^1 = R^3 = H$, R^2 = Me
e; $R^1 = R^2 = H$, R^3 = Cl



(6)[e]

a; R = H
b; R = Cl



(7)[f]

[a] Ref. 10; [b] ref. 11; [c] ref. 12; [d] ref. 8; [e] ref. 9; [f] ref. 13.

Thus the present study offers a useful and practical autorecycling system for the reduction of carbonyl compounds to alcohols, and we believe that stereospecific autorecycling reduction could be achieved by modifying the

structure of the 5-deazaflavin. This autorecycling system is reminiscent of the enzymic formate- and 5-deazaflavin-*dependent* $NADP^+$ reduction in methane-producing bacteria.[14]

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