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Mendeleev Commun., 2011, **21**, 272–273
Mendeleev Communications

Separation of magnolol from an extract of *Cortex Magnoliae Officinalis* by selective clathration

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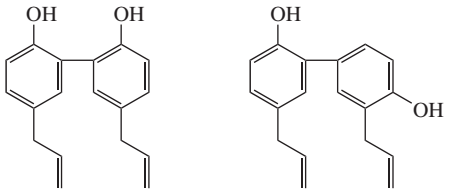
DOI: 10.1016/j.mencom.2011.09.014

The selective clathration of magnolol with diethylenetriamine (2:1 molar ratio) renders an amenable method for separating magnolol from an extract of *Cortex Magnoliae Officinalis* (purity, 98%; yield, 76%).

The extract of *Cortex Magnoliae Officinalis*, a well known Chinese traditional medicine,[1,2] contains magnolol and its isomer honokiol as the main bioactive compounds. Magnolol shows various bioactivities, such as hydroxyl radical scavenging[3] and antioxidative,[4] anxiolytic,[5] neurotrophic,[6] antimicrobial,[7] and antifungal[8] effects. The selective clathration of host–guest molecules has drawn increasing attention in separating natural products, such as neoabietic acid,[9] α/β-ionone[10] and honokiol.[11] Here we report on separation of magnolol as a host molecule from an extract by selective clathration using diethylenetriamine (DETA) as a guest molecule.



Magnolol Honokiol

HPLC analysis showed that the extract used consisted of magnolol (45.7%), honokiol (49.1%) and other unknown substances (5.2%). The extract (10.0 g) and DETA (1.5 g) were dissolved in 90% ethanol (25 ml) by heating to 80 °C, and yellow crystals were formed upon keeping the solution for 4 h at temperatures from –10 to 10 °C. The crystals† of the complex of magnolol, DETA and water (2:1:2) were filtered off and recrystallized from ethanol. Afterward, the crystals were gathered, then dissociated by dilute HCl, and warmed to 50 °C for two days, giving powder magnolol‡ in a quantitative yield.

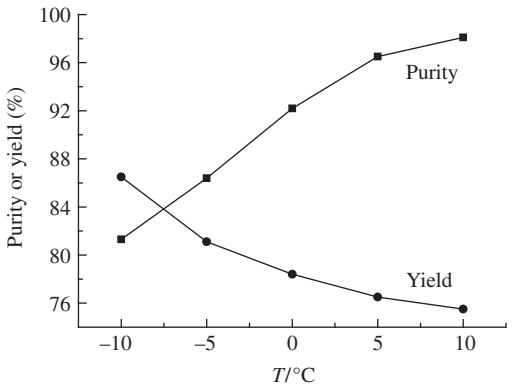


Figure 1 Effects of temperature on the yield and purity of magnolol.

By fixing the proportion of raw materials, meanwhile changing the temperature, magnolol was obtained in 81.3–98.1% purity (HPLC) and 86.7–75.5% yield (Figure 1).

According to X-ray diffraction (Figure 2),† the complex contains two magnolol entities (a neutral molecule and an anion), one DETA cation (HDETA) and two water molecules; they are linked by N(3)–H···O(3), O(1)–H···O(6), N(2)–H···O(5) and O(6)–H···O(4) hydrogen bonds. The bond lengths of C(1)–O(1) [1.353(3) Å], C(19)–O(3) [1.355(3) Å] and C(28)–O(4) [1.341(3) Å] fall in the range of phenolic C–O bonds, while the length of C(10)–O(2) [1.203(3) Å] is different, indicating a phenolate C–O bond. The dihedral angles between the benzene rings of the two magnolol molecules are 35.6° and 36.7°, respectively. As the skeleton of HDETA is flexible, it may adopt different conformations resembling bended to streight lines in different extensions. In this study, HDETA demonstrated a curlable conformation, which is similar to that observed in the crystal of HDETA dichloride.[12]

† Complex of magnolol with diethylenetriamine (2:1 molar ratio): yellow crystals, mp 87 °C. IR (KBr, ν/cm^{-1}): 3344, 2926, 2802, 2748, 2548, 2502, 1640, 1460, 1340, 1238, 1112, 996, 567. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 2.59 (d, 2H, DETA, J 7.0 Hz), 2.69 (d, 2H, DETA, J 7.0 Hz), 3.28 (d, 4H, H-7, H-7′, J 6.7 Hz), 4.98–5.08 (m, 4H, H-9, H-9′), 5.90–6.00 (m, 2H, H-8, H-8′), 6.63 (d, 2H, H-3, H-3′, J 8.3 Hz), 6.85 (d, 2H, H-6, H-6′, J 2.2 Hz), 6.99 (dd, 2H, H-4, H-4′, J_1 8.3 Hz, J_2 2.2 Hz).

Crystal data: $2(C_{18}H_{18}O_2)\cdot C_4H_{13}N_3\cdot 2H_2O$, triclinic, space group $P\bar{1}$, a = 9.7322(11), b = 10.7929(13) and c = 18.962(2) Å, α = 85.600(2)°, β = 79.890(3)°, γ = 87.426(3)°, V = 1954.03(4) Å^3, Z = 2. A Bruker APEX area-detector diffractometer was used at room temperature in measuring reflections from a crystal with a size of 0.33×0.39×0.44 mm. Among 10 159 total reflections, 5177 were unique ones. The structure was solved and refined to R = 0.0703 (wR = 0.1588) and GOOF = 1.155.

CCDC 765546 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif. For details, see 'Notice to Authors', *Mendeleev Commun.*, Issue 1, 2011.

‡ Magnolol: yellowish powder, mp 103 °C. IR (KBr, ν/cm^{-1}): 3158, 1638, 1610, 1496, 1439, 1410, 1384, 1228, 1135, 992, 903, 820, 783, 731, 663, 563, 529. ^{1}H NMR (500 MHz, $CDCl_3$) δ: 3.37 (d, 4H, H-7, H-7′, J 6.7 Hz), 5.06–5.12 (m, 4H, H-9, H-9′), 5.93–6.01 (m, 2H, H-8, H-8′), 6.95 (d, 2H, H-3, H-3′, J 8.3 Hz), 7.08 (d, 2H, H-6, H-6′, J 2.2 Hz), 7.14 (dd, 2H, H-4, H-4′, J_1 8.3 Hz, J_2 2.2 Hz).

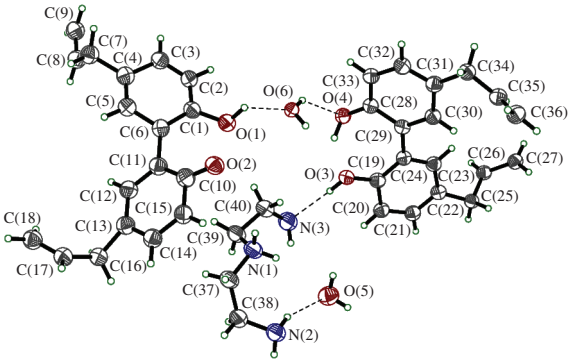


Figure 2 Molecular structure of the complex of magnolol, diethylenetriamine and water (2:1:2). Selected bond lengths (Å) and angles (°): N(1)–C(37) 1.426(4), N(2)–C(38) 1.455(4), N(1)–C(39) 1.431(4), N(3)–C(40) 1.450(4), O(1)–C(1) 1.353(3), O(2)–C(10) 1.203(3), C(4)–C(7) 1.507(4), C(6)–C(11) 1.475(4), C(7)–C(8) 1.450(4), C(8)–C(9) 1.346(4), C(16)–C(17) 1.460(4), C(17)–C(18) 1.357(4); C(8)–C(7)–C(4) 108.5(3), C(9)–C(8)–C(7) 117.6(3), C(37)–N(1)–C(39) 103.6(2); O(1)···O(6) 2.451, O(1)–H···O(6) 113.6, O(6)···O(4) 2.825(2), O(6)–H(6B)···O(4) 135.1, O(3)···N(3) 2.843, O(3)–H···N(3) 142.0, N(2)···O(5) 2.981, N(2)–H···O(5) 158.4, N(3)···O(4) (–*x* + 1, –*y*, –*z* + 1) 2.732(3), N(3)–H···O(3) (–*x* + 1, –*y*, –*z* + 1) 150.4.

As shown in Figure 3, the crystal structure is characterized by a layered arrangement. The hydrophilic entities including the magnolol hydroxyl, HDETA and water molecules are placed in a layer, while the hydrophobic allyl group of magnolol is in another one. Water molecules play an important role in filling the supramolecular hole between the host and guest molecules, and in pasting two magnolol entities. As a comparison, in the crystal of a complex of honokiol with triethylenediamine, honokiol is bound with triethylenediamine, forming a spiral chain of hydrogen bonds.[11]

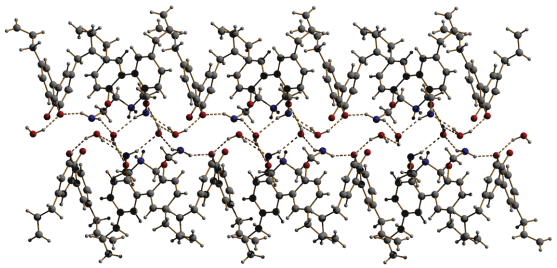


Figure 3 The layered structure of magnolol with HDETA viewed down along the *a* axis. Hydrogen bonds are illustrated by dashed lines.

It is easily predicted that both magnolol and honokiol molecules can form a supramolecular complex with DETA by N–H···O and/or O–H···N hydrogen bonds. Generally, the combination of DETA with magnolol in a crystal is preferable to that of honokiol.

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Received: 18th March 2011; Com. 11/3700