Selective Reduction of Carbonyl Compounds with Diisobutyldialkylaminoalanes

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Details are described of reaction of carbonyl compounds with diisobutyldialkylaminoalane (DIBAL-NR_2; R=Et, *i*-Bu, Ph) in order to establish their reduction characteristics. The reagents were extremely mild and reduced only aldehydes and ketones effectively in ethyl ether at 25 ℃. The stereoselectivity in the reduction of representative cyclic ketones appeared not so high but quite different from that obtained by DIBAL-H itself. The reagents reduced α,β-unsaturated aldehydes and ketones to the corresponding allylic alcohols without any detectable 1,4-reduction products. DIBAL-NR_2 also achieved the selective reduction of aldehydes or ketones in the presence of keto or other readily reducible functional group, however the chemoselectivity was less satisfactory than that achieved by diisobutylethoxyalane (DIBAL-OEt).

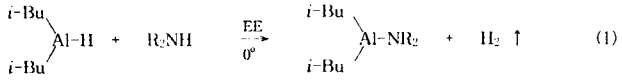
Introduction

Very recently, we reported that diisobutylalane derivatives bearing chloro or alkoxy groups bound to aluminum atom (DIBAL-Cl and DIBAL-OR) are highly selective reducing agents for the reduction of enals and enones to the corresponding allylic alcohols,[1,2] and for the reduction of aldehyde or ketone groups in the presence of many other readily reducible functional groups.[3,4] We attributed such a high selectivity to the cyclic mechanism in which the β-hydride of the isobutyl group is shifted to the carbonyl carbon of the substrate. Thus, the reduction is very similar to a Meerwein-Ponndorf-Verley type process.[5] These unique reactions led us to extend our investigation to the dialkylamino derivatives of diisobutylaluminum hydride (DIBAL-H) as a reducing agent. We prepared a series of diisobutyldialkylaminoalanes (DIBAL-NR_2; R=Et, *i*-Bu, Ph), examined their reactivity toward general organic functional groups, and finally investigate their selectivity in the reduction of aldehydes and ketones, in the hope of better understanding the nature of reagents and exploring their scope in organic synthesis.

In this article, we described the results of our study on the reduction characteristics of diisobutyldialkylaminoalane and compared them with those of the alkoxy derivative.

Results and Discussion

DIBAL-NR_2 was conveniently prepared by a simple reaction between DIBAL-H and the corresponding dialkylamines in ethyl ether (EE) solution (Eq. 1).



$$i\text{-Bu}_2\text{Al-H} + R_2NH \xrightarrow[0^\circ]{EE} i\text{-Bu}_2\text{Al-NR}_2 + H_2\uparrow \quad (1)$$

R= Et ; DIBAL-NEt_2, R= *i*-Bu ; DIBAL-N^iBu_2, R= Ph ; DIBAL-NPh_2

The ^{27}Al NMR spectra of DIBAL-NR_2 in EE revealed a broad singlet at δ 68 for DIBAL-NPh_2.

Reactivities toward Carbonyl Compounds and Other Reducible Compounds. The reactivities of DIBAL-NR_2 toward some representative carbonyl compounds and other reducible compounds were examined, and the results are summarized in Table 1. In general, the relative reactivity is in order of DIBAL-NEt_2≥DIBAL-N^iBu_2>DIBAL-NPh_2. Both diethylamino and diisobutylamino derivatives readily reduced a wide variety of aldehydes and ketones to the corresponding alcohols at 25 ℃. However, the diphenylamino derivative showed much weaker reactivity, requiring excess reagent or prolonged reaction time. The striking feature of the reagents observed from the results is their rate differences toward structurally different carbonyl compounds and their ability to reduce α,β-unsaturated aldehydes and ketones to the corresponding allylic alcohols. In addition, DIBAL-NR_2 appears to be extremely mild. Various representative functional groups, such as ester, nitrile and epoxide, are inert to the reagents. Even acid chloride, the most susceptible functional group, is compatible. This interesting characteristics led us to investigate their selectivities in the reduction of aldehydes and ketones in detail.

The dialkylamino derivatives appear to be milder than the corresponding alkoxy derivatives. Apparently, such a reactivity difference between DIBAL-NR_2 and DIBAL-OR arises from both steric and electronic effects of the dialkylamino and alkoxy substituents. Thus, the larger steric size of NR_2 than OR and the more ready electron donation from nitrogen to aluminum than from oxygen to aluminum cause the coordination of substrate to the aluminum atom of DIBAL-NR_2 to be relativity more difficult than to the aluminum atom of DIBAL-OR. Such inhibitory effects for coordination, in turn, retard the reduction rate, DIBAL-NR_2 being milder than DIBAL-OR.

Stereoselectivities in the Reduction of Cyclic Ketones. The stereoselectivity of DIBAL-NR_2 toward representative monocyclic and bicyclic ketones was examined. Consequently, it was of interest to explore whether the results with DIBAL-NR_2 would exhibit any significant difference from those with the parent DIBAL-H[6] or DIBAL-H·SMe_2 complex.[7] The results are summarized in Table 2.

The stereochemical results in reductions by DIBAL-NR_2 are quite different from these by DIBAL-H, as expected, due

Table 1. Reaction of Representative Carbonyl Compounds and Other Reducible Compounds with DIBAL-NR_2 in Ethyl Ether at 25 °C[a]

Compound	Time. h	Yield of alcohol,[b] %		
		DIBAL-NEt_2	DIBAL-N^iBu_2	DIBAL-NPh_2
butanal	0.5	97	98	90
	1.0	98	99	95
	3.0	100	100	98
	6.0			100
hexanal	0.5	96	97	89
	1.0	98	98	93
	3.0	100	100	97
	6.0			100
benzaldehyde	0.5	98	97	95
	1.0	100	100	97
	3.0			100
p-anisaldehyde	0.5	88	85	80
	1.0	92	89	82
	3.0	95	93	87
	6.0	97	95	92
	12.0	100	100	98
	24.0			100
cyclopentanone	0.5	72	69	67
	1.0	79	76	73
	3.0	87	82	81
	6.0	93	94	89
	12.0	100	100	95
	24.0			100
cyclohexanone	0.5	77	75	70
	1.0	83	79	75
	3.0	94	90	87
	6.0	96	98	91
	12.0	100	100	98
	24.0			100
2-heptanone	0.5	55	50	35
	1.0	62	57	43
	3.0	77	68	57
	6.0	85	79	69
	12.0	94	90	82
	24.0	100	100	92
	48.0			100
acetophenone	0.5	62	60	47
	1.0	75	69	55
	3.0	89	77	60
	6.0	98	89	78
	12.0	100	98	82
	24.0		100	97
	48.0			100
benzophenone	0.5	44	40	20
	1.0	56	60	23
	3.0	73	75	27
	6.0	89	88	35
	12.0	93	95	49
	24.0	100	100	68
	48.0			89
	72.0			100
1,2-butylene oxide	24.0	0	0	0
hexanoyl chloride	24.0	2	0	0
ethyl caproate	24.0	0	0	0
benzonitrile	24.0	0	0	0

[a] Ten % excess reagent was utilized. [b] GC yields with suitable internal standard.

Table 2. Stereochemistry in the Reduction of Cyclic Ketones with DIBAL-NR_2 in Ethyl Ether at 25 °C[a,b]

Ketone	ratio of less stable epimer (total yield of alcohol)[c]		
	DIBAL-NEt_2	DIBAL-N^iBu_2	DIBAL-NPh_2
2-methylcyclohexanone	60 (93)	60 (97)	69 (46)
3-methylcyclohexanone	40 (91)	45 (90)	42 (83)
4-methylcyclohexanone	45 (93)	50 (91)	46 (88)
4-*t*-butylcyclohexanone	35 (91)	35 (87)	39 (40)
3,3,5-trimethylcyclohexanone	80 (96)	85 (94)	84 (88)
norcamphor	89 (97)	95 (99)	93 (79)
camphor	75 (77)	84 (72)	92 (67)

[a] A 2 : 1 ratio for reagent to ketone was utilized. [b] Reacted for 24 hrs. [c] Figures are in percentage determined by GC.

to the different modes of reduction. The reduction with DIBAL-H involves hydride shift from the aluminum; the reduction with DIBAL-NR_2 involves hydride shift from the β-carbon atom.

The stereochemical outcome appears to be independent upon the steric size of *N*-substituents. Thus the ratios of less stable isomers produced in the reduction of cyclic ketones by these three derivatives are not significantly different. This implies that the reduction process by these derivatives involves only the isobutyl group after the coordination of reagent to the carbonyl oxygen of substrate under these reaction conditions.

Selective Reduction of α,β-Unsaturated Aldehydes and Ketones. Selective 1,2-reduction of α,β-unsaturated aldehydes and ketones with metal hydride reducing agents is after difficult due to competing 1,2- *vs* 1,4-attack by hydride.[8] However, as summarized in Table 3, all DIBAL-NR_2 converted various α,β-unsaturated aldehydes and ketones examined to the corresponding allylic alcohols : no conjugate reduction or conjugate addition[9] to the α,β-unsaturated system occurred. The reduction of simple conjugate aldehydes, such as crotonaldehyde, 2-hexenal and cinnamaldehyde, afforded cleanly corresponding allylic alcohols, resulting only from 1,2-reduction. Acyclic enones, such as 3-penten-2-one, benzalacetone and chalcone, were also specifically reduced to the corresponding allylic alcohols in essentially quantitative yields at 25 °C. Both 2-cyclopentene-1-one and 2-cyclohexen-1-one were also converted to the desired 2-cycloalkenols cleanly. Similarly, isophorone was readily reduced to 3,3,5-trimethyl-2-cyclohexen-1-ol.

Results summarized in Table 3 clearly reveal that DIBAL-NR_2 is really an ideal reducing agent for the selective reduction of α,β-unsaturated aldehydes and ketones to the corres-

Table 3. Reduction of α,β-Unsaturated Aldehydes and Ketones with DIBAL-NR_2 in Ethyl Ether at 25 °C[a]

Compound	Reagent	Time, h	Product ratio[b] 1,2 : 1,4	yield[b] %
crotonaldehyde[c]	DIBAL-NEt_2	12	100 : 0	>99.9
	DIBAL-N^iBu_2	12	100 : 0	100
	DIBAL-NPh_2	24	100 : 0	99.9
2-hexenal[c]	DIBAL-NEt_2	12	100 : 0	99.9
	DIBAL-N^iBu_2	12	100 : 0	99
	DIBAL-NPh_2	72	100 : 0	99
cinnamaldehyde[c]	DIBAL-NEt_2	24	100 : 0	100
	DIBAL-N^iBu_2	24	100 : 0	99
	DIBAL-NPh_2	72	100 : 0	97
3-penten-2-one[d]	DIBAL-NEt_2	12	100 : 0	100
	DIBAL-N^iBu_2	12	100 : 0	100
	DIBAL-NPh_2	24	100 : 0	100
benzalactone[e,c]	DIBAL-NEt_2	148	100 : 0	99
	DIBAL-N^iBu_2	148	100 : 0	98
	DIBAL-NPh_2	148	100 : 0	98
chalcone[e,c]	DIBAL-NEt_2	240	100 : 0	100
	DIBAL-N^iBu_2	240	100 : 0	98
	DIBAL-NPh_2	240	100 : 0	98
2-cyclopenten-1-one	DIBAL-NEt_2	24	100 : 0	100
	DIBAL-N^iBu_2	24	100 : 0	100
	DIBAL-NPh_2	72	100 : 0	100
2-cyclohexen-1-one	DIBAL-NEt_2	24	100 : 0	100
	DIBAL-N^iBu_2	24	100 : 0	100
	DIBAL-NPh_2	24	100 : 0	100
isophorone	DIBAL-NEt_2	72	100 : 0	100
	DIBAL-N^iBu_2	72	100 : 0	100
	DIBAL-NPh_2	72	100 : 0	100

[a] Ratio for reagent to compound was 2 : 1, except where otherwise indicated. [b] Determined by GC using calibrated internal standard. [c] A *trans* isomer. [d] A mixture of 69% 3-penten-2-one and 31% mesityl oxide : the same ratio of 3-penten-2-ol and 4-methyl-3-penten-2-ol was obtained. [e] Four equivalents of reagent were used.

ponding allylic alcohols. The selectivity is 100%. Furthermore, DIBAL-NR_2 is extremely mild : almost all other reducible functional groups are compatible. In this context, DIBAL-NR_2 is comparable to diisopinocampheylchloroborane (Ipc2BCl),[10] diisopinocampheylalkoxyborane (Ipc_2BOR),[2] diisobutylchloroalane (DIBAL-Cl)[1] and diisobutylalkoxyalane (DIBAL-OR)[4] other mild, selective reducing agents for such purpose.[11]

Chemoselectivity in the Competitative Reduction between Carbonyl Compounds. Chemoselective reduction of one carbonyl group in the presence of other such groups affords an important methodology in organic synthesis. In recent years, various reagents have been developed for such selective reductions.[14] More recently, we reported that Ipc$_2$BCl,[13] Ipc_2BOR,[14] DIBAL-Cl[3] and DIBAL-OEt[14] achieve such chemoselective reduction with very high selectivity.

Similarly, we applied DIBAL-NR_2 for the selective reduc-

Table 4. Competitive Reduction between Carbonyl Compounds with DIBAL-NR_2 in Ethyl Ether at 25 °C[a]

Entry	Starting mixture	Reagent	Time, h	Ratio of redn products[b]
1	butanal/hexanal	DIBAL-NEt_2	3	80 : 20
		DIBAL-N^iBu_2	3	82 : 18
		DIBAL-NPh_2	6	70 : 30
2	butanal/benzaldehyde	DIBAL-NEt_2	1	30 : 70
		DIBAL-N^iBu_2	1	27 : 73
		DIBAL-NPh_2	3	25 : 75
3	butanal/*p*-anisaldehyde	DIBAL-NEt_2	3	80 : 20
		DIBAL-N^iBu_2	3	85 : 15
		DIBAL-NPh_2	6	80 : 20
4	hexanal/benzaldehyde	DIBAL-NEt_2	1	25 : 75
		DIBAL-N^iBu_2	1	25 : 75
		DIBAL-NPh_2	3	30 : 70
5	hexanal/*p*-anisaldehyde	DIBAL-NEt_2	3	80 : 20
		DIBAL-N^iBu_2	3	85 : 15
		DIBAL-NPh_2	6	70 : 30
6	bezaldehyde/*p*-anisaldehyde	DIBAL-NEt_2	3	80 : 20
		DIBAL-N^iBu_2	3	85 : 15
		DIBAL-NPh_2	6	80 : 20
7	bezaldehyde/cyclohexanone	DIBAL-NEt_2	1	98 : 2
		DIBAL-N^iBu_2	1	97 : 3
		DIBAL-NPh_2	3	95 : 5
8	hexanal/cyclohexanone	DIBAL-NEt_2	3	70 : 30
		DIBAL-N^iBu_2	3	80 : 20
		DIBAL-NPh_2	6	70 : 30
9	hexanal/2-heptanone	DIBAL-NEt_2	3	70 : 30
		DIBAL-N^iBu_2	3	87 : 13
		DIBAL-NPh_2	6	70 : 30
10	hexanal/acetophenone	DIBAL-NEt_2	3	90 : 10
		DIBAL-N^iBu_2	3	92 : 8
		DIBAL-NPh_2	6	70 : 30
11	hexanal/benzophenone	DIBAL-NEt_2	3	92 : 8
		DIBAL-N^iBu_2	3	95 : 5
		DIBAL-NPh_2	6	90 : 10
12	*p*-anisaldehyde/ cyclohexanone	DIBAL-NEt_2	6	70 : 30
		DIBAL-N^iBu_2	6	75 : 25
		DIBAL-NPh_2	12	70 : 30
13	cyclohexanone/ cyclopentanone	DIBAL-NEt_2	12	70 : 30
		DIBAL-N^iBu_2	12	76 : 24
		DIBAL-NPh_2	24	75 : 25
14	cyclohexanone/2-heptanone	DIBAL-NEt_2	12	75 : 25
		DIBAL-N^iBu_2	12	80 : 20
		DIBAL-NPh_2	24	60 : 40
15	cyclohexanone/acetophenone	DIBAL-NEt_2	12	70 : 30
		DIBAL-N^iBu_2	12	75 : 25
		DIBAL-NPh_2	24	60 : 40
16	cyclohexanone/ benzophenone	DIBAL-NEt_2	12	80 : 20
		DIBAL-N^iBu_2	12	85 : 15
		DIBAL-NPh_2	24	80 : 20
17	acetophenone/2-heptanone	DIBAL-NEt_2	12	80 : 20
		DIBAL-N^iBu_2	12	86 : 14
		DIBAL-NPh_2	24	55 : 45

18	acetophenone/benzophenone	DIBAL-NEt₂	12	75 : 25
		DIBAL-N^{t}Bu₂	12	90 : 10
		DIBAL-NPh₂	24	65 : 35
19	2-heptanone/benzophenone	DIBAL-NEt₂	12	75 : 25
		DIBAL-N^{t}Bu₂	12	79 : 21
		DIBAL-NPh₂	24	80 : 20
20	2-heptanone/hexanoyl chloride	DIBAL-NEt₂	12	100 : 0
		DIBAL-N^{t}Bu₂	12	100 : 0
		DIBAL-NPh₂	24	100 : 0
21	2-heptanone/ethyl caproate	DIBAL-NEt₂	12	100 : 0
		DIBAL-N^{t}Bu₂	12	100 : 0
		DIBAL-NPh₂	24	100 : 0
22	2-heptanone/benzonitrile	DIBAL-NEt₂	12	100 : 0
		DIBAL-N^{t}Bu₂	12	100 : 0
		DIBAL-NPh₂	24	100 : 0

[a] One equivalent of reagent was utilized for the competitive reduction of equimolar mixture of two compounds tested. [b] Normalized ratio determined by GC with appropriate internal standard; the total yields of reduction products were ≥99%.

tion of carbonyl group in the presence of another carbonyl group. Competition experiments were carried out by adding one equivalent of DIBAL-NR₂ to an equimolar mixture of two carbonyl compounds to be examined in ethyl ether at 25 °C. As listed in Table 4, twenty-two representative pairs of carbonyl compounds were tested : six aldehydealdehyde pairs (entries 1-6), six aldehyde-ketone pairs (entries 7-12), seven ketone-ketone pairs (entries 13-19), and three ketone-other reducible compound pairs (entries 20-22). Generally, the selectivity achieved by DIBAL-NR₂ appears to be less satisfactory than that we expected: the selectivity is lower than that achieved by DIBAL-OR.[4] Nevertheless, in some cases of aldehyde-ketone pairs (entries 7, 10 and 11) and ketone-other reducible compound pairs (entries 20-22) the reagents showed good selectivities which are synthetically applicable. Among the reagents of DIBAL-NR₂, the diisobutylamino derivative appears the most selective reducing agent. However, obviously, there would be no point to the use of DIBAL-NR₂ for such chemoselective reduction. Instead, DIBAL-OR is more feasible for such purpose.

Conclusion

Diisobutyldialkylaminoalane (DIBAL-NR₂; R=Et, *i*-Bu, Ph) is readily prepared by treating the corresponding dialkylamines with diisobutylaluminum hydride (DIBAL-H) in ethyl ether at 0 °C. The reagents are milder than diisobutylalkoxyalane (DIBAL-OR) and diisobutylchloroalane (DIBAL-Cl) : DIBAL-NR₂ can reduce only aldehydes and ketones effectively at 25 °C. The stereoselectivity in the reduction of cyclic ketones by DIBAL-NR₂ appeared not so high but quite different from that obtained by DIBAL-H itself. The reagents reduce α,β-unsaturated aldehydes and ketones to the corresponding allylic alcohols with 100% selectivity, resulting from the clean 1,2-reduction. DIBAL-NR₂ also achieves the selective reduction of aldehydes or ketones in the presence of keto or other readily reducible functional group. However, the chemoselectivity appeared to be less satisfactory than that achieved by DIBAL-OR. Consequently, the present systematic study reveals the full scope of reduction characteristics of DIBAL-NR₂, that provides a basic knowledge having to understand the nature of diisobutylaluminum derivatives.

Experimental Section

Techniques for handling air-sensitive compounds have been previously described.[15] All glassware used were dried thoroughly in a dry oven, assembled hot, and cooled under a stream of dry nitrogen prior to use. All reactions and manipulations of air- and moisture-sensitive materials were carried out under a static pressure of nitrogen. All chemicals were commercial products of the highest purity which were purified further by standard methods before use. Ethyl ether (EE) was dried over sodium-benzophenone ketyl and distilled. Diisobutylaluminum hydride (DIBAL-H) was purchased from the Aldrich Chemical Co. GC analyses were performed on a Donam DS 6200 FID chromatograph equipped with a Youngin D520 B computing integrator, using a 10% Carbowax 20 M capillary column (25 m). All GC yields were determined with use of a suitable internal standard and authentic mixtures. ^{27}Al NMR spectra were recorded on a Bruker AMX-300 spectrometer, and chemical shifts are with reference to $[Al(H_2O)_6]^{3+}$.

Preparation of Diisobutyldialkylaminoalane (DIBAL-NR₂) in EE. The following procedure for the preparation of DIBAL-NEt₂ is illustrative. To an oven- dried, 250-mL flask with a sidearm and a reflux condenser leading to a mercury bubbler were 35.6 mL of DIBAL-H (28.4 g, 200 mmol) and 30 mL of EE. It was cooled to 0 °C, and 21.7 mL of diethylamine (15.4 g, 210 mmol) was added dropwise with vigorous stirring. After the hydrogen evolution ceased, the solution of DIBAL-NEt₂ was diluted with EE to 2 M using a mass cylinder. The ^{27}Al NMR spectrum of the solution showed a broad singlet at δ 159 ppm.

DIBAL-N^{t}Bu₂ and DIBAL-NPh₂ were also prepared by the identical procedure described above and the ^{27}Al NMR spectra showed a broad singlet at δ 169 and 68 ppm, respectively.

General Reduction Procedure. The following procedure is illustrative to examine the rate of reduction of carbonyl compounds with DIBAL-NR₂ (Table 1). An oven-dried, 50-mL flask, fitted with a sidearm and a bent adapter connected to a mercury bubbler, was charged with 2.5 mL of a 2 M cyclopentanone solution (0.42 g, 5 mmol) in EE and dodecane as an internal standard. The solution was maintained at 25 °C in a water bath. To this solution was added 2.75 mL of a 2 M DIBAL-NEt₂ solution (5.5 mmol) in EE and the reaction mixture was stirred at that temperature. At the appropriate time intervals, an aliquot was withdrawn by a syringe with a 6-inch needle and hydrolyzed with 3 N HCl. The aqueous layer was than saturated with magnesium sulfate and the ether layer was dried over potassium carbonate. Gas chromatographic analyses showed the presence of cyclopentanol in yields of 72% at 0.5 h, 79% at 1.0 h, 87% at 3.0 h, 93% at 6.0 h and 100% at 12.0 h.

Reduction of Cyclic Ketones. The following procedure is illustrative to examine the stereoselectivity in the reduction of cyclic ketones (Table 2). An oven-dried, 10-mL vial equipped with a small magnetic stirring bar, was sealed

with a rubber septum. Two mL of a stock solution of DIBAL-N^{t}Bu$_2$ (2 M, 4 mmol) was injected into the vial and the solution was maintained at 25 ℃ in a water bath. To this 0.23 g of 2-methylcyclohexanone (2 mmol) was added as a neat, and the reaction mixture was stirred for 24 hrs at that temperature. The reaction mixture was then hydrolyzed with 3 N HCl and the ether layer was dried over potassium carbonate. GC analysis showed the presence of 60% *cis* epimer and 40% *trans* epimer in a total yield of 97%.

Reduction of α,β-Unsaturated Carbonyl Compounds to Allylic Alcohols. The following procedure for the reaction of crotonaldehyde with DIBAL-NPh$_2$ is representative. An oven-dried, 25 mL flask equipped with a sidearm fitted with a rubber septum, a magnetic stirring bar, and a reflux condenser connected to a mercury bubbler, was charged with 5 mL of a stock solution of DIBAL-NPh$_2$ (2 M, 10 mmol) and 0.60 mL of *n*-tridecene (2.5 mmol) as an internal standard. The solution was maintained at 25 ℃ in a water bath. To this solution was added 0.42 mL of freshly-distilled crotonaldehyde (0.35 g, 5 mmol) with stirring, and the reaction mixture was stirred at that temperature. After the reaction for 24 hrs, the reaction mixture was hydrolyzed with 3 N HCl. The aqueous layer was then saturated with magnesium sulfate and the ether layer was dried over potassium carbonate. Gas chromatographic analysis showed the presence of crotyl alcohol as a sole product in a yield of 99.9% (Table 3).

Competitive Reduction. The following procedure for the competitive reaction between benzaldehyde and cyclohexanone with DIBAL-NEt$_2$ is representative. An oven-dried, 50-mL flask was charged with equimolar mixture of benzaldehyde (4 mmol) and cyclohexanone (4 mmol) in 4 mL of EE. The solution was maintained at 25 ℃ in a water bath and 2.0 mL of a 2 M solution of DIBAL-NEt$_2$ (4 mmol) in EE was added rapidly with vigorous stirring. The reaction mixture was stirred for 1 h at 25 ℃, and the mixture was then quenched with 3 N HCl followed by addition of dodecane as an internal standard. The aqueous layer was saturated with magnesium sulfate and the ether layer was dried over potassium carbonate. GC analysis showed the presence of 98% benzyl alcohol and 2% cyclohexanol in a total yield of 100% (Table 4).

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References

1. Cha, J. S.; Kwon, O. O.; Kwon, S. Y. *Bull. Korean Chem. Soc.* **1995**, *16*, 1009.
2. Cha, J. S.; Kwon, O. O.; Kwon, S. Y. *Org. Prep. Proced. Int.* **1996**, *28*, 271.
3. Cha, J. S.; Kwon, O. O.; Kwon, S. Y.; Kim, J. M.; Seo, W. W.; Chang, S. W. *Synlett* **1995**, 1055.
4. Cha, J. S.; Kwon, O. O.; Kwon, S. Y.; Kim, J. M.; Seo, W. W.; Chang, S. W. *Bull. Korean Chem. Soc.* **1996**, *17*, 221.
5. (a) Heinsohn, G. E.; Ashby, E. C. *J. Org. Chem.* **1973**, *38*, 4232. (b) Ashby, E. C.; Yu, S. H.; Lardicci, L. *Tertahedron Lett.* **1971**, 4135.
6. Yoon, N. M.; Gyoung, Y. S. *J. Org. Chem.* **1985**, *50*, 2443.
7. Cha, J. S.; Jeong, M. K.; Kwon, O. O.; Lee, K. D.; Lee, H. S. *Bull. Korean Chem. Soc.* **1994**, *15*, 873.
8. (a) House, H. O. *Modern Synthetic Reactions*, 2nd Ed.; W. A. Benzamin: Menlo Park, CA, 1972. (b) Ho, T.-L. *Hard and Soft Acids and Bases Principles in Organic Chemistry*; Academic Press: New York, 1977.
9. In the reaction of α,β-unsaturated ketones with triisobutylaluminum (TIBAL), the 1,2-addition of the isobutyl group bound to the aluminum atom is generally competitive with the reaction.
10. (a) Cha, J. S.; Kim, E. J.; Kwon, O. O.; Kim, J. M. *Bull. Korean Chem. Soc.* **1994**, *15*, 1033. (b) *Idem. Ibid.* **1996**, *17*, 50.
11. For selective 1,2-reduction with other hydride reagents, see; (a) Mordenti, L.; Bruner, J. J.; Caubere, I. *J. Org. Chem.* **1979**, *44*, 2203. (b) Chaikin, S. W.; Brown, W. G. *J. Am. Chem. Soc.* **1949**, *71*, 122. (c) Cain, M. E. *J. Chem. Soc.* **1964**, *47*, 3532. (d) Brown, H. C.; Hess, H. M. *J. Org. Chem.* **1969**, *34*, 2206. (e) Semmelhack, M. F.; Stauffer, R. D.; Yamashita, A. *J. Org. Chem.* **1977**, *42*, 3180. (f) Gemal, A. L.; Luche, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 5454. (g) Hutchins, R. O.; Kandsamy, D. *J. Org. Chem.* **1975**, *40*, 2530. (h) Corey, E. J.; Becker, K. B.; Verma, R. K. *J. Am. Chem. Soc.* **1972**, *94*, 8616. (i) Brown, H. C.; Mathew, C. P.; Pyun, C.; Son, J. C.; Yoon, N. M. *J. Org. Chem.* **1984**, *49*, 3091. (j) Sande, A. R.; Jagadale, M. H.; Mane, R. B.; Salunkhe, M. M. *Tetrahedron Lett.* **1984**, *25*, 3051.
12. (a) Hutchins, R. O.; D. Kandasamy, *J. Am. Chem. Soc.* **1973**, *95*, 6131. (b) Gribble, G. W.; Ferguson, D. C. *J. Chem. Soc., Chem. Commun.* **1975**, 535. (c) Sell, C. S. *Aust. J. Chem.* **1975**, *28*, 1383. (d) Maki, Y.; Kikuchi, K.; Sugiyama, H.; Seto, S. *Tetrahedron Lett.* **1977**, 263. (e) Posner, G. H.; Runquist, A. W.; Chapdelaine, M. *J. Org. Chem.* **1977**, *42*, 1202. (f) Brown, H. C.; Kulkarni, S. V. *J. Org. Chem.* **1977**, *42*, 4169. (g) Yoon, N. M.; Cha, J. S. *J. Korean Chem. Soc.* **1978**, *22*, 259. (h) Fung, N. Y. M.; deMayo, P.; Schauble, J. H.; Weedorn, A. C. *J. Org. Chem.* **1978**, *43*, 3977. (i) Midland, M. M.; Tramontano, A. *J. Org. Chem.* **1978**, *43*, 1470. (j) Risbood, P. A.; Ruthoven, D. M. *J. Org. Chem.* **1979**, *44*, 3969. (k) Sorrell, T. N.; Pearlman, P. S. *J. Org. Chem.* **1980**, 3963. (l) Fleet, G. W. J.; Harding, P. J. C. *J. Org. Chem.* **1981**, 675. (m) Krishnamurthy, S. *J. Org. Chem.* **1981**, *46*, 4628. (n) Yoon, N. M.; Park, G. B.; Gyoung, Y. S. *Tetrahedron Lett.* **1983**, 5367. (o) Kim, S.; Kang, H. J.; Yang, S. *Tetrahedron Lett.* **1984**, 2985. (p) Kim, S.; Yang, S. *Bull. Korean Chem. Soc.* **1988**, *9*, 188. (q) Ward, D. E.; Rhee, C. K. *Synth. Commun.* **1988**, *18*, 1927. (r) Ward, D. E.; Rhee, C. K.; Zoghaib, W. M. *Tetrahedron Lett.* **1988**, *29*, 517. (s) Maruoka, K.; Araki, Y.; Yamamoto, H. *Tetrahedron* **1988**, *29*, 3101. (t) Ranu, B. C.; Chakraborty, R. *Tetrahedron* **1990**, *31*, 7663. (u) Sarkas, D. C.; Das, A. R.; Ranu, B. C. *J. Org. Chem.* **1990**, *55*, 5799. (v) Firouzabadi, H.; Tamami, B.; Goudarzian, N. *Synth. Commun.* **1981**, *21*, 2275. (w) Yamamoto, T.; Toi, T.; Sonoda, A.; Murahashi, S. I. *J. Am. Chem. Soc.* **1976**, *98*, 1965. (x) Andrews, G. C. *Tetrahedron Lett.* **1980**, 697. (y) Yoon, N. M.; Kim, K. E.; Kaang, J.

J. Org. Chem. **1986**, *51*, 226.
13. Cha, J. S.; Kim, E. J.; Kwon, O. O.; Kim, J. M. *Synlett* **1995**, 331.
14. (a) Cha, J. S.; Kim, E. J.; Kwon, O. O.; Kwon, S. Y.; Seo, W. W.; Chang, S. W. *Org. Prep. Proced. Int.* **1995**, *27*, 541. (b) Cha, J. S.; Kim, E. J.; Kwon, O. O.; Kim, J. M. *Bull. Korean Chem. Soc.* **1995**, *16*, 691. (c) *Idim. Ibid.* **1996**, *17*, 50.
15. Brown, H. C.; Kramer, G. W.; Midland, M. M. *Organic Synthesis via Boranes*; Wiley-Interscience: New York, 1975.

Substrate Specificity of Cabbage Phospholipase D with Phospholipids Having Different Head Groups

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A substrate specificity of cabbage phospholipase D (PLD) was studied using the synthetic phospholipids having different head groups. The phospholipids were synthesized from phosphatidylcholine and appropriate bases by transphosphatidylation of PLD. The bases used were ethanolamine, serine, ethanol and γ-hydroxybutyric acid. The phosphatidic acid, the product of PLD, was separated in TLC and measured densitometrically. The kinetic parameters were estimated for each substrate and the effects of pH, SDS, Ca^{2+} and other metal ions were examined. V_{max} values found were 3.75, 2.36, 5.59, 1.63, 2.30 nmol/min/μg protein for phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylethanol, and phosphatidylburytic acid, respectively. These results indicate a broad specificity of cabbage PLD toward phospholipids with different head groups. Particularly phosphatidylserine was most easily hydrolyzed by PLD and its activity did not depend on Ca^{2+}.

Introduction

Phospholipase D (PLD: phosphatidylcholine phosphosphatido hydrolase : E.C. 3.1.4.4) catalyzes hydrolytic cleavage of terminal diester bond of glycerophospholipids with formation of phosphatidic acid and corresponding base.[1] In addition, PLD also can catalyze a transphosphatidylation reaction in which phosphatidate is transferred to various primary alcohols such as ethanol producing phosphatidylethanol (PEt).[2] PLD was first discovered in carrot roots and spinach leaves[3] and since then has been found to occur widely in plants, microorganisms, and mammalian tissues.[4] In animals a great deal of evidence now points that the hydrolytic pathway(s) of intracelluar PLD is one of major route for receptor-linked phospholipid signal pathways.[5] The physiological role of PLD in plants are not well defined. However several reports indicate a possible involvement of PLD in various processes, such as germination,[6] stress-induced changes in PLD activities[7] and membrane composition.[8] The plant PLDs are purified from peanut seeds,[9] cabbage leaves,[10~12] rice bran,[13] and endosperm of castor bean.[14] Recently cDNA for castor bean PLD has been cloned.[15] Subsequently genes encoding PLD activity are identified from rice,[16] human,[17] and yeast.[18]

Although there is a surge of reports on possible function of PLD in animal cell as well as plant tissue, only a limited amount of information on the line of enzymology of PLD are available. Assay system for PLD is not fully established yet since the complication of interfacial interaction.[19] Inevitably *in vitro* assay system usually include amphiphatic substance like SDS or organic solvent such as diethylether. The requirement of Ca^{2+} for PLD activity has been assumed to be essential. However some of recent data implicate it is not always true. A couple of data suggest that Ca^{2+} is more likely related to a structural stability of PLD rather than catalytic function, for example, Ca^{2+} was a crucial factor for hydrophobic binding[20] and in some model substrate, the activity did not depend on Ca^{2+} concentration.[21] There was no systematic study on substrate-specificity for plant PLD. Generally phosphatidylcholine has been accepted as most favorable substrate for hydrolytic activity of PLD without any extensive study.[22~24] Recently there were several studies for structure-reactivity relationship using model substrates such as alkyl phosphoryl choline[25] and *p*-nitrophenyl phosphoryl derivatives.[21] For effect of acyl chain length, PCs with different acyl chains were examined.[26] However the model substrates examined so far have been limited on the effect of acyl chain length and these substrates were usually complicated by the presence of different amount of detergent in the assay system.

In view of the complication stemmed from different acyl chain length, present substrate-specificity study uses tailored phospholipids with different head groups but has exactly identical acyl chains. This was achieved by exchanging the head groups through transphosphatidylation reaction catalyzed by PLD with same batch of egg PC. This approach would reveal head group specificity of cabbage PLD without any