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Enantioselective Michael addition of aldehydes to maleimides organocatalysed by chiral 1,2-diamines: an experimental and theoretical study

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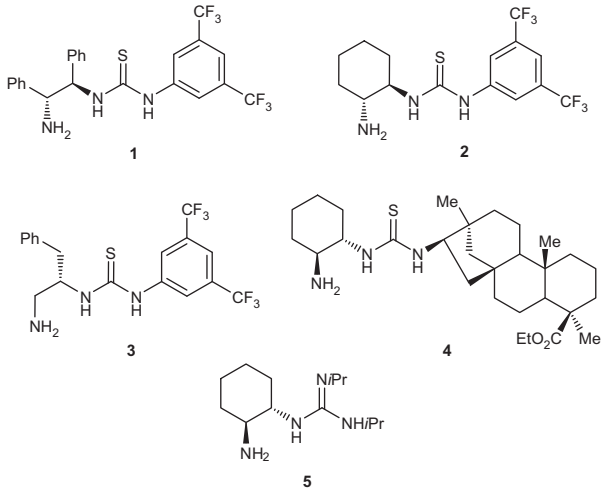
ABSTRACT

Simple and commercially available chiral 1,2-diamines were used as organocatalysts for the enantioselective conjugate addition of aldehydes, including α,α-disubstituted, to maleimides. The reaction was carried out in the presence of hexanedioic acid as an additive in aqueous solvents at room temperature. By employing (1*S*,2*S*)- and (1*R*,2*R*)-cyclohexane-1,2-diamine as organocatalysts, the corresponding Michael adducts bearing new stereocenters were obtained in high or quantitative yields with enantioselectivities of up to 92%, whereas the use of (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine gave a much lower ee. Theoretical calculations were used to justify the observed sense of the stereoinduction.

1. Introduction

Maleimides have been successfully used in different asymmetric organocatalytic transformations.[1] Among the compounds that can be prepared by the organocatalytic functionalization of maleimides, succinimides are one of the most important, since the succinimide moiety is present in natural products and some clinical drug candidates.[2] Moreover, succinimides can be transformed into other interesting compounds such as γ-lactams,[3] which are important in the treatment of epilepsy,[4] HIV,[5] neurodegenerative disease and depression.[6]

The most direct and simple way of preparing enantioenriched succinimides is by the organocatalytic enantioselective Michael addition of carbon nucleophiles to maleimides.[1] These carbon nucleophiles are usually generated by α-deprotonation of pro-nucleophiles by means of chiral bifunctional organocatalysts bearing both an acidic moiety and a tertiary amine.[1] The subsequent formation of a transition state involving the co-ordination of the maleimide and the enolate generated after deprotonation by the tertiary amine, leads to an enantioselective process. However, when the aldehydes are used as pro-nucleophiles, the corresponding succinimides can be obtained using primary amine-bearing organocatalysts amenable to create transition states after formation of a transient enamine with the reacting aldehyde. Thus, the first enantioselective conjugate addition of aliphatic aldehydes to *N*-aryl-maleimides used α,α-phenylprolinol silyl ether as an organocatalyst.[7] However, the use of α,α-disubstituted aldehydes as pro-nucleophiles resulted in much lower enantioselectivities.



Since then, several bifunctional primary amine organocatalysts have been developed and applied to the enantioselective Michael addition of α,α-disubstituted aldehydes to maleimides giving excellent results,[8] such as the trifluoromethylated primary amine thioureas **1**,[8a,b] **2**[8a,b] and **3**,[8e] the beyerane-containing thiourea **4**,[8f] a primary amine guanidine **5**,[9] and a cinchonidine-derived primary amine.[10]

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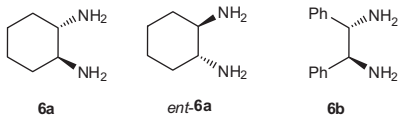
As observed, chiral 1,2-diamines, mainly cyclohexane-1,2-diamines, are used as a source of chirality for the preparation of several of these organocatalysts. Therefore, it would be interesting to see if these untransformed simple starting diamines could themselves act as chiral organocatalysts. The literature shows a few recent examples confirming this assertion. Thus, chiral cyclohexane-1,2-diamines, such as **6a** and its enantiomer *ent*-**6a**, have been used as very effective organocatalysts in an enantioselective vinylogous Michael addition reaction of cyclopentanone[11] or γ-butenolides[12] to chalcones, as well as in aldol reactions of ketones to aromatic aldehydes[13] or cyclohexanone to isatins.[14] In addition, other chiral 1,2-diamines such as (1*R*,2*R*)-1,2-diphenyl-1,2-ethanediamine *ent*-**6b**, have been used as organocatalysts in the enantioselective Michael addition reactions of aryl methyl ketones with 2-furanones,[15] or in the enantioselective synthesis of 3,4-dihydropyran derivatives via organocatalytic Michael reactions of α,β-unsaturated enones.[16] However, relatively low to moderate enantioselectivity was observed when chiral (1*R*,2*R*)-cyclohexane-1,2-diamine *ent*-**6a** or (1*R*,2*R*)-1,2-diphenyl-1,2-ethanediamine *ent*-**6b** were employed as organocatalysts for the enantioselective Michael addition of isobutyraldehyde to *N*-phenylmaleimide, respectively, with the reaction being performed in the presence of benzoic acid as the additive and in dichloromethane as the solvent.[8a]

Herein we report how the use of appropriate reaction conditions allows the use of simple and commercially available chiral 1,2-diamines as organocatalysts for the direct enantioselective reaction of aldehydes to maleimides, particularly using the difficult α,α-disubstituted aldehydes. In addition, DFT calculations were used to explain the observed enantioselectivity.

2. Results and discussion

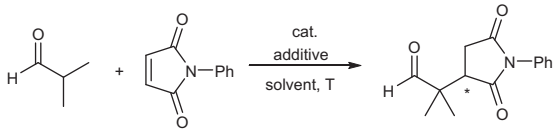
We chose the most commonly employed (1*S*,2*S*)-cyclohexane-1,2-diamine **6a** as the initial organocatalyst in the model Michael conjugate addition of isobutyraldehyde to *N*-phenylmaleimide under different reaction conditions (Table 1).



6a *ent*-**6a** **6b**

Thus, the use of a 20 mol % loading of **6a** in toluene as the solvent gave rise to an almost quantitative yield of succinimide (*R*)-**9aa** with 48% ee (Table 1, entry 1). The absolute configuration was determined according to the order of elution of the corresponding enantiomers in chiral HPLC (see Section 4).[8b] Changing the solvent to dichloromethane gave a good yield for **9aa** but in a racemic form, whereas the use of other solvents such as acetone, *tert*-butyl methyl ether (TBME), nitromethane or DMF gave lower yields and low enantioselectivities for (*R*)-**9aa** (Table 1, entries 3–6). However, when neat water was used as solvent, a good yield of (*R*)-**9aa** with 60% ee was observed (Table 1, entry 7). When a mixture of DMF/water (1:1) was employed (*R*)-**9aa** was isolated quantitatively in 71% ee. In addition, changing the DMF/water ratio

Table 1
Screening and optimization of the reaction conditions for the enantioselective Michael addition



7a **8a** **9aa**

Entry	Catalyst (mol %)	Additive[a] (mol %)	Solvent	*T* (°C)	*t* (d)	Yield[b] (%)	ee[c] (%)
1	**6a** (20)	—	PhMe	25	2	97	48 (*R*)
2	**6a** (20)	—	CH_2Cl_2	25	2	90	0
3	**6a** (20)	—	Acetone	25	2	60	34 (*R*)
4	**6a** (20)	—	TBME	25	2	40	35 (*R*)
5	**6a** (20)	—	$MeNO_2$	25	2	35	6 (*R*)
6	**6a** (20)	—	DMF	25	2	80	28 (*R*)
7	**6a** (20)	—	H_2O	25	2	90	60 (*R*)
8	**6a** (20)	—	DMF/H_2O[d]	25	2	99	71 (*R*)
9	**6a** (20)	—	DMF/H_2O[e]	25	2	99	85 (*R*)
10	**6a** (20)	—	DMF/H_2O[f]	25	2	99	80 (*R*)
11	**6a** (10)	—	DMF/H_2O[e]	25	4	99	85 (*R*)
12	**6a** (20)	Imidazole (20)	DMF/H_2O[e]	25	1	99	85 (*R*)
13	**6a** (20)	$PhCO_2H$ (20)	DMF/H_2O[e]	25	1	99	75 (*R*)
14	**6a** (20)	$MeCO_2H$ (20)	DMF/H_2O[e]	25	1	99	77 (*R*)
15	**6a** (20)	HDA (20)	DMF/H_2O[e]	25	1	99	91 (*R*)
16	**6a** (20)	HDA (20)	DMF/H_2O[e]	0	1	99	85 (*R*)
17	**6b** (20)	HDA (20)	DMF/H_2O[e]	25	5	50	50 (*S*)
18	*ent*-**6a** (20)	HDA (20)	DMF/H_2O[e]	25	1	99	92 (*S*)

[a] HDA: hexanedioic acid.
[b] Isolated yield after flash chromatography.
[c] Enantioselectivities and absolute stereochemistry determined by chiral HPLC.[8b]
[d] 1/1, v/v.
[e] 2/1, v/v.
[f] 4/1, v/v.

allowed us to increase the enantioselectivity of the process. Thus, the use of a 2:1 DMF/water ratio increased the enantioselectivity for (*R*)-**9aa** up to 85%, although the use of a 4:1 ratio lowered it down to 80% (Table 1, entries 9 and 10). Finally, we diminished the organocatalyst loading down to 10 mol %, obtaining (*R*)-**9aa** quantitatively with 85% ee, although the reaction time doubled (Table 1, entry 11).

Next, we considered the influence of the addition of additives to the model reaction. Thus, the addition of imidazole (20 mol %), increased the enantioselectivity of this reaction when using primary amine–guanidine as an organocatalyst,[9b] increased the reaction rate considerably but kept the enantioselectivity for (*R*)-**9aa** at 85% (Table 1, entry 12). The addition of some acid additives, such as benzoic or acetic acids, which has proven to be effective in increasing the enantioselectivity of this process,[8a] also increased the reaction rate, probably facilitating the formation of the initial enamine, but gave lower enantioselectivity (Table 1, entries 13 and 14). However, the addition of hexanedioic acid (HDA, 20 mol %), an additive, that has been very effective in chiral cyclohexane-1,2-diamine-catalysed transformations,[11–14] also accelerated the reaction, giving rise quantitatively to (*R*)-**9aa** in 91% ee (Table 1, entry 15). Lowering the reaction temperature to 0 °C did not improve the enantioselectivity of the process (Table 1, entry 16).

We also explored the use of (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine **6b** as an organocatalyst for the model addition reaction under more effective reaction conditions [DMF/water 2:1, HDA (20 mol %), rt], but the reaction was very slow, yielding only a 50% yield of the corresponding Michael adduct in 50% ee after **5d** (Table 1, entry 17). However, it is noteworthy that in this case the reaction was biased towards the opposite (*S*)-**9aa**, although the configuration of 1,2-diamines **6a** and **6b** is 'similar'. This contrary enantioselection has recently been observed in a Michael addition of aryl methyl ketones with 2-furanones organocatalysed by *ent*-**6a** and *ent*-**6b**.[15] In addition, expecting to achieve an opposite enantioselection for **9aa** using the enantiomer of **6a**, that is, *ent*-**6a**, as an organocatalyst, we performed the reaction under the best reaction conditions, obtaining the expected adduct (*S*)-**9aa** with 92% ee (Table 1, entry 18).

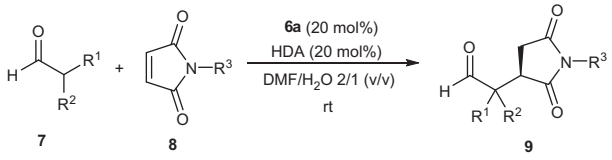
Once the most effective organocatalyst and reaction conditions were established [**6a** (20 mol %), DMF/water 2:1, HDA (20 mol %), rt] we extended the application of this organocatalytic methodology to other aldehydes and maleimides (Table 2). As in the case of the model reaction, the absolute configuration of the known succinimides was assigned according to the elution order of their enantiomers in chiral HPLC when compared to the literature (see Section 4).

Thus, when isobutyraldehyde was reacted with *N*-phenylmaleimides bearing halogens on the phenyl ring, such as a chloro atom at the 3- and 4-position **8b** and **8c** or a bromo atom at the 4-position **8d**, the enantioselectivities for the obtained succinimides (*R*)-**9ab**, (*R*)-**9ac** and (*R*)-**9ad** were 72%, 59% and 80%, respectively (Table 2, entries 2–4). In addition, when methoxy or acetoxy groups were present on the phenyl ring of the maleimide, as in the case of **8e** and **8f**, the enantioselectivities for the corresponding succinimides (*R*)-**9ae** and (*R*)-**9af** were 74% and 75%, respectively (Table 2, entries 5 and 6).

Non-*N*-arylated maleimides were also used for the conjugate addition with isobutyraldehyde. Thus, *N*-benzylmaleimide **8g** quantitatively afforded the corresponding succinimide (*R*)-**9ag** with 75% ee, whereas *N*-methylmaleimide **8h** gave adduct (*R*)-**9ah** also quantitatively in 70% ee (Table 2, entries 7 and 8). The simple maleimide **8i** was also explored, yielding quantitatively the succinimide (*R*)-**9ai** with an enantioselectivity of 68% (Table 2, entry 9).

Other α,α-disubstituted aldehydes were employed for the organocatalysed Michael addition reaction to *N*-phenylmaleimide. Thus, 2-ethylbutanal **7b** afforded succinimide (*R*)-**9ba** in 77% ee, with cyclopentane-**7c** and cyclohexane carbaldehyde **7d** gave succinimides (*R*)-**9ca** and (*R*)-**9da** in 78% with 67% ee, and in 96% and 93% yield, respectively (Table 2, entries 11 and 12). In addition, the use of α-monosubstituted aldehydes such as propanal **7e** and 3-phenylpropanal **7f** afforded the Michael adducts (*S*,*R*)/(*R*,*R*)-**9ea** and (*S*,*R*)/(*R*,*R*)-**9fa**, respectively, as mixtures of diastereomers with

Table 2
Enantioselective Michael addition of aldehydes to maleimides organocatalysed by 1,2-diamine 6a



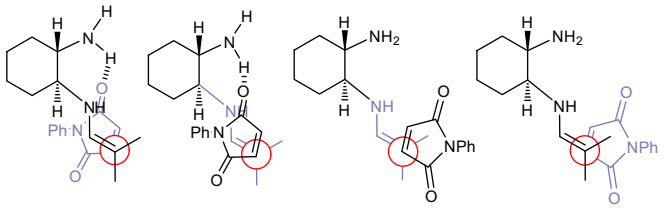
Entry	Aldehyde			Maleimide		*t* (d)	Adduct No.	Yield[a] (%)	ee[b,c] (%)
	R^1	R^2	No.	R^3	No.				
1	Me	Me	**7a**	Ph	**8a**	1	(*R*)-**9aa**	99	91
2	Me	Me	**7a**	3-ClC_6H_4	**8b**	1	(*R*)-**9ab**	95	72
3	Me	Me	**7a**	4-ClC_6H_4	**8c**	1	(*R*)-**9ac**	98	59
4	Me	Me	**7a**	4-BrC_6H_4	**8d**	1	(*R*)-**9ad**	94	80
5	Me	Me	**7a**	2-$MeOC_6H_4$	**8e**	1	(*R*)-**9ae**	91	75
6	Me	Me	**7a**	4-$AcOC_6H_4$	**8f**	1	(*R*)-**9af**	90	74
7	Me	Me	**7a**	Bn	**8g**	1	(*R*)-**9ag**	99	75
8	Me	Me	**7a**	Me	**8h**	1	(*R*)-**9ah**	99	70
9	Me	Me	**7a**	H	**8i**	1	(*R*)-**9ai**	99	68
10	Et	Et	**7b**	Ph	**8a**	2	(*R*)-**9ba**	92	77
11	$-(CH_2)_4-$		**7c**	Ph	**8a**	1	(*R*)-**9ca**	96	78
12	$-(CH_2)_5-$		**7d**	Ph	**8a**	2	(*R*)-**9da**	93	67
13	H	Me	**7e**	Ph	**8a**	1	(*S*,*R*)/(*R*,*R*)-**9ea**	97[d]	79/82
14	H	Bn	**7f**	Ph	**8a**	1	(*S*,*R*)/(*R*,*R*)-**9fa**	90[e]	69/63

[a] Isolated yield after flash chromatography.
[b] Enantioselectivities determined by chiral HPLC.
[c] Absolute configuration assigned by the order of elution of the enantiomers in chiral HPLC (see Section 4).
[d] Mixture of diastereomers 1.2/1 determined by ^1H NMR (300 MHz) in the reaction crude.
[e] Mixture of diastereomers 1.9/1 determined by ^1H NMR (300 MHz) in the reaction crude.

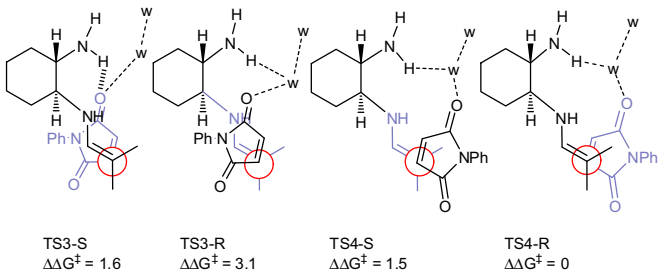
enantioselectivities of up to 82% and 69%, respectively, for the major isomer [Table 2, entries 13 and 14, see footnotes (d) and (e)].

Concerning the sense of the enantioinduction achieved in this organocatalysed reaction by using these chiral 1,2-diamines, several doubts arose. Thus the observed (*R*)-stereochemistry in all the formed succinimides **9**, which was achieved employing organocatalyst **6a**, is the same as that observed when using primary amine-thiourea organocatalysts prepared from enantiomeric *ent*-**6a**.[8b] This suggests that a different transition state is operating in this addition reaction when 1,2-diamine **6a** is the organocatalyst. In addition, the opposite (*S*)-stereochemistry observed for **9aa** when employing **6b** as the organocatalyst (see Table 1), indicates different mechanistic behaviour for 1,2-diamines **6a** and **6b**.

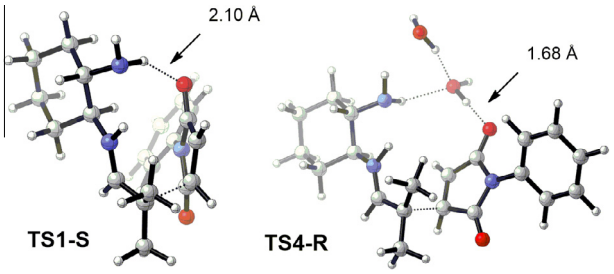
In order to gain further insight into the origin of the observed enantioselectivity, we carried out DFT theoretical calculations at the B3LYP/6-311+G**(IEFPCM, water) computational level. Based on our own previous experience,[9b] the sense of induction achieved with catalyst **6a** was unexpected. First, we located the most stable transition states with **6a**, finding that the two lowest in energy (TS1-S and TS1-R) proceed through a synclinal conformation, with the formation of a weak H-bond between one of the O atoms of the maleimide and the NH_2 moiety of the diamine (TS1-S). The comparison of their energies would anticipate the preferential formation of the (*S*)-enantiomer, in contrast to the experimental observations. When we broke the H-bonding interaction, and computed the open transition structures TS2-S and TS2-R, the activation energies increased ($\Delta\Delta G^{\ddagger}$ = 1.2 and 5.0 kcal/mol higher than TS1-S) due to the lack of stabilization of the negative charge that develops in the maleimide portion during the transition state.



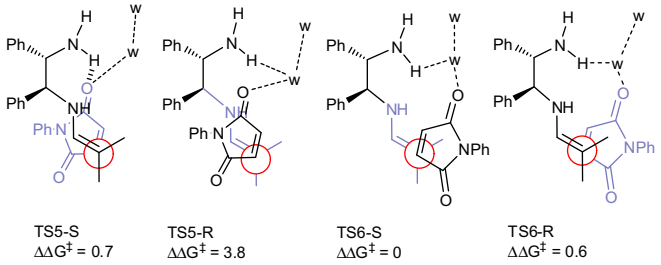
The relative activation energies of TS2-S (+5.0 kcal/mol) and TS2-R (+1.5 kcal/mol) would be in accordance with the experimental formation of the (*R*)-enantiomer, if we could surpass their lack of stabilization. In this regard, gas-phase computational methods are especially inefficient in dealing with developing charges, and solvent stabilization is required in order to obtain accurate results. We thought that the introduction of some explicit water molecules in conjunction with computation in a solvent model would help us to compare more accurately the TS1 and TS2-type transition structures. Gratifyingly, TS3 and TS4-type transition structures, which contain two molecules of water (identified as w in the Figure) in each case, fairly reproduce the experimental sense of induction.



The new lowest in energy transition state is TS4-R, 1.5 kcal/mol lower than TS4-S, predicting ca. 10:1 enantioselectivity in favour of the (*R*)-enantiomer. The activation of the maleimide and stabilization of the developing charge were achieved by hydrogen-bonding with a water molecule,[17] which bridges the oxygen atom and the NH_2 moiety.



We next applied this concept to the study of the reaction catalysed by (1*S*,2*S*)-1,2-diphenylethane-1,2-diamine **6b**, and again found an agreement between the experimental and computational results. The operative transition state in the presence of **6b** is TS6-S, leading to the formation of the (*S*)-enantiomer. With regard to the computed structures, we do not have a complete explanation for the opposite enantioinduction observed with **6a** and **6b**, but it seems to be related to the higher flexibility of the latter, and the relative disposition of the two phenyl rings. In any case, the flexibility of **6b** also results in a measurable decrease in the energy differences between transition states TS5-S, TS6-S and TS6-R (0.7, 0, and 0.6 kcal/mol relative energies), which is in accordance with the worse performance of **6b** as a catalyst, leading to a modest 50% ee.



3. Conclusion

It can be concluded that commercial, enantiomerically pure 1,2-diamines can be used as organocatalysts in enantioselective conjugate additions of aldehydes, mainly α,α-disubstituted, to different maleimides in an aqueous solvent. The enantioselectivities obtained when chiral *trans*-cyclohexane-1,2-diamines are employed as organocatalysts are much higher than those obtained when chiral 1,2-diphenyl-1,2-ethanediamine is used, a contrary sense of enantioselectivity for both 1,2-diamines being observed. The sense of enantioinduction has been explained by theoretical calculations, which reveal the participation of an open transition state, in which the maleimide is hydrogen-bond activated by the surrounding water molecules. One of these molecules acts as a bridge between the oxygen atom of the maleimide and the NH_2 moiety of the catalyst.

4. Experimental

4.1. General procedure for the enantioselective Michael addition reaction

To a solution of **6a**, *ent*-**6a** or **6b** (0.04 mmol), the maleimide (0.2 mmol) and hexanedioic acid (0.04 mmol) in DMF/H_2O (2:1, v/v) (0.5 mL) was added the aldehyde (0.4 mmol) and the mixture was stirred at room temperature until reaction completion (TLC). The reaction was then quenched with HCl 2 M (10 mL) and the mixture was extracted with AcOEt (3 × 10 mL). The organic phase was washed with a saturated solution of $NaHCO_3$ (10 mL) and H_2O (10 mL), dried over $MgSO_4$, and the filtrate was concentrated to give a crude product, which was purified by silica gel chromatography (*n*-hexane/AcOEt).

The already reported adducts **9** were identified by comparison of their spectroscopic data with those in the literature.[9] Their enantiomeric excesses and absolute configurations were determined by chiral HPLC.[9b]

4.2. Calculations

All structures were optimized using the functional B3LYP[18] and the 6-31G* basis set as implemented in GAUSSIAN 09,[19] and the energies were single-point refined in a solvent model at B3LYP/6-311G++ level on the previously optimized structures, including polarization functions for better description of hydrogen bonds involved in the reaction. The solvation factors were introduced with the IEF-PCM method,[20] using water as the solvent. The stationary points were characterized by frequency calculations in order to verify that they have the right number of imaginary frequencies. The intrinsic reaction coordinates (IRC)[21] were followed to verify the energy profiles connecting each TS to the correct associated local minima.

Acknowledgments

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