Reduction by a Model of NAD(P)H. 34. Substituent Effect on Asymmetric Reduction of Trifluoroacetophenones

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Substituted and unsubstituted α,α,α-trifluoroacetophenones were reduced by a chiral NAD(P)H-model (*RR*-Me_2PNPH). Both electron-releasing and -withdrawing substituents give better optical yields than unsubstitued compound. The result has been interpreted in terms of three-step mechanism which involves initial electron-transfer process.

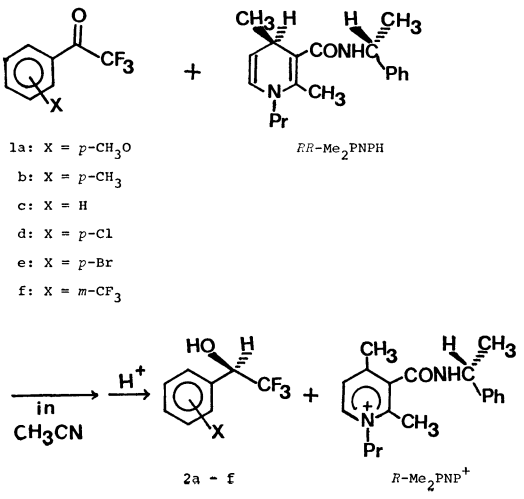
Kinetics, isotope effects, and other evidence have proved that the reduction of certain ketones by 1,4-dihydronicotinamide derivatives proceeds through three-step electron-proton-electron transfer processes.[1] Magnesium ion catalyzes the reduction by assisting the initial electron-transfer process.

On the other hand, it has been demonstrated that the reduction proceeds with excellent stereospecificity when a chiral 1,4-dihydronicotinamide derivative is used as a reductant.[2] Stereospecificity is also catalyzed by magnesium ion. Namely, substituted and unsubstituted α,α,α-trifluoroacetophenones are reduced by a chiral *N*-(α-methylbenzyl)-1-propyl-2,4-dimethyl-1,4-dihydronicotinamide (Me_2PNPH) in more than 90% enantiomer excess in the presence of magnesium ion.[2] Magnesium ion plays a role to freeze the conformation of transition state complex,[3] and electronic substituent effect is more important than the steric effect to difine the stereochemical course.[3,4]

We have been interested in to study whether the reduction of a series of α,α,α-trifluoroacetophenones without magnesium ion results in variation of enantiomer excess due to electronic substituent effect and whether the stereochemical result can be explained by the proposed three-step mechanism without contradiction.

Results

α,α,α-Trifluoroacetophenone and its *p*-methoxy, *p*-methyl, *p*-chloro, *p*-bromo, and *m*-trifluoromethyl derivatives were reduced by *RR*-Me_2PNPH in dry acetonitrile at room temperature in the dark.



The enantiomer excess in the product alcohols (**2**) and their absolute configurations were determined on ^{1}H- and ^{19}F-NMR spectroscopies[5] as well as by VPC (15% BDS, 1 m) after the alcohols were converted into their corresponding α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) esters. Chemical yield, conversion percentage, enantiomer excess, and the configuration of the product are summarized in Table 1. In Fig. 1 logarithms of the isomer ratios are plotted against Hammett σ-values for the substituent.

Discussion

Both electron-releasing and -withdrawing substituents increase the stereospecificity of the reduction. The

Table 1. Chiral reduction of substituted and unsubstituted α,α,α-trifluoroacetophenones

Product	Yield/%[a]	Conversion/%[b]	e.e./%	Configuration
2a	78.4	97	80.2	*R*
2b	33.6	95	76.4	*R*
2c	68.0	100	71.3	*R*
2d	55.3	99	82.5	*R*
2e	52.5	100	82.2	*R*
2f	58.0	99	85.9	*R*

a) Isolated yield. b) The amount of consumed substrate.

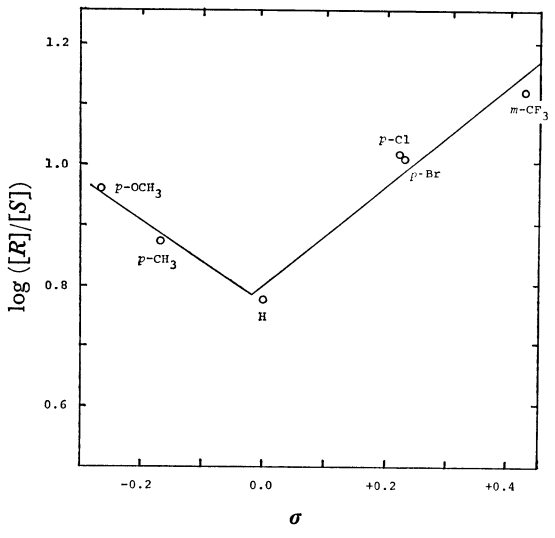


Fig. 1. A plot of log[*R*]/[*S*] against σ.

result cannot be accounted for by simple steric or electronic substituent effect in a unit reaction.

However, the multi-step mechanism with an initial electron-transfer process explains the variation of stereospecificity. An electron-releasing substituent reduces the electron-affinity of a substrate and the electron-transfer to a substrate of this sort requires high activation energy as shown in Fig. 2a. In this category, only a substrate which has proper intermolecular arrangement can form an electron-transfer complex with Me_2PNPH. Since the intermediate electron-transfer complex is an unstable species, the following proton-transfer step proceeds almost spontaneously. That is, the stereochemistry of the net reduction is defined kinetically in the process of initial electron-transfer.

The selectivity-reactivity relationship[6] predicts that the less the electron-releasing power of a substituent on the substrate, or the less the activation energy for the electron-transfer process, the less the difference in energy between preferred and other conformations (Fig. 2b). Consequently, the reduction becomes less stereospecific.

With a strongly electron-withdrawing substituent on a substrate, on the other hand, the electron-transfer takes place quite rapidly and the intermediate electron-transfer complex becomes more stable than the reactant system (Fig. 2c). The preferential course of reduction in this category is, therefore, controlled by thermodynamic stability of the intermediate. It is noteworthy that the reaction mixture with **1d**, **1e**, or **1f** turned dark green during the reaction and the color disappered at the end of the reaction. The color change suggests the formation of a stable long-living intermediate. Thus, stereochemical course of the reduction is determined by the complex-forming process. When the complex is unstable, stereochemistry is controlled kinetically, whereas when the complex is stable, thermodynamics controls the course. Since magnesium ion catalyzes the electron-transfer process, stereochemistry of the reduction in the presence of magnesium ion is controlled thermodynamically yielding quite high enantiomer excess.[2]

The energy diagrams shown in Fig. 2 are the same as those proposed previously. In conclusion, we would like to emphasize that not only kinetic bihavior but

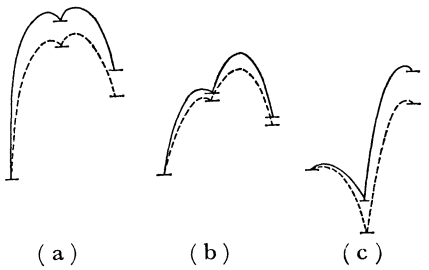


Fig. 2. Schematic representation of energy diagram for the reduction. Electron-withdrawing power increases in the order: (a)<(b)<(c).

Table 2. Optical rotation of product alcohol[a]

Alcohol	$[\alpha]_D$	c
2a	−35.9	1.35
2b	−24.0	0.825
2c	−9.32	1.18
2d	−19.0	1.05
2e	−21.5	1.04
2f	−17.1	1.58

a) In ethanol at 20 °C.

Table 3. VPC analysis of product alcohol and its (+)-MTPA ester[a]

Alcohol	Column temp/°C	Retention time/min		
		Alcohol	Ester of (*R*)-alcohol	Ester of (*S*)-alcohol
2a	170	7.9	24.5	30.7
2b	150	5.5	19.7	25.0
2c	150	4.0	14.0	17.6
2d	170	5.9	13.0	16.6
2e	170	10.0	21.4	27.9
2f	135	6.9	17.0	21.3

a) The analyses were done on a Yanaco G-1800F with a 1 m, 15% BDS column.

Table 4. ^1H- and ^{19}F-NMR spectra of (+)-MTPA esters of product alcohols

Alcohol	Config. of alcohol	^1H Chemical shift[a]		^{19}F Chemical shift[b]	
		Acid-OMe	Alcohol-H	Acid-CF_3	Alcohol-CF_3
2a	*R*	3.58	6.18	72.31	76.31
	S	3.46	6.26	72.31	76.49
2b	*R*	3.58	6.21	72.31	76.26
	S	3.47	6.29	72.31	76.47
2c	*R*	3.59	6.24	72.29	76.13
	S	3.46	6.31	72.29	76.39
2d	*R*	3.60	6.22	72.18	76.25
	S	3.47	6.29	72.18	76.47
2e	*R*	3.60	6.21	72.18	76.26
	S	3.47	6.28	72.18	76.48
2f	*R*	3.60	6.30	72.21	76.13
	S	3.46	6.37	72.21	76.42

a) δ from TMS in $CDCl_3$. b) δ from CCl_3F in $CDCl_3$.

also stereochemical result can be explained by the three-step reduction mechanism which proposes initial electron-transfer step as the driving force of the reduction.

Experimental

Instruments and general procedure for the reduction were described in a previous paper.[1,3] Melting and boiling points were not corrected.

Materials. Me_2PNPH,[2] acetonitrile,[1,3] and magnesium perchlorate[1,3] were prepared or purified as described before.

p-Methoxy- (**1a**) (bp 114—115 °C/20 mmHg),[7] *p*-methyl- (**1b**) (bp 77.5—78 °C/20 mmHg),[7] unsubstituted (**1c**) (150 °C/760 mmHg),[7] *p*-chloro- (**1d**) (81 °C/20 mmHg),[8] *p*-bromo- (**1e**) (95 °C/4 mmHg),[9] and *m*-trifluoromethyl-α,α,α-trifluoroacetophenone (**1f**) (77 °C/50 mmHg)[1] were synthesized according to the literature procedures.

Configurational Analyses of Products. Optical rotations of the product alcohols are listed in Table 2. Results of VPC-analyses and chemical shifts in ^1H- and ^{19}F-NMR spectra of MTPA esters of the alcohols are summarized in Tables 3 and 4, respectively.

Correlation of Physical Units. Physical units used in this report are correlated with SI-units by the following relationship.

1 M=1 mol dm^{-3}, $t/°C = T/K - 273.15$, p mmHg = $13.5951 \times 980.665 \times 10^{-2}$ p Pa.

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