Sodium Diethylpiperidinohydroaluminate, a New Selective Reducing Agent†

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Sodium diethyldihydroaluminate (SDDA) is an attractive aluminohydride with two available hydrides for reduction. Since many selective metal hydride reducing agents such as diisobutylaluminum hydride[1] (DIBAH) and lithium triethoxyaluminum hydride[2] contain only one available hydride, it was of interest to us to prepare such a hydride from SDDA, replacing one hydride with another group. We tried various alcohols, thiols, and amines and found that even an excess secondary amine reacts rapidly with only one of the hydrides of SDDA and very slowly with the second hydride. Thus, we were able to prepare sodium diethylpiperidinohydroaluminate (SDPA) from equimolar SDDA and piperidine in THF–toluene and found SDPA to be an excellent reagent for the synthesis of aldehydes, starting from the corresponding esters.[3] In order to apply SDPA effectively to organic syntheses, it is necessary to know the reactions of SDPA with many common functional groups. Therefore we have undertaken a systematic study of the reactions of SDPA with organic compounds containing representative functional groups.

Results and Discussion

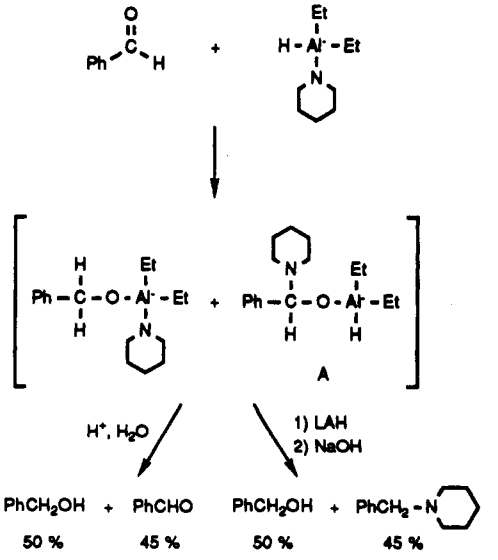
Preparation of SDPA. In order to identify the most effective method for replacing one of the two hydrides, reactions of SDDA with excesses of active hydrogen compounds (2 equiv of alcohols or *sec*-amines) were examined. It was found that *sec*-amines, such as piperidine or dibenzylamine, react rapidly with only one of the hydrides of SDDA and very slowly with the second hydride. Therefore, standard solutions of SDPA were prepared by adding 1.1 equiv of piperidine to SDDA solution in THF–toluene (1:1) at 0 °C and stirring for 3 h to give complete hydrogen evolution. The SDPA solution thus prepared was usually ~0.85 M in hydride and stable at 0 °C for 6 months.

Reduction of Representiative Organic Compounds. The general procedure adopted was the addition of 2.5 mmol of the organic compound in THF to 10 mmol of SDPA in THF–toluene (1:1) to give 20 mL of solution at 0 °C. This procedure produces a reaction mixture 0.5 M in SDPA and 0.125 M in the compound under examination. The ratio of THF to toluene in the mixed solvent was approximately 12:8. Hydrogen evolution on addition of the organic compound to the reagent was noted. The reaction mixture was maintained at 0 °C, and aliquots were removed at appropriate intervals and analyzed for "residual hydride" with *tert*-butyl alcohol–THF (1:1) at 0 °C. In this way, it was possible to establish both the rate at which reduction proceeds and the stoichiometry of the reaction, i.e., the number of hydrides utilized per mole of compound when the reaction comes to an effective halt. In most cases, we can judge the product from the stoichiometry; however, the product was analyzed by GC or isolation when necessary. These results are summarized in Table I.

Aldehydes and Ketones. Benzaldehyde and cinnamaldehyde are rapidly reduced to the corresponding alcohols, but only partially. Only a 50% yield of benzyl alcohol was obtained from the reduction of benzaldehyde. When the reaction mixture of benzaldehyde and SDPA was treated with excess LAH, the products were benzyl alcohol (50%) and *N*-benzylpiperidine (45%). It is assumed that the *N*-benzylpiperidine arises from ((α-piperidylbenzyl)oxy)aluminate [A], which we know to be stable under the experimental conditions.[4] This suggests that the carbonyl carbon is attacked by both the hydride and the piperidyl group competitively, as shown in Scheme I. Trimethylacetaldehyde, however, is reduced to the corresponding alcohol quantitatively. Aldehydes and ketones containing α-hydrogens are reduced with accompanying hydrogen evolution (enolization). Thus 50% enolization was observed with acetophenone; however, when the piperidyl group was replaced by the more bulky dibenzylamino group, enolization decreased to 10%. This suggests that direct attack of hydride on the α-hydrogen is unlikely, and the reaction likely proceeds as shown in Scheme II. Apparently, hydrogen abstraction by the piperidyl group is more effective than that by the dibenzylamino group in competing with the reduction. Benzophenone is reduced to the corresponding alcohol quantitatively.

Carboxylic Acid, Acid Chloride, and Esters. Benzoic acid evolved 1 equiv of hydrogen instantly with an accompanying white precipitate; however, almost no

Scheme I



† This paper is dedicated to Professor Herbert C. Brown on the occasion of his 80th birthday.

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(2) Brown, H. C.; Tsukamoto, A. *J. Am. Chem. Soc.* **1964**, *86*, 1089.

(3) Yoon, N. M.; Jeong, K. H.; An, D. K. *Bull. Korean Chem. Soc.* **1991**, *12*, 7.

(4) *N*-Benzoylpiperidine could be reduced to benzaldehyde almost quantitatively by the reduction with equimolar SDDA (100% excess hydride) even at room temperature.

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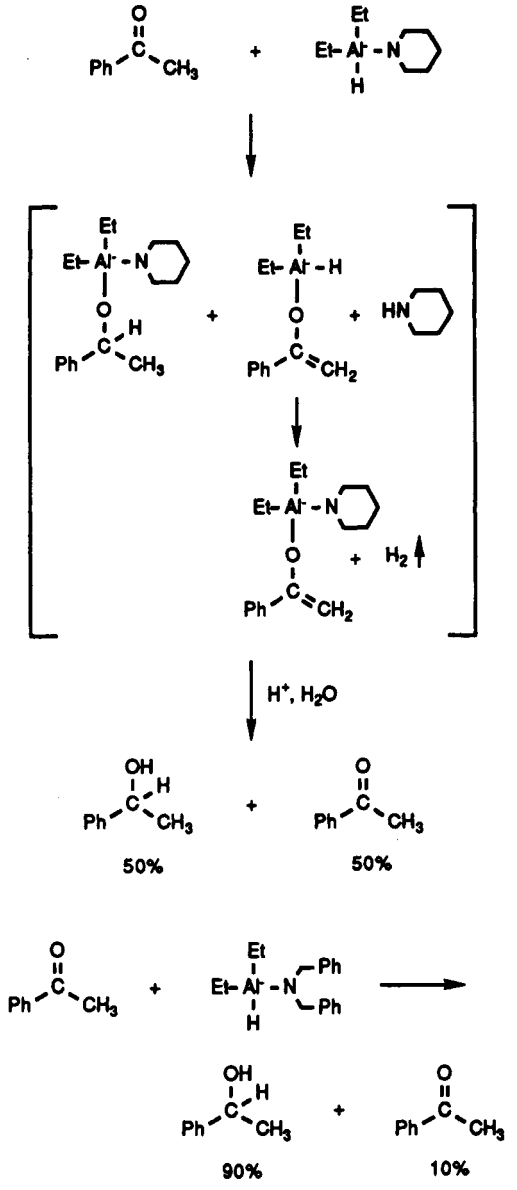
Scheme II



reduction occurred thereafter, presumably due to the precipitate formation. The precipitate seems to be carboxylic acid salts, since no precipitate is formed in the reaction of carboxylic acid with Lewis acid type hydrides such as AlH_3[5] and DIBAH.[1] Benzoyl chloride was reduced to give a mixture of benzaldehyde (52%), benzyl alcohol (28%), and *N*-benzylpiperidine (18%). Using 1.1 equiv of SDPA, we were able to increase the yield of aldehyde to 67%. Esters consumed 1 equiv of hydride rapidly, but the second hydride only very slowly. Reduction of esters with 1.1 equiv of SDPA at 0 °C gave excellent yields of the corresponding aldehydes. All of the aromatic esters tested were reduced quantitatively to the corresponding aldehydes; however, the yields of aldehydes from aliphatic esters varied from 60 to 90%, depending on the structure.[3] In contrast, the parent hydride SDDA gave only 22% of benzaldehyde using 1.1 equiv of hydride. SDPA seems to be a reagent of choice for aldehyde syntheses from esters, since other representative hydrides such as DIBAH,[6] lithium tris(diethylamino)aluminum hydride, $Li(Et_2N)_3$-AlH,[7] and diaminoaluminum hydride[8] require either very low temperatures (−70 °C) or longer reaction times (6–10 h) at elevated temperatures (65 °C). In contrast to esters, lactones reacted with accompanying hydrogen evolution (0.36 equiv of H_2 from α-butyrolactone and 0.60 equiv of H_2 from phthalide), and almost no lactol was obtained with SDPA. When the reaction mixture consisting of ethyl benzoate and equimolar SDPA was further reduced with LAH, we obtained a 94% yield of *N*-benzylpiperidine. This suggests the formation of a stable intermediate, ((α-piperidylbenzyl)oxy)aluminate similar to A in Scheme I.

Table I. Reduction of Representative Organic Compounds with SDPA in THF–Toluene at 0 °C

compound	H⁻/compd	time (h)	products	yield[a] (%)
Aldehydes and Ketones				
benzaldehyde	4	3	benzyl alcohol	50
			benzaldehyde	50
cinnamaldehyde	4	3	cinnamyl alcohol	50
			cinnamaldehyde	25
timethylacetaldehyde	4	3	neopentyl alcohol	100
acetophenone	4	3	1-phenylethanol	50
			acetophenone	50
2-heptanone	4	3	2-heptanol	70
			2-heptanone	30
benzophenone	4	6	diphenylmethanol	99
Carboxylic Acids, Acid Chlorides and Esters				
benzoic acid	4	12	benzoic acid	(94)[b]
benzoyl chloride	4	3	benzaldehyde	52
			N-benzylpiperidine	18
			benzyl alcohol	28
	1.1	3	benzaldehyde	67
			benzyl alcohol	0
ethyl benzoate	4	24	benzaldehyde	76
			benzyl alcohol	20
			N-benzylpiperidine	4
ethyl benzoate	1.1	0.5	benzaldehyde	99
ethyl 4-chlorobenzoate	1.1	0.5	4-chlorobenzaldehyde	96 (79)[b]
ethyl 4-nitrobenzoate	1.1	0.5	4-nitrobenzaldehyde	98 (77)[b]
ethyl hexanoate	1.1	1	hexanal	85
			1-hexanol	11
ethyl pivalate	1.5	3	trimethylacetaldehyde	60
			neopentyl alcohol	34
Epoxides				
1-methyl-1,2-cyclohexene oxide	4	6	1-methylcyclohexanol	98
			2-methylcyclohexanol	trace
styrene oxide	4	1	1-phenylethanol	98
			2-phenylethanol	trace
Amides and Nitriles				
N,N-dimethylbenzamide	4	24	benzaldehyde	45
			benzyl alcohol	40
			N,N-dimethylbenzylamine	10
	1.1	1	benzaldehyde	99
			N,N-dimethylbenzylamine	1
N,N-dimethylhexanamide	2.0	3	hexanal	96
N-benzoylpiperidine	1.1	3	benzaldehyde	98
N,N-dimethyl-4-nitrobenzamide	1.1	1	4-nitrobenzaldehyde	96
benzonitrile	4	24	benzaldehyde	35
			benzylamine	63
	1.5	3	benzaldehyde	98
4-chlorobenzonitrile	1.5	0.5	4-chlorobenzaldehyde	98 (84)[b]
Nitrogen and Sulfur Compounds				
pyridine	4	12	pyridine	(98)[b]
methyl *p*-tolyl sulfide	4	12	methyl *p*-tolyl sulfide	(98)[b]
phenyl disulfide	4	3	thiophenol	(98)[b]
diphenyl sulfone	4	12	diphenyl sulfone	(95)[b]

[a] The yields were determined by GC. [b] Isolated yields.

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(6) Zakharkin, L. I.; Khorlina, I. M. *Izv. Akad. Nauk. SSSR* **1963**, 316.
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The mechanism of aldehyde synthesis from esters is discussed elsewhere.[9]

Halides and Epoxides. Although *n*-butyl chloride was inert to SDPA, benzyl chloride was reduced in 9 h at 0 °C. *n*-Butyl bromide and iodide were reduced instantly. This is similar to LAH and in contrast with the Lewis acid type hydrides such as DIBAH,[1] which is inert to halides. The reduction of both styrene oxide and 1-methyl-1,2-cyclohexene oxide proceeded with hydride attack from the less hindered site exclusively, giving 1-phenylethanol and 1-methylcyclohexanol, respectively.

***tert*-Amides and Nitriles.** Primary amides liberate 1 equiv of hydrogen rapidly, and further hydrogen evolution and reduction proceed very slowly. Tertiary amides, however, consumed 1 equiv of hydride rapidly and the second hydride only very slowly. *N,N*-Dimethylbenzamide and *N,N*-dimethylhexanamide gave the corresponding aldehydes in 99% and 96% yields, respectively, by reduction with SDPA at 0 °C. Several reducing agents have been reported for the partial reduction of *tert*-amides to the corresponding aldehydes. Among them, lithium triethoxyaluminum hydride[2] has proven the best reducing agent, yielding 70–90% of aldehyde at 0 °C. Thus SDPA could serve as a good alternative to lithium triethoxyaluminum hydride. Hexanenitrile reacted with the reagent with accompanying evolution of 0.35 equiv of hydrogen, and no aldehyde could be detected even with a limited amount of SDPA. However, aromatic nitriles gave the corresponding aldehydes quantitatively at 0 °C. Therefore, we believe SDPA is also an excellent alternative to DIBAH[10] for the synthesis of aromatic aldehydes from nitriles.

Nitrogen and Sulfur Compounds. 1-Nitropropane rapidly evolved 1 equiv of hydrogen with no hydride consumed for reduction. Nitrobenzene, on the other hand, was slowly reduced to the hydroxylamine stage. Azobenzene was inert whereas azoxybenzene was reduced with consumption of two hydrides, one for hydrogen evolution and the other for reduction, presumably to azobenzene. Cyclohexanone oxime was slowly reduced to the hydroxylamine stage. SDPA did not show any reactivity toward pyridine. Methyl *p*-tolyl sulfide proved stable to the reagent under the standard conditions, similar to LAH. Disulfides were rapidly reduced to the corresponding thiols with utilization of 2 equiv of hydride, one for reduction and the other for hydrogen evolution. Dimethyl sulfoxide also consumed 2 equiv of hydride rapidly, giving dimethyl sulfide, whereas diphenyl sulfone was inert to this reagent. Sulfonic acid liberated hydrogen quantitatively, but no reduction was observed under the standard conditions.

Conclusions

The reducing characteristics of SDPA in THF–toluene (~12:8) have been catalogued through a systematic study of its reactions with representative organic compounds. SDPA gives excellent yields of aldehydes from aromatic esters, *tert*-amides, and nitriles and good yields from aliphatic esters and *tert*-amides. The piperidyl group of SDPA competitively attacks aldehydes and the α-hydrogens of carbonyl compounds. Carboxylic acids, sulfonic acids, pyridine, sulfone, and chlorides are all inert under the standard conditions.

Experimental Section

General. The reaction flasks and other glassware used for the experiments were predried at 150 °C for several hours, assembled while hot, and cooled under a stream of dry nitrogen. All reactions were carried out under a static pressure of nitrogen in flasks fitted with a septum-covered side arm, using standard techniques for handling air-sensitive materials. Hypodermic syringes were used at all times to transfer solutions.

Materials. Most of the organic compounds utilized in this study were commercial products of the highest purity. They were further purified by distillation or recrystallization when necessary. SDDA was purchased from Aldrich Chemical Co. as a 25 wt % (2.0 M) solution in toluene. THF was distilled from sodium metal and benzophenone and stored under a dry nitrogen atmosphere.

Selective Hydrolysis of SDDA. First, we estimated the concentration of SDDA by hydrolyzing it with 1 N HCl solution. However, the acid solution hydrolyzes both hydride and ethyl groups in SDDA at 25 °C and gives a rather large amount of gas (~100 mL, 4 mmol) per millimole of SDDA. Therefore, we tried to develop a hydrolysis system that hydrolyzes only the hydride of SDDA, selectively. As the result of these efforts, we found that a 1:1 mixture of *tert*-butyl alcohol–THF hydrolyzes the hydride of SDDA and SDPA selectively, without attacking the ethyl groups, at 0 °C.

Preparation of SDPA. Into a 500-mL flask, thoroughly dried in an oven and cooled under nitrogen, 150 mL (300 mmol) of 2 M SDDA solution in toluene and 150 mL of THF were introduced. The solution was cooled to 0 °C, and then, 32.6 mL (330 mmol) of distilled piperidine was added with vigorous stirring. Stirring was continued for an additional 3 h to give complete hydrogen evolution. The resulting SDPA solution was transferred into a tightly closed bottle by a double-ended needle. The solution was kept in a refrigerator under a slightly positive nitrogen atmosphere. The SDPA solution thus prepared was 0.88 M in hydride as standardized by hydrolysis with *tert*-butyl alcohol–THF (1:1 mixture). The SDPA solution was stable in the refrigerator for 6 months without any appreciable loss of hydride content.

Reduction of a Representative Organic Compound. The reduction of ethyl benzoate is described as an example. A 50-mL flask was oven-dried and cooled in a steam of nitrogen. The flask was fitted with a rubber septum on an inlet tube, a magnetic stir bar, and a reflux condenser connected to a gas buret and immersed in an ice bath. Into the flask, 3.6 mL of THF was introduced, followed by 11.4 mL (10 mmol) of a 0.88 M solution of SDPA. The flask was then maintained at 0 °C. Finally, 5 mL (2.5 mmol) of a 0.5 M solution of ethyl benzoate and naphthalene (as an internal standard) in THF was injected into the reaction flask. Thus, the reaction mixture was 0.5 M in SDPA and 0.125 M in ethyl benzoate. No hydrogen was evolved when the ester was added. After 0.5 h, a 2.0-mL aliquot of the reaction mixture (0.25 mmol of the compound) was removed with a hypodermic syringe and injected into the hydrolyzing solution of *tert*-butyl alcohol–THF (1:1) which had been precooled to 0 °C in an ice bath. The hydrogen evolved amounted to 0.73 mmol as compared to 1.00 mmol for a blank reaction. The difference of 0.27 mmol represents the number of millimoles of hydride used per 0.25 mmol of compound added (1.08 mmol/mmol of compound). Aliquots were also removed and hydrolyzed after 1.0, 3.0, 6.0, 12.0, and 24.0 h of reaction time. It was found that 1.15, 1.17, 1.20, 1.25, and 1.27 mmol of SDPA had reacted, respectively, per millimole of ester. After 24.0 h, the reaction mixture was hydrolyzed with 20 mL (40 mmol) of 2 N NaOH solution, treated with NaCl. The organic layer was dried with anhydrous magnesium sulfate. GC analysis showed 76% benzaldehyde, 20% benzyl alcohol, and 6% *N*-benzylpiperidine.

Reduction of Benzaldehyde with SDPA. A 50-mL flask similarly equipped as above was immersed in an ice bath. Into the flask were introduced 11.4 mL of 0.88 M SDPA (10 mmol) and 3.6 mL of THF, and the reaction was begun by adding 5 mL

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(10) Zakharkin, L. I.; Khorlina, I. M. *Dokl. Akad. Nauk. SSSR* **1957**, *116*, 422.

of 0.5 M (2.5 mmol) benzaldehyde solution in THF containing 2.5 mmol of naphthalene as an internal standard. The hydrolysis of aliquots at 0.5 h revealed 0.49 equiv of hydride consumed for reduction per mole of compound, and no further reduction ensued. After 3.0 h, the reaction mixture was hydrolyzed with 10 mL of 2 N sulfuric acid. The organic layer was dried with anhydrous magnesium sulfate. GC analysis showed 45% benzaldehyde and 50% benzyl alcohol. However, when this mixture was allowed to react further with excess LAH for 3 h at room temperature, the products were *N*-benzylpiperidine (45%) and benzyl alcohol (50%).

Reduction of Ethyl Benzoate with SDPA. A 50-mL flask, similarly equipped as above, was immersed in an ice bath. Into the flask were introduced 2.8 mL of THF and 1.0 mL (1.0 mmol) of ethyl benzoate solution in THF containing mesitylene as an internal standard, followed by 1.25 mL (1.1 mmol) of a 0.88 M solution of SDPA. The solution was maintained at 0 °C with stirring. After 0.5 h, the mixture was divided into two portions. One portion was hydrolyzed with 5 mL of 2 N HCl, treated with NaCl, and extracted with ether. The ether layer was dried over anhydrous magnesium sulfate and analyzed by GC (99% yield of benzaldehyde). The other portion was added to excess LAH at room temperature. After 3.0 h, the mixture was hydrolyzed with NaOH solution, treated with NaCl, and extracted with ether. The ether layer, which was dried over anhydrous potassium carbonate, showed a 94% yield of *N*-benzylpiperidine by GC analysis.

Preparation of 4-Nitrobenzaldehyde from Ethyl 4-Nitrobenzoate. Into a 500-mL flask was introduced 9.75 g (50 mmol) of ethyl 4-nitrobenzoate in THF (50 mL). The solution was maintained at 0 °C, and 62.5 mL (55 mmol) of a 0.88 M solution of SDPA was added. After 1.0 h, the reaction mixture was hydrolyzed with 100 mL of 2 M H_2SO_4 and the product was extracted with ethyl ether (100 mL × 3). The ether layer was poured into 150 mL of saturated aqueous sodium bisulfite solution. To this solution was added 100 mL of THF, and the mixture was stirred for 2 h. At this time the crystalline bisulfite adduct of 4-nitrobenzaldehyde was apparent. The solution was cooled in an ice bath to ensure complete crystallization of the adduct. The adduct was collected by filtration, washed with pentane (3 × 50 mL), and dried. The adduct was placed in 100 mL of saturated aqueous magnesium sulfate solution, 100 mL of pentane and 20 mL of a 37% formaldehyde solution were added, and the mixture was stirred for 1 h. The pentane layer was separated and dried over anhydrous magnesium sulfate. Evaporation of all volatile materials gave a 77% yield of pure 4-nitrobenzaldehyde, mp 107 °C (lit.[11] mp 106–107 °C).

Partial Reduction of *N,N*-Dimethylbenzamide to Benzaldehyde with SDPA. A 50-mL flask, similarly equipped as above, was immersed in an ice bath. Into the flask was introduced 2.8 mL of THF, followed by 1.0 mL (1.0 mmol) of *N,N*-dimethylbenzamide in THF containing mesitylene as an internal standard. The flask was maintained at 0 °C. Finally, 1.2 mL (1.06 mmol) of a 0.88 M solution of SDPA was injected into the reaction flask with stirring. After 3.0 h, 5 mL of acetaldehyde was added to the reaction mixture to destroy the excess hydride, and the mixture was hydrolyzed with 5 mL of water. The resulting solution was extracted with 10 mL of ethyl ether, and the organic layer was dried over anhydrous potassium carbonate. GC analysis showed a 99% yield of benzaldehyde.

Preparation of 4-Chlorobenzaldehyde from 4-Chlorobenzonitrile. In a 500-mL flask, 1.38 g (10 mmol) of 4-chlorobenzonitrile in 32 mL of THF was allowed to react with 18 mL of 0.85 M (15.3 mmol) SDPA at 0 °C for 0.5 h. The reaction mixture was hydrolyzed with 100 mL of 2 N H_2SO_4 and extracted three times with 50 mL of ether. The ether layer was dried over anhydrous potassium carbonate. After removal of the ether, the residue was dissolved in 30 mL of ethanol, and upon addition of water, a crystalline product appeared. The crude product was sublimed at 55 °C under high vacuum, and pure 4-chlorobenzaldehyde (1.18 g, 84%) was obtained: mp 47–48 °C (lit.[11] mp 47.5 °C). The ^1H NMR spectrum agreed with that of an authentic sample.

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