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Crystal Structure of 1:1 Complex of Honokiol and 1,4-Diazabicyclo[2.2.2]octane: Separation of Honokiol by Molecular Recognition

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Abstract

Phenomenon of molecular recognition between honokiol and 1,4-diazabicyclo[2.2.2]octane (DABCO) is discovered, and applied to separation of honokiol from extract of magnolia bark. Effects of material ratio on the yield and the purity were investigated. Honokiol (purity up to 97.3% and yield up to 83.9%) is obtained from *Magnolia* bark extract (honokiol 49.1%, magnolol 31.7%, others unknown 19.2%) on a favorable condition. The title complex, $C_{18}H_{18}O_2{\cdot}C_6H_{12}N_2$, is characterized by IR and ^{1}HNMR and its crystal structure is determined by X-ray diffraction method. It crystallizes in monoclinic space group C2/c with $a = 38.860(3)$, $b = 9.205(3)$, $c = 12.588(4)$ Å, $\beta = 102.730(10)°$, $V = 4392(2)$ Å^3, $Z = 8$ and $R = 0.0500$. Hinokiol molecules join to DABCO via O–H···N hydrogen bonds to form infinite chains. There are two symmetry independent DABCO molecules occupying in the crystal special positions of different point symmetries, C2 and Ci. Those located around the inversion center are disoredered as DABCO molecule is devoid of this symmetry element.

Introduction

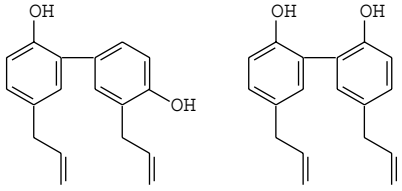
Honokiol, 5,3′-diallyl-biphenyl-2,4′-diol, exists in extract from *Magnolia obovata Thunberg* [1, 2], a medicinal plant, which has been well known as an important component of many Chinese traditional medicines for more than 2000 years. Nowadays, it is known as anxiolytic [3], neurotrophic [4], antimicrobial [5] and antifungal agents [6]. It is difficult to obtain pure honokiol from the extract, which contains mainly honokiol and its isomer magnolol (Scheme 1). Host–guest molecular recognition has drawn increasing attentions in applying to separate of natural product [7, 8]. Recently, as a part interest in supramolecular chemistry, molecular recognition of 1,4-diazabicyclo[2.2.2]octane (DABCO) is discovered in our lab and applied to separation process of honokiol. The procedure of separation and the X-ray crystal structure of the 1:1 complex of honokiol with DABCO are reported herein.

Experimental

Materials, chemical and physical measurements

Magnolia officinalis Rehd. et Wils was collected from Lishui, Zhejiang Provine, PR China. Chloroform extract of magnolia bark and vacuum to dryness gave the raw material used in this work, which was assayed by HPLC to consist of honokiol 49.1%, magnolol 31.7% and other substances unknown 19.2%, respectively.

The HPLC system was comprised of a Waters Symmetry ODS-C_{18} column (250 × 4.5 mm, 3.5 μm), a mobile phase consisting of methanol–water 78:22 (v:v) at a flow rate of 1.1 ml/min, and a UV detector set at



Scheme 1. Honokiol (left) and magnolol (right).

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294 nm. Carbon, nitrogen and hydrogen atoms were determined with a Carlo Erba 1106 elemental analyzer. IR spectra were recorded on a Perkin-Elmer FTIR-1750 spectrophotometer as a KBr pellet. The ^{1}HNMR spectra of the crystalline complexes were recorded on a Bruker Avance DMX500 spectrometer operating at 25 °C, using DMSO-d as the solvent and TMS as the internal standard.

Typical separation procedure

The dried extract and DABCO were dissolved in ethanol and heated to a temperature of 80 °C to make a clear solution, yellow precipitate of title complex was created when the solution cooled down to 20 °C. To remove DABCO, the precipitate was dissociated by sufficient dilute HCl (1.0 N), and warmed to 50 °C for one day. Crop of honokiol was collected by filtration and washed with water.

The title complex was washed with petroleum ether and dried under vacuum for 24 h, and used in chemical and physical measurements: MP: 144.7–145.1 °C. Found: C, 76.13; H, 7.97, N 7.43%; calc for $C_{18}H_{18}O_2{\cdot}C_6H_{12}N_2$: C, 76.15; H, 7.99, N 7.40%. IR (KBr): 2945 (s), 2878 (s), 2560 (vs), 1816, 1637, 1605, 1510, 1433 (s), 1358, 1322, 1270 (s), 1244, 1222, 1128, 1058, 999, 920, 823, 780 (vs), 745 cm^{-1}. ^{1}HNMR (500 MHz, DMSO-d): δ 2.61 (s, 12H, DABCO-CH_2), 3.27 (d, 2H, $J = 6.5$ Hz, H-7), 3.31 (d, 2H, $J = 6.5$ Hz, H-7′), 4.99 (d, 1H, $J = 9.9$ Hz, H-9), 5.01 (d, 1H, $J = 9.9$ Hz, H-9), 5.04 (d, 1H, $J = 17.1$ Hz, H-9′), 5.08 (d, 1H, $J = 17.1$ Hz, H-9′), 5.95 (m, 2H, H-8, H-8′), 6.80 (d, 2H, $J = 8.1$ Hz, Ar–H), 6.88 (d, 1H, $J = 8.1$ Hz, Ar–H), 6.97 (s, 1H, Ar–H), 7.18 (dd, 1H, $J = 9.3$ Hz, Ar–H), 7.20 (s, 1H, Ar–H) ppm. Chemical shifts for the H attached to the C and C′ with same numbering may be inversed. The IR and ^{1}HNMR are in consistent with the crystal structure described below.

HCl dissociation of the title complex gave honokiol with quantitative yield. Honokiol was collected, washed with water and dried at room temperature, and subjected to chemical and physical analyses: MP: 86.9–87.3 °C. Found: C, 81.14; H, 6.82%, calc for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81%. UV (ethanol, λ): 294, 257, 211 nm. IR (KBr): 3298 (vs), 3081 (w), 3000 (w), 2978 (w), 2901 (w), 1637, 1605, 1510, 1497 (vs), 1432, 1372, 1325, 1275, 1217 (vs), 1130, 987, 906, 824, 777, 709, 624, 601, 556 cm^{-1}. ^{1}HNMR (500 MHz, CDCl3): δ 3.35 (d, 2H, $J = 6.7$ Hz, H-7), 3.46 (d, 2H, $J = 6.3$ Hz, H-7′), 5.04–5.27 (d, 4H, H-9, H-9′), 6.00 (m, 2H, H-8, H-8′), 6.89 (1H, $J = 4.0$ Hz, Ar–H), 6.90 (d, 1H, $J = 3.6$ Hz, Ar–H), 7.02–7.04 (2H, Ar–H), 7.21 (s, 1H, C6–H), 7.22 (1H, $J = 8.0$ Hz, Ar–H) ppm. Chemical shifts for the H attached to the C and C′ with same numbering may be inversed.

X-ray crystallographic determination

The structure of the title complex was determined by single crystal X-ray diffraction method. A colorless prismatic crystal of the title complex with dimensions of $0.20 \times 0.20 \times 0.30$ mm^3 was mounted on a glass fiber. Cell dimension measurements and data collection were performed on a Bruker Smart Apex CCD diffractometer with graphite-monochromatized MoKα ($\lambda = 0.7107$ Å) radiation by Smart program at room temperature. Data reduction was performed with Saint program. The crystal structure was solved by direct methods and refined through the use of the SHELXTL program. The three carbon atoms of the disordered DABCO molecule were split into six moieties entitled C1 and C1′, C2 and C2′, C3 and C3′, respectively with 0.5 occupancy. Two

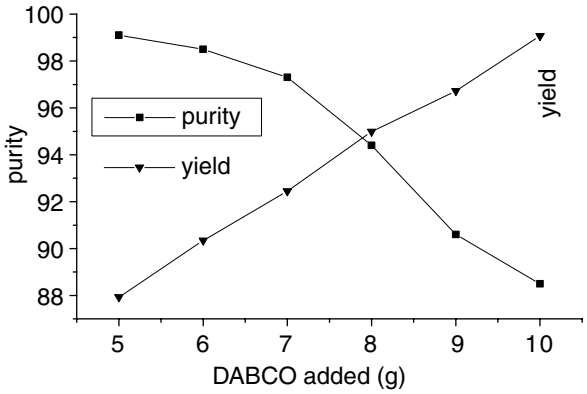

Figure 1. Effects of material ratio on the yield and the purity.

Table 1. Crystal data and details of the structure determination of the title complex

CCDC no.	208986
Formula	$C_{18}H_{18}O_2{\cdot}C_6H_{12}N_2$
Formula weight	378.50
Crystal system	Monoclinic
Space group	C2/c (no. 15)
a, *b*, *c* [Å]	38.860(3), 9.205(3), 12.588(4)
α β [°]	90, 102.730(10), 90
V [Å^3]	4392(2)
Z	8
D (calc) [g/cm^3]	1.145
Mu(MoKα) [mm^{-1}]	0.073
F(0 0 0)	1632
Crystal size [mm]	$0.20 \times 0.20 \times 0.30$
Data collection	
Temperature (K)	293
Radiation [Å]	MoKα 0.71073
Theta min–max [°]	2.2, 26.0
Dataset	−47: 47; −10: 11; −15: 14
Tot., uniq. data, *R* (int)	11456, 4302, 0.013
Observed data [$I>2.0\ \sigma(I)$]	2502
Refinement Nref, Npar	4302, 282
R, wR_2, *S*	0.0500, 0.1489, 0.98
$w = 1/[\sigma_c{}^2$ (Fo^2) + $(0.0650P)^2$ + 1.9900*P*]	where $P = (Fo^2 + 2Fc^2)/3$
Max. and av. shift/error	0.00, 0.00
Min. and max. resd. dens. [eÅ^{-3}]	−0.54, 0.32

side chains of allyl group are somewhat disordered, which is indicated by slightly high value of anisotropic displacement parameters. However, the disorder atoms could not be split into two halves. All of hydrogen atoms were positioned geometrically and included in the refinement in a riding-model approximation with Uiso equal to 1.2 Ueq of the carrier atoms. The final *R* factor was 0.0500 ($Rw = 0.1489$).

Table 2. Final coordinates and equivalent isotropic displacement parameters for the non-hydrogen atoms of the title complex

Atom	*x*	*y*	z	*U*(eq) [Å^2]
O1	0.18123(4)	−0.11728(1-9)	0.16863(13)	0.0716(7)
O2	0.04325(5)	0.24466(19)	0.06022(14)	0.0757(7)
C7	0.17478(6)	−0.2215(3)	0.48371(19)	0.0632(8)
C8	0.20279(7)	−0.2668(3)	0.4415(2)	0.0688(9)
C9	0.20547(7)	−0.2350(3)	0.3372(2)	0.0676(9)
C10	0.17903(6)	−0.1541(3)	0.26928(19)	0.0596(8)
C11	0.15053(6)	−0.1038(2)	0.30886(18)	0.0564(8)
C12	0.14933(6)	−0.1410(2)	0.41571(19)	0.0603(8)
C13	0.12205(5)	−0.0152(2)	0.24285(17)	0.0526(8)
C14	0.10611(6)	−0.0539(3)	0.13578(18)	0.0589(8)
C15	0.08002(6)	0.0308(3)	0.07507(19)	0.0625(8)
C16	0.06897(6)	0.1562(3)	0.1168(2)	0.0652(9)
C17	0.08449(6)	0.1968(3)	0.22466(19)	0.0616(9)
C18	0.11046(6)	0.1091(3)	0.28348(19)	0.0613(8)
C19	0.17130(7)	−0.2593(3)	0.5973(2)	0.0748(10)
C20	0.14816(7)	−0.3868(3)	0.5988(2)	0.0716(10)
C21	0.15397(7)	−0.4981(3)	0.6587(2)	0.0760(10)
C22	0.07511(6)	0.3422(3)	0.2645(2)	0.0697(9)
C23	0.04981(7)	0.3405(3)	0.3386(2)	0.0785(11)
C24	0.05776(8)	0.3788(3)	0.4383(2)	0.0784(10)
N2	0.01669(5)	0.1815(2)	0.85058(15)	0.0643(7)
C4	0.03771(6)	0.2527(3)	0.7836(2)	0.0739(10)
C5	0.01010(7)	0.0330(3)	0.8092(2)	0.0763(10)
C6	−0.01747(7)	0.2567(3)	0.8377(2)	0.0774(10)
N1	0.23070(5)	0.7754(2)	0.06610(16)	0.0653(8)
*C1	0.26988(13)	0.8025(7)	0.1155(4)	0.0719(19)
*C1′	0.20747(13)	0.7269(6)	−0.0382(4)	0.0702(19)
*C2	0.25295(13)	0.6497(6)	0.1043(4)	0.0667(19)
*C2′	0.22214(13)	0.8744(6)	−0.0265(4)	0.073(2)
*C3	0.22834(14)	0.6359(6)	0.0311(4)	0.0700(19)
*C3′	0.24952(14)	0.8935(6)	0.0543(4)	0.0698(19)

U(eq) = 1/3 of the trace of the orthogonalized *U* tensor.

Results and discussion

Separation

The crystalline formation of the title complex is the key step in the whole separation procedure. Other chemicals similar to DABCO in structure, such as morphine, *N*-methyl-morphine and piperazine, are tried but failed in forming crystalline complex with any one of components of the extract at room temperature.

Effects of material ratio, in forming the title complex, on the yield and the purity have been investigated. By changing DABCO amount and fixing the amount of ethanol and the dry extract, honokiol with purity ranging from 88.5% to 99.1% and yield varying from 76.5% to 94.5% is obtained (Figure 1). Honokiol (10.3 g, purity 97.3% and yield 83.9%) is gained on a favorable condition at ethanol (40 ml) solution of the dried extract and DABCO (25.0 and 7.0 g), at temperature of 20 °C.

Crystal structure

A summary of data collection, structure refinement is given in Table 1. The final atomic parameters are given in Table 2.

Figure 2 shows the cell unit of the title complex, comprising of honokiol, a half of disordered and a half of ordered DABCO. Generally, the geometry of honokiol molecule in the title complex is consistent with the result of a previous structure of honokiol [9]. DABCO has been observed to be disordered across the N–N axis in several cases such as 1:1 DABCO-biphenol [10], 1:1 DABCO-perchloric acid [11], and

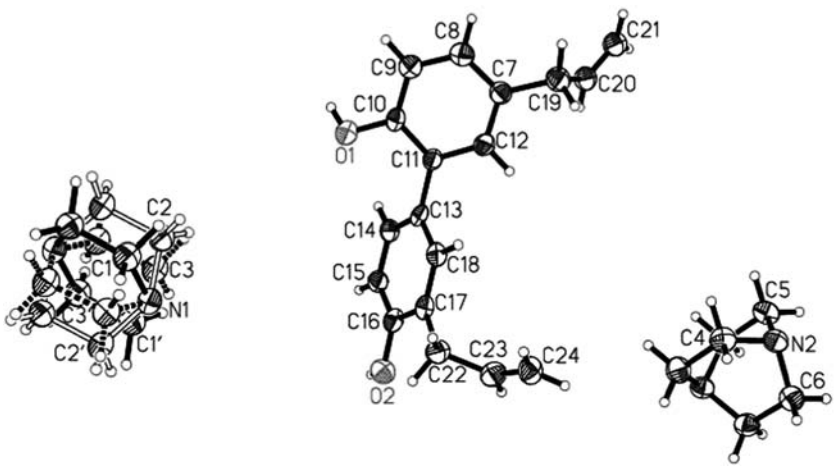

Figure 2. An illustration of the title complex, showing 35% probability displacement ellipsoids.

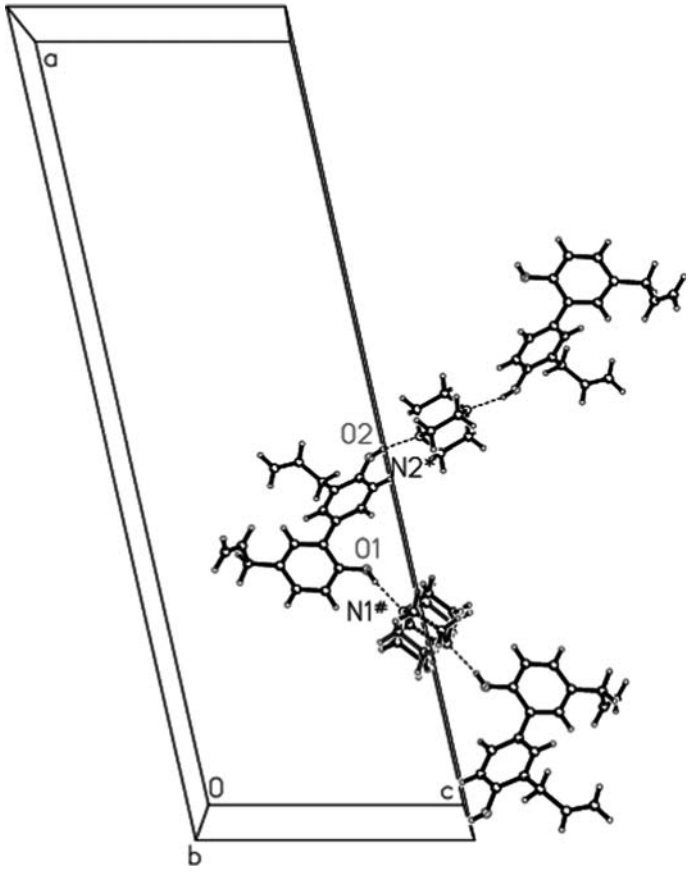

Figure 3. Every honokiol is linked by hydrogen bonds of O2–H2···N2* and O1–H1···N1#, respectively [*: (x, y, $-1+z$), #: (x, $-1+y$, z)].

1:2 DABCO-maleic acid [12]. Both of disordered or ordered DABCO appear in the title complex. Every honokiol is linked with disordered and ordered DABCO by hydrogen bonds of [O2–H2···N2(x, y, $-1+z$), 2.677(3) Å, 156°] and [O1–H1···N1(x, $-1+y$, z)], 2.726(3) Å, 155°], respectively, to establish infinite supramolecular chain along the direction of [1 0 1], which may be described in graph set [13, 14] of $C_4^4(28)$ (Figure 3). Owing to effects of O–H···N hydrogen bond, the strong hydroxyl bond at 3298 cm^{-1} is vanished in the IR spectrum of the title complex, in comparison with the IR spectrum of honokiol. The soft hydrogen bond [15] of [C14–H14···O1, 2.916(3) Å, 101°] counteracts the force of hydrogen bonds of O2–H2···N2(x, y, $-1+z$) and O1–H1···N1(x, $-1+y$, z) to withdraw the two phenyl ring, which are skewed to an angle with a value of 48.0(3)°. In a known structure of honokiol [9], such angle is 58.7°, and the corresponding distance of CH···O (2.85 Å) is out of the hydrogen bonding range.

There are two symmetry independent DABCO molecules occupying in the crystal special positions of different point symmetries, C2 and Ci (Figures 4 and 5). Those located around the inversion center are disodered as DABCO molecule is devoid of this symmetry element. The side chain of C18–C17–C22–C23 is bended obviously, while the side chain of C12–C7–C19–C20 is more freely arranged. As an effect, the hole round the ordered DABCO is more compact than that round the disordered DABCO, which may in turn interpret the reason why one of DABCO is disordered while the other being ordered. Subordinated hydrogen bonds of C–H···O take roles in establishing the structure, among which the shortest ones are C14–H14···O1 and C22–H22B···O2.

Conclusion

We have succeeded in finding the phenomenon of molecular recognition between honokiol and DABCO, which is then applied to separating honokiol from extract of magnolia bark. Through procedure based on molecular recognition, pure honokiol is obtained easily from the extract of magnolia bark. X-ray diffraction shows that supramolecular complex of honokiol-DABCO (1:1) is established by O–H···N hydrogen bonds between honokiol and ordered DABCO, between honokiol and disordered DABCO, respectively. Determination of the ability of honokiol as well as magnolol to form complexes with other compounds is under investigation in our laboratories.

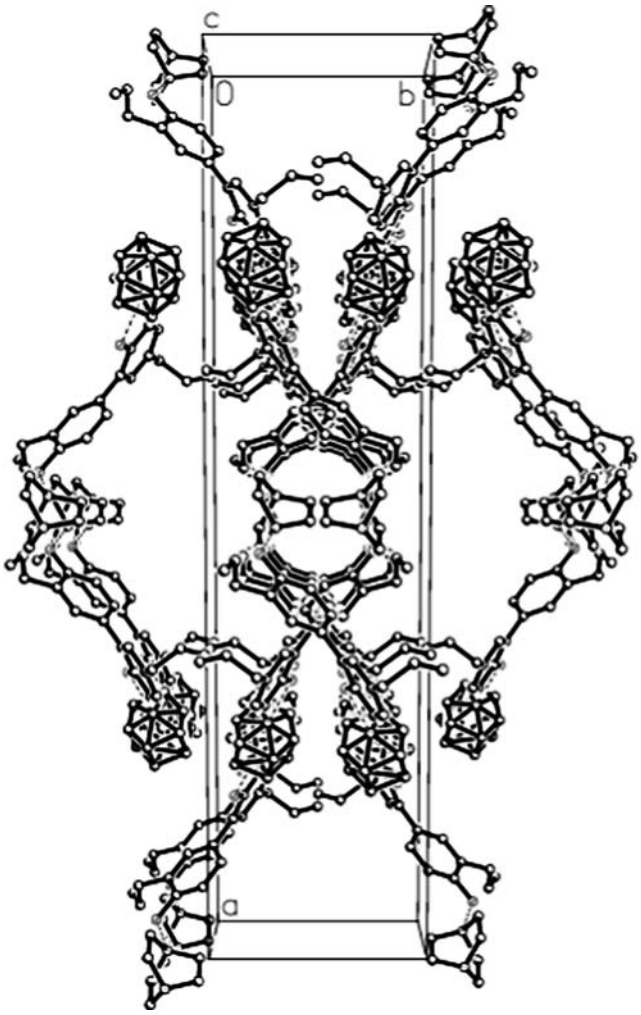

Figure 4. The packing diagram of the title complex, viewed down along the *c* axis.

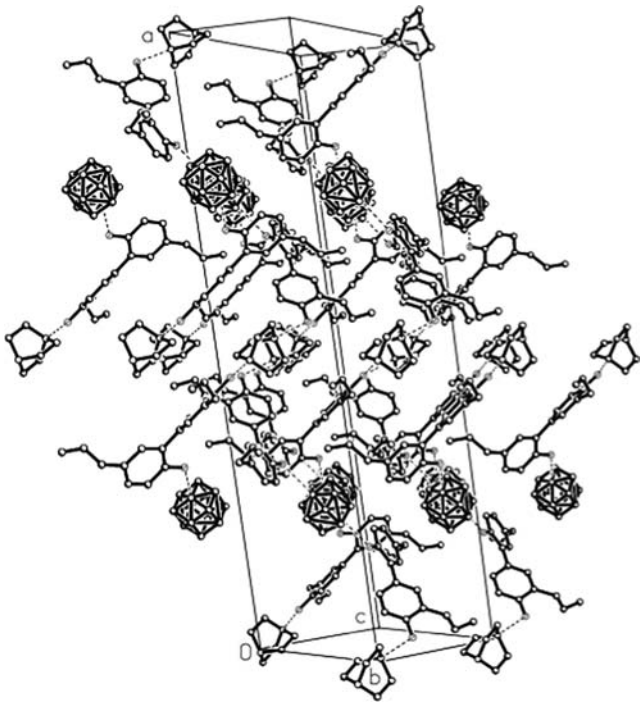

Figure 5. A three-dimension view of the packing diagram, showing DABCO included in different supramolecular holes.

Acknowledgements

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