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Study and optimization of Diels-Alder reaction of piperine in aqueous ionic solutions using Gn.HCl as a catalyst

V. Rama Subbarao[a]*

[a]*Natural Products Laboratory, Organic Chemistry Division-I, Indian Institute of Chemical Technology, Habsiguda, Hyderabad 500007, India.*

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ABSTRACT

Study and optimization of Diels-Alder reaction of piperine in aqueous ionic solutions using Gn.HCl as a catalyst. The semi-synthesis of these products using intermolecular [4+2] cycloaddition reaction has been described. Obtained products were characterized using IR, HNMR, CNMR and Mass Spectroscopy.

*Corresponding author. e-mail: ramsiict@gmail.com

Introduction

An outsized number of phenomena concern to and are conducted in liquid phase involving ionic species (Millions of years ago, Mother Nature discovered the secrets of water molecule) in different biological and other natural processes. Salt present in the oceans, a striking example from Nature, is a multi component salt solution reflecting the distant marine origin of life on earth together with the composition of physiological fluids. In general the ionic solutions play roles in several industrial and geological processes in addition to their deep impact on the biological molecules. This enormous power of ionic solutions is based on the interactions of ion with solvent. In this work, we present some interesting results with comprehensive implications on the application of ion-solvent (i-s) interactions on organic reactions.

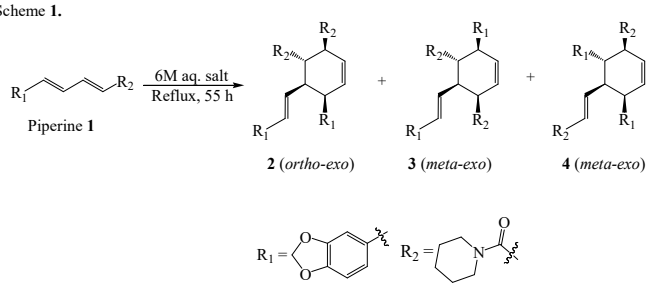
Ion-Solvent interactions

Cohesion among molecules in the liquid phase results from intermolecular forces. These forces include hydrogen-bonding, dipole-dipole, multi polar, dispersion interactions and also interactions emerging from the repulsion between two molecules. The cohesion due to intermolecular forces gives rise to a 'pressure' which is experienced by the solvent molecules**.** A liquid undergoing a small, isothermal volume expansion does work against the cohesive forces which causes a change in the internal energy, U. The function $(\partial U/\partial V)_T$, is called as internal pressure (Pi) of a liquid and is supported by the equation of state. Internal pressure increases upon the addition of some solutes like NaCl, KCI, etc. and decreases by salts like of guanidinium salts.

Diels-Alder Reaction in aqueous medium

For long time water was not a popular solvent for the Diels-Alder reaction. Before 1980 its use had been reported only incidentally. Diels and Alder themselves performed the reaction between furan and maleic acid in an aqueous medium in 1931,[27] an experiment which was repeated by Woodward and Baer in 1948. [28] They noticed a change in *endo-exo* selectivity when comparing the reaction in water with ether. The extreme influence of water can exert on the Diels-Alder reaction was rediscovered by Breslow in 1980, much by coincidence [29,30] while studying the effect of β-cyclodextrin on the rate of a Diels-Alder reaction in water, accidentally.

Scheme **1.**



Alternatively, *Grieco et al.,* have repeatedly invoked the internal pressure of water as an explanation of the rate enhancement of Diels-Alder reactions in these solvents. [31] They probably inspired by the well known large effects of the external pressure on rates of cycloadditions. However the internal pressure of water is very low and offers no valid explanation for its effects on the Diels-Alder reaction. The internal pressure is defined as the energy required bringing about an infinitesimal change in the volume of the solvent at constant temperature. Due to the open and relatively flexible hydrogen-bond network of water, a small change in volume of these solvents does not require much energy. A related, but much more applicable solvent parameter is the cohesive energy density. This quantity is a measure of energy required for evaporation of the solvent per unit volume. The reactions in water were less accelerated by pressure than those in organic solvents, which is in line with notion that pressure diminishes hydrophobic interactions.

The effect of water on the selectivity of Diels-Alder reactions

Three years after the Breslow report on the large effects of water on the rate of the Diels-Alder reaction, he also demonstrated that the *endo-exo* selectivity of this reaction benefits markedly from employing aqueous media. Based on the influence of salting-in and salting-out agents, Breslow pinpoints hydrophobic effects as the most important contributor to the enhanced endo-exo selectivity. Hydrophobic effects are assured to stabilize the more compact *endo* transition state more than the extended *exo* transition state. In Breslow option the polarity of water significantly enhances the *endo-exo* selectivity.

In conclusion, the special influence of water on the *endo-exo* selectivity seems to be a result of the fact that this solvent combines in it three characteristics that all favors formation of the *endo/exo* adduct. 1. water is strong hydrogen bond donor 2. water is polar and water induces hydrophobic interactions.

Study of salting-out and salting-in reagents towards the Diels-Alder reaction of piperine (1):

The special effects of water as solvent for valuable Diels-Alder reaction (Scheme **1**) of piperine (**1**), greatly altered by the addition of ionic solutes (Table **1**) such as LiCl, LiBr, $LiClO_4$, NaCl, NaBr, KF, KCl, KBr, $MgCl_2$, $CaCl_2$, guanidinium chloride, guanidinium carbonate, guanidinium nitrate.

Aqueous salts solutions accelerated cycloaddition reactions (Scheme **1**) of piperine (**1**) to give resultant cycloadducts **2, 3** and **4** among them **2** is major *ortho-exo* cyclohexene type dimeric amide alkaloid and also known as chabamide, which is previously isolated from this plant, isomer **3** is also known adduct and previously isolated from *Piper nigrum*. [21] Cycloadduct **4** was synthesized from piperine by Diels-Alder reaction by *Wei. et al*. its physical and spectroscopic data were identical with reported data[22] (^{1}H-NMR & Mass spectra).

Table 1: Study of different salts towards the Diels-Alder reaction of piperine (**1**).

entry	Salt	Overall yield (%)[a]
1	LiCl	30
2	LiBr	20
3	$LiClO_4$	15
4	NaF	15
5	NaCl	35
6	NaBr	20
7	NaI	10
8	$NaBF_4$	5
8	KF	30
9	KCl	50
10	KBr	40
11	KI	20
12	$MgCl_2$	10
13	**$CaCl_2$**	**79**
14	**Gn.HCl**	**81**
15	$Gn.CO_3$	70
16	$Gn.NO_3$	75
17	Gn.SCN	40

[a]Overall yield of adducts after HPLC, un-reacted piperine was recovered in all reactions.

Reaction showed good overall yield and more *exo* selectivity. This reaction showed completely regioselectivity (yield of **2**+**3**>**4**) due to maximum involvement of α-double bond rather than γ-double bond of **1** during Diels-Alder reaction.

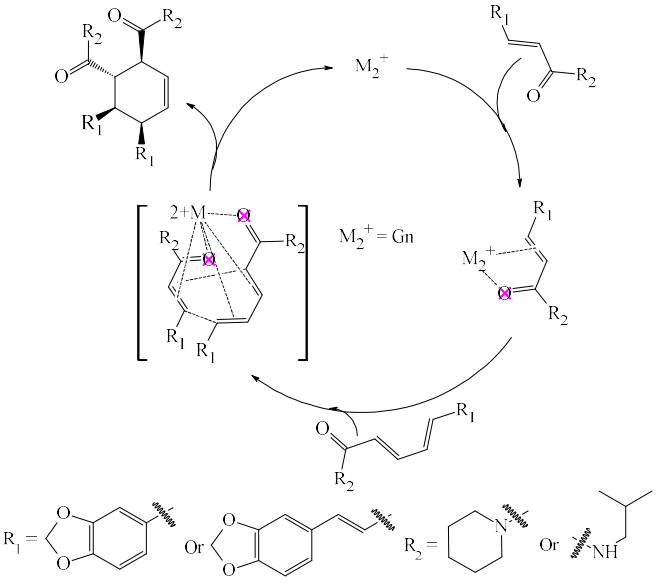
Table 2: Comparision of salting-out and salting-in reagents towards the Diels-Alder reaction of piperine (**1**).

salt	Cycloadduct ratio (%)			over all yield %
	2	**3**	**4**	
$CaCl_2$	69	21	10	79
Gn.HCl	80	15	5	81

Study of Salting-out reagents

Increased rate in Diels-Alder reaction (over all yield up to 79 %) of piperine (**1**) has been attributed to the hydrophobic effect. Owing to the difference in polarity between water and the reactants, water molecules tend to associate amongst themselves, excluding the organic reagents and forcing them to associate together forming small drops surrounded by water.

A further method of increasing the rate of Diels-Alder reaction in water is so called 'salting-out' effect. Among the salting-out reagents used (Table **1**) in this methodology $CaCl_2$ is the best reagent and gave 79 % over all yield. If anion size increases, reaction yield decreases, where as cation size increases, reaction yield increases. Here a salt such as calcium chloride is added to the aqueous solution. In this case water molecules attracted to the polar ions, increasing the internal pressure and reducing the volume. This has the effect of further excluding the organic reagents. For reactions such as Diels-Alder, which have negative activation volumes, the rates are enhanced by this increase in internal pressure in much the same way as expected for an increase in external pressure. This salting-out reagent showed good *exo* selectivity, due to formation of cycloadduct **2** (*ortho-exo*) is major up to 69 % (cycloadduct ratio) compare to cycloadducts **3** (21 %, *meta-exo*) and **4** (10%, meta-exo) are poor in yield.



Scheme 2: Plausible mechanism of Diels-Alder reaction catalyzed by Gn.HCl.

Study of Salting-in reagents

Among the tested salting-in reagents used in this methodology (Table **1**) guanidinium chloride (Gn.HCL) is the best reagent and gave 81 % overall yield, where as $LiClO_4$ end up with only 15 % overall yield. Gn.HCL reagent exhibited well selectivity towards the Diels-Alder reaction of piperine in given conditions (scheme **1**). Formation of cycloadduct 2 in 80 %, 3 in 15 % and 4 in 5 % ratio is clearly indicates this methodology received good attention towards the *exo* selectivity in Diels-Alder reaction of piperine. Overall yield is also high with salting-in reagents when compare to salting-out reagents.

Procedure for aqueous ionic salts catalyzed Diels–Alder reactions of piperine (1):

To a stirred mixture of piperine (**1**) (50.0 mg, 0.175 mmol), 6M aqueous guanidinium. Hydrochloride (2 mL) in a round bottom flask fitted with condenser and refluxed for 70 h in an oil bath. After completion of the reaction, monitored by TLC (dipped in 5% solution of phosphomolybdic acid in methanol and heating), the reaction mixture was cooled to room temperature and diluted with water (3 mL). Then extracted with EtOAc (2x5 mL), the combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. The residue obtained was then purified by reversed-phase (RP) HPLC (column: Phenomenex Luna C18, 250 x 10 mm, 10µ), solvent system: 80% acetonitrile in water, flow rate: 1.5 mL/min, to give pure compounds of adducts (**2**) 0.065 g, (**3**) 0.012 g and (**4**) 0.004 g.

Cycloaddition reaction between piperine (1a) and pellitorine (1b):

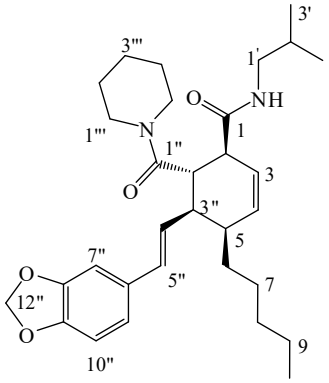
Our aim of this cycloaddition reaction is to explain to study different cycloadducts and selectivity of diene among piperine and pellitorine (Scheme **4**). This biomimetic synthesis will explain the probability of diene, which participated in Diels-Alder reaction between piperine (**1a**) and pellitorine (**1b**) both were isolated from same plant (*P. chaba*). **Nigramide N**, which is formed biosynthetically via cycloaddition reaction between piperine and pellitorine, this adduct previously isolated from roots of *P. nigrum* [21] by *Wei. et. al.*

Lewis acid catalyzed cycloaddition reactions of piperine (**1a**) and pellitorine (**1b**) under organic and aqueous solvent conditions to give resultant cycloadducts **2c**, **3c**, **4c, 2a** and **3b.** Cycloadduct **2c** and **3c** is new cycloadducts and their structures were illustrated by 1D and 2D spectral data.

Structure elucidation of compound 2c:

Compound **2c** was obtained as pale yellow liquid. The molecular formula of **2c** was established as $C_{31}H_{44}N_2O_4$ by HRESIMS (Fig-**18**), which provided a molecular ion peak at *m/z* 509.3381 [M^++H], in conjunction with its ^{13}C NMR spectrum (Fig-**12**). The IR spectrum displayed absorption bands diagnostic of carbonyl (1640 cm^{-1}) (Fig-**10**). The 300 MHz ^1H NMR spectrum (in $CDCl_3$) indicated the presence of two signals at δ 5.86 (dd, J = 15.6, 10.1 Hz) and 6.27 (d, J = 15.6 Hz), which were assigned to *trans*-olefinic protons by the coupling constant of 15.6 Hz. It also displayed aromatic protons due to two 1, 3, 4-trisubstituted aromatic rings at δ 6.82 (1H, br s), 6.76 (1H, dd, J = 7.8, 1.4 Hz), 6.75 (1H, d, J = 7.8 Hz) (Fig-**11**), (Table 4).

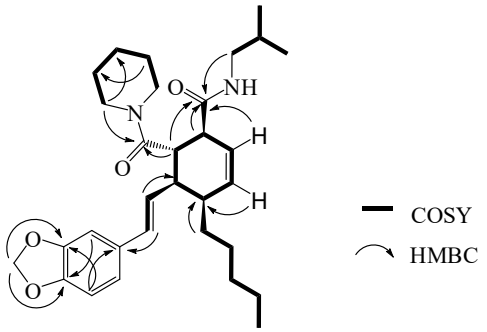
In addition to the above-mentioned moieties, combined inspection of ^{1}H NMR and ^{1}H–^{1}H COSY revealed the presence of cyclohexene ring, one isobutylamide and one pyrrolidine ring.



Compound **2c**

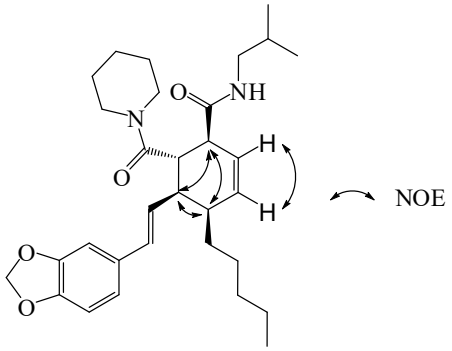
The ^{13}C NMR spectrum (Fig-**12**) displayed the presence of 31 carbon atoms and were further confirmed by DEPT experiments (Fig-**13**) into categories of 11 methylenes, 12 methines and 5 quaternary carbons including two carbonyls (δ 173.01 and 172.50). On the basis of these characteristic features, database and literature search led the skeleton of compound **2c** as a dimeric alkaloidal framework.

A comprehensive analysis of the 2D NMR data of compound **2c** facilitated the proton and carbon assignments. ^{1}H–^{1}H COSY spectrum (Fig-**16**) suggested the sequential correlations of δ 3.51 (dq, J = 5.0, 2.6 Hz)/5.62 (dt, J = 9.8, 2.6 Hz)/6.10 (ddd, J = 9.8, 1.5 Hz)/2.20 (m)/2.72 (ddd, J = 11.1, 10.1, 5.2 Hz)/3.35 (dd, J = 11.1, 9.8 Hz) assignable to H-2-H-3-H-4-H-5-H-3"-H-2" of the cyclohexene ring.



COSY and importent HMBC correlations of compound **2c**

Concerning the connections of the *n*-amyl and 3, 4-methylenedioxy styryl groups, HMBC spectrum (Fig-**15**) showed correlations of H-4, H-6, H-7/C-5; H-5", H-4"/C-3", which implies that these units were bonded to the cyclohexene ring at C-5 and C-3". Further, HMBC correlations of two methylene protons at δ 5.95 with 147.91 (C-8"), 146.87 (C-9"), confirmed the location of methylenedioxy group at C-8", and C-9". Remaining units, isobutylamine and pyrrolidine (rings) were connected through carbonyl groups at C-2 and C-2", which was confirmed by HMBC correlations of H-2 and H-1' to C-1 (δ 173.01) and H-2" and H-1''' to C-1" (δ 172.50).



Key NOE correlations of compound **2c**

The assignment of the relative configuration of compound **2c**, and confirmation of overall structure were achieved by the interpretation of the NOESY spectral data and by analysis of ^{1}H NMR coupling constants. The large vicinal coupling constants of H-2"/H-2 (11.1 Hz) and H-2"/H-3" (11.1 Hz) indicated anti-relations of H-2"/H-2 and H-2"/H-3" and the axial orientations for these protons. In the NOESY spectrum (Fig-**17**), the occurrence of the correlations between H-2/H-3" and the absence of NOE effects between H-2/H-2" and H-2"/H-3" supported the above result. This data indicated β-orientation for H-2" and α-orientation for H-2 and H-3". The α-orientation of H-5 was suggested by the coupling constant of H-5/H-3" (5.2 Hz) and the absence of the NOESY correlations between H-3" and H-2". On the basis of these spectral data, the structure of compound **2c** was unambiguously established and trivially named as **chabamide M**.

Compound 3a:

Yellow liquid, $[\alpha]_{D}^{25} = 0$ (c 0.75, $CHCl_3$)

IR (KBr) νmax: 2923, 2855,1628, 1489, 1242, 1128, 1035 cm-1

δ ppm 0.69 & 1.25 (2H, m, H-2'''), 1.15 & 1.23 (2H, m, H-4'''), 1.31 & 1.40 (2H, m, H-3'''), 1.52 (2H, m, H-2'), 1.56 (2H, m, 4'), 1.61 (2H, m, H-3'), 2.94 (1H, td, J = 10.1, 10.1, 5.5 Hz, H-3"), 3.02 & 3.60 (2H, m, H-5'''), 3.09 & 3.32 (2H, m, H-1'''), 3.51 (2H, m, H-1'), 3.61 (1H, m, H-2), 3.61 (2H, m, H-5'), 3.78 (1H, dq, J = 10.0, 2.3 Hz, H-5), 4.07 (1H, t, J = 10.1, H-2"), 5.72 (1H, ddd, J = 9.8, 5.0, 2.7 Hz, H-3), 5.88 (2H, s, H-12), 5.89 (1H, dt, 10.3, 1.8 Hz, H-4), 5.90 (1H, J =15.8, 9.8 Hz, H-4"), 5.92 (1H, s, H-12"), 6.37 (1H, d, J = 15.8 Hz, H-5"), 6.68 (1H, brs, H-7), 6.69 (1H, d, J = 8.0 Hz, H-10"), 6.70 (1H, dd, J = 8.0, 1.4 Hz, H-11), 6.69 (1H, d, J = 8.0 Hz, H-10), 6.74 (1H, dd, J = 8.0, 1.6 Hz, H-11"), 6.79 (1H, brs, H-7").

ESIMS (m/z): 571 [M+ +H]

Table 4: ^{1}H & ^{13}C NMR data of cycloadduct **2c** in $CDCl_3$ (300 MHz, δ in ppm, mult, J in Hz)

No.	^{13}C, δ	Compound 2c
		^{1}H, δ (mult, J, Hz)
1	173.01	-C-
2	47.73	3.51 (dq, 5.0, 2.6)
3	124.31	5.62 (dt, 9.8, 2.6)
4	132.63	6.10 (ddd, 9.8, 1.5)
5	39.12	2.20 (m)
6	32.20	1.35 (m)
7	27.23	1.22 (m)
8	31.92	1.23 (m)
9	22.69	1.28 (m)
10	14.08	0.08 (t, 5.5)
1'	46.90	3.09 (t, 5.8)
2'	28.54	1.53 (m)
3'	20.07	0.85 (d, 6.5)
	20.07	0.88 (d, 6.5)
1"	172.50	-C-
2"	39.49	3.35 (dd, 11.1, 9.8)
3"	45.17	2.72 (ddd, 11.1, 10.1, 5.2)
4"	127.32	5.86 (dd, 15.6, 10.1)
5"	131.53	6.27 (d, 15.6)
6"	132.03	-
7"	105.36	6.82 (br s)
8"	147.91	-
9"	146.87	-
10"	108.26	6.75 (d, 7.8)

11"	120.74	6.76 (dd, 7.8, 1.4)
12"	100.99	5.95 (br s)
1'''	47.21	3.52 (m)
2'''	26.62	1.62 (m)
3'''	24.51	1.66 (m)
4'''	25.61	1.55 (m)
5'''	43.09	3.50 (m)
NH	-	2.30 (t, 7.1)

Compound 4a:

Yellow liquid, $[\alpha]_D^{25} = 0$ (*c* 0.75, $CHCl_3$)

IR (KBr) νmax: 2926, 2857,1627, 1484, 1440, 1240, 1034 cm-1

1H NMR (300 MHz, CDCl3): δ ppm 0.81 & 1.35 (2H, m, H-2'), 1.29 & 1.47 (2H, m, H-4'), 1.35 (2H, m, H-2'''), 1.36 & 1.51 (1H, m, H-3'), 1.47 (2H, m, H-4'''), 1.51 (2H, m, H-3'''), 2.92 (2H, m, H-1'''), 2.99 (1H, ddd, *J* = 12.5, 9.7, 5.5 Hz, H-4"), 3.22 (2H, m, H-1'), 3.29 & 3.71 (2H, m, H-5'), 3.38 (1H, m, H-4'''), 3.44 (1H, dd, *J* = 12.1, 10.1 Hz, H-5"), 3.59 (1H, t, *J* = 5.3 Hz, H-5), 3.70 (1H, dq, *J* = 12.1, 2.1, H-2), 5.65 (1H, dd, *J* = 15.6, 9.5 Hz, H-3"), 5.70 (1H, dt, *J* = 9.9, 1.6, H-3), 5.81 (1H, d, *J* = 15.6 Hz, H-2"), 5.84 (1H, s, H-12"), 5.90-5.92 (2H, brs, H-12), 5.96 (1H, ddd, *J* = 9.2, 5.8, 2.6 Hz, H-4), 6.55 (1H, dd, *J* =7.9, 1.5 Hz, H-11"), 6.61 (1H, d, *J* = 8.2 Hz, H-10"), 6.62 (1H, d, *J* = 1.4 Hz, H-7"), 6.79 (1H, d, *J* = 7.9 Hz, H-10), 6.92 (1H, dd, *J* = 8.0, 1.5 Hz, H-11), 7.01 (1H, d, *J* = 1.5 Hz, H-7).

ESIMS (m/z): 571 [M+ +H]

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