Caffeic Acid Phenethyl Ester (CAPE): Synthesis and X-Ray Crystallographic Analysis

Sopheak Son,[a] Emil B. Lobkowsky,[b] and Betty A. Lewis*,[c]

Department of Food Science,[a] Department of Chemistry and Chemical Biology,[b] and Division of Nutritional Sciences,[c] Cornell University, Ithaca, NY 14853, U.S.A. Received July 3, 2000; accepted November 10, 2000

The structure of caffeic acid phenethyl ester [2-propenoic acid, 3-(3,4-dihydroxyphenyl)-, 2-phenethyl ester] (I), $C_{17}H_{16}O_4 \cdot 1/2C_6H_6$, synthesized by base-catalyzed alkylation of caffeic acid salt with β-bromoethylbenzene in HMPA (hexamethylphosphoramide) and recrystallized from benzene, was confirmed by single crystal X-ray diffraction. The crystals are triclinic, space group $P\bar{1}$, $Z=2$, unit cell dimension $a=5.8129$ (9) Å, $b=11.122$ (2) Å, $c=13.226$ (2) Å, $\alpha=97.080$ (3)°, $\beta=101.467$ (3)°, $\gamma=95.405$ (3)°, $V=825.4$ (2) Å^3, $D_{calc}=1.301$ g/cm^3, $F(000)=342$. The packing of the molecule is stabilized by intermolecular $O_1H\cdots O_4$ (2.69 Å) and $O_1\cdots HO_2$ (2.82 Å) hydrogen bonds.

Key words caffeic acid phenethyl ester; alkylation reaction; X-ray diffraction; hydroxycinnamic acid derivative; phenolic compound

Caffeic acid phenethyl ester (CAPE), a plant-derived phenolic compound and an active component of propolis from honeybee hives, is known to have antiviral,[1] antibacterial,[2] anti-inflammatory,[3,4] antiatherosclerotic,[5] antioxidative,[6,7] immunostimulatory[8] and tumor growth inhibition activity.[9,10] This compound has also been shown to be a potential inhibitor of some enzymes such as ornithine carboxylase,[11] 5-α reductase,[12] protease,[13] lipoxygenase,[14,15] cyclooxygenase,[15,16] and human immunodeficiency virus (HIV)-1 integrase.[17,18]

CAPE has been chemically synthesized from caffeic acid and phenethyl alcohol *via* acid-catalyzed esterification using *p*-toluenesulfonic acid as a catalyst,[6,14,17,19] and *via* the coupling reaction with dicyclohexylcarbodiimide (DCC) as a coupling agent.[6,20] It can also be prepared by base-catalyzed alkylation of caffeic acid with β-bromoethylbenzene in dipolar aprotic solvents such as hexamethylphosphoramide (HMPA).[21] The latter reaction has been reported to give a high yield (*ca*. 70%) of product compared to the first two reactions which give only 40% yield.

To confirm the structure of CAPE, which we synthesized by alkylation of caffeic acid salt with β-bromoethylbenzene using HMPA as solvent, we subjected the product of the reaction to single crystal X-ray crystallography. The X-ray diffraction data showed that the ester structure (I) is the reaction product and not the ethers (II, III) (Chart 1).

Experimental

Thin-layer chromatography (TLC) was performed on precoated Silica gel F_{254} plates (Merck) and on microscope slides (2.5×7.5 cm) coated with silica gel G containing fluorescent indicator (Fluorescent Brightener 80). Detection was by iodine vapor and by UV light (UV lamp, model UVG-54). Column chromatography was performed on Silica gel H (32—63 mesh) from Selecto Scientific. $MgSO_4$ was used as the drying agent for organic extracts. Solvents were evaporated under vacuum. Melting points were determined on a Fisher–Johns melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 683 IR spectrophotometer. Single crystal X-ray analysis was performed using a Bruker SMART with 1K CCD detector. Data were collected using SMART Software. Cell refinement and data reduction were performed using the *SAINT* program. SHELXS86[22] was used to solve the structure and SHELXL93[23] to refine the structure. SHELXTL was used to display molecular graphics and to prepare publication material.

Materials Caffeic acid (3,4-dihydroxycinnamic acid, 98%); β-bromoethylbenzene (phenethylbromide); HMPA (99%); diethyl ether; and ethyl acetate were from Aldrich.

Synthesis CAPE was synthesized according to Hashimoto *et al.*[21] To a solution of caffeic acid (1.98 g) in 25 ml of HMPA, 2.28 ml of 25% NaOH was added. After stirring for 1 h, a solution of β-bromoethylbenzene (5.7 ml) in 10 ml HMPA was added dropwise with a separatory funnel and the solution was stirred for 52 h at room temperature. The reaction mixture was poured into ice water (50 ml), and the product was extracted with diethyl ether (2×50 ml). The ether extract was washed successively with 1 N HCl (20 ml) and water (20 ml), dried over $MgSO_4$ (10—15 g), and evaporated under vacuum. The product dissolved in ether was chromatographed on a silica gel column (150 g), eluted with $CHCl_3$ and then with increasing proportions of ethyl acetate. The fraction eluted with 30% ethyl acetate contained the desired product. Recrystallization from ether/*n*-hexane gave compound (I) (CAPE) as a pale-yellow powder; mp 124.5—126 °C; yield *ca*. 70%. IR (neat) cm^{-1}: 3490, 3100, 1685, 1640—1610, 1100.

Single-Crystal X-Ray Analysis of CAPE Single crystals of I suitable for X-ray analysis were obtained by slow evaporation from benzene. Data were collected from a colorless thin plate crystal of dimensions 0.20×0.10×0.02 mm on a Bruker SMART with 1K CCD detector with Mo$K\alpha$ radiation ($\lambda=0.71073$ Å; graphite monochromated) employing 0.3°ω scanning technique. The final refinement of the structure was achieved by the full-matrix least-squares method with anisotropic displacement parameters for all non-hydrogen atoms and fixed isotropic displacement parameters for all hydrogen atoms. Crystallographic data are listed in Table 1.

Results and Discussion

The IR spectrum showed a peak for phenolic OH (br, 3490 cm^{-1}), a peak for C–H stretch (m, 3100 cm^{-1}), a peak

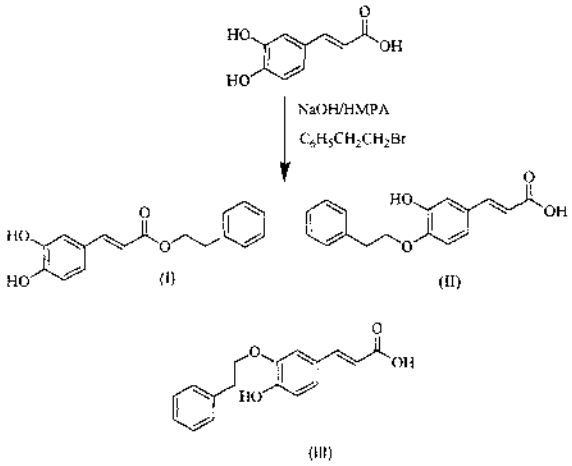

Chart 1. Possible Products of the Alkylation of Caffeic Acid

* To whom correspondence should be addressed. e-mail: bal4@cornell.edu

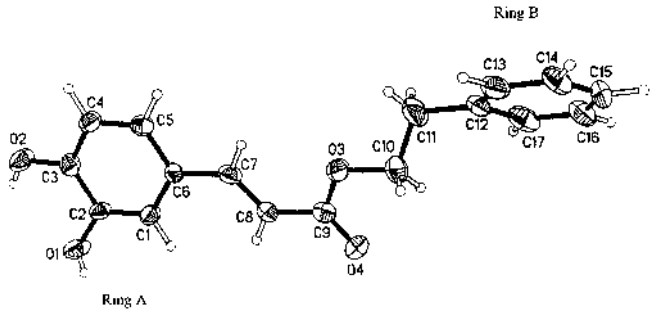

Fig. 1. A Perspective View of (I) Showing the Atom Numbering Scheme

Displacement ellipsoids are drawn at the 50% probability level; H atoms are shown as spheres of arbitrary radii.

Table 1. X-Ray Crystallographic Data of CAPE

Molecular formula	$C_{17}H_{16}O_4 \cdot 1/2C_6H_6$
Formula weight	323.35
Crystal size (mm^3)	0.20×0.10×0.02, colorless plates
Crystal system	Triclinic
Space group	$P\bar{1}$
a (Å)	5.8129 (9)
b (Å)	11.122 (2)
c (Å)	13.226 (2)
α (°)	97.080 (3)
β (°)	101.467 (3)
γ (°)	95.405 (3)
V ($Å^3$)	825.4
D_{calc} ($g \cdot cm^{-3}$)	1.301
Z	2
F(000)	342
Diffractomer	Bruker SMART with 1K CCD detector
Radiation	Mo$K\alpha$, λ=0.71073 Å; graphite monochromated
Temperature (K)	173
μ (mm^{-1})	0.090
Scan mode	0.3°ω
Transmission coefficients	0.566—1.0
Reflections collected	4064
Independent reflections	2761 (R_{int}=0.0492)
θ_{max} (°)	26.22
Limiting indices	$-6 \le h \le 5$, $-12 \le k \le 13$, $-16 \le l \le 15$
Refined method	Full-matrix least-squares on F^2
Data/restraints/parameters	1681/0/238
Goodness-of-fit on F^2	1.047
Final R indices [$I>2\sigma(I)$]	R_1=0.0599, wR_2=0.1197
R indices (all data)	R_1=0.1931, wR_2=0.1917
Extinction coefficient	0.02335
Largest diff. peak and hole	0.216 and −0.248 $e Å^{-3}$

Table 2. Atomic Coordinates [$\times 10^4$] and Equivalent Isotropic Displacement Parameters [$Å^2 \times 10^3$]

Atom	x	y	z	U (eq)
O (1)	6080 (8)	1398 (4)	5115 (4)	46 (1)
O (2)	1499 (7)	585 (3)	4318 (3)	47 (1)
O (3)	6427 (6)	7362 (3)	2952 (3)	54 (1)
O (4)	10237 (7)	7210 (3)	3567 (3)	48 (1)
C (1)	5646 (9)	3249 (4)	4342 (3)	30 (1)
C (2)	4777 (9)	2142 (4)	4540 (4)	30 (1)
C (3)	2417 (9)	1690 (4)	4137 (4)	30 (1)
C (4)	946 (9)	2362 (4)	3546 (4)	32 (1)
C (5)	1849 (9)	3490 (4)	3350 (4)	30 (1)
C (6)	4228 (9)	3955 (4)	3743 (3)	25 (1)
C (7)	5088 (9)	5121 (4)	3494 (3)	31 (1)
C (8)	7358 (9)	5604 (4)	3665 (3)	32 (1)
C (9)	8155 (11)	6788 (4)	3403 (4)	35 (1)
C (10)	7119 (11)	8568 (5)	2712 (5)	76 (2)
C (11)	5459 (11)	8819 (4)	1840 (4)	61 (2)
C (12)	5998 (10)	10064 (4)	1545 (4)	35 (1)
C (13)	4692 (9)	10986 (5)	1742 (4)	40 (1)
C (14)	5157 (10)	12127 (5)	1470 (4)	42 (2)
C (15)	7015 (10)	12374 (5)	997 (4)	40 (2)
C (16)	8375 (9)	11462 (5)	795 (4)	43 (2)
C (17)	7877 (10)	10320 (5)	1064 (4)	44 (2)
C (1S)	608 (12)	5784 (5)	939 (5)	42 (2)
C (2S)	2144 (11)	4999 (6)	659 (5)	48 (2)
C (3S)	1522 (12)	4218 (5)	−282 (6)	47 (2)

U (eq) is defined as one-third of the trace of the orthogonalized U_{ij} tensor. Carbons C (1S), C (2S), and C (3S) derived from one-half molecule of solvent benzene in the crystal unit cell.

Table 3. Selected Geometric Parameters (Å, °)

O(1)–C(2)	1.372 (6)	C(1)–C(6)	1.393 (6)
O(2)–C(3)	1.361 (5)	C(2)–C(3)	1.390 (6)
O(3)–C(9)	1.322 (6)	C(12)–C(17)	1.393 (6)
O(4)–C(9)	1.223 (6)	C(16)–C(15)	1.375 (6)
O(3)–C(10)	1.455 (5)	C(13)–C(14)	1.378 (6)
C(4)–C(5)	1.388 (6)		
C(9)–O(3)–C(10)	116.3 (4)	O(4)–C(9)–O(3)	122.6 (5)
C(1)–C(2)–O(1)	124.7 (5)	C(11)–C(10)–O(3)	109.7 (5)
O(1)–C(2)–C(3)	115.4 (4)	C(10)–C(11)–C(12)	113.6 (5)
O(2)–C(3)–C(4)	118.5 (5)	C(12)–C(13)–C(14)	122.3 (5)
C(3)–C(4)–C(5)	119.4 (5)	C(16)–C(17)–C(12)	121.0 (5)
C(1)–C(6)–C(5)	117.6 (4)	C(16)–C(15)–C(14)	118.8 (5)
C(5)–C(6)–C(7)	118.8 (5)	C(13)–C(12)–C(11)	121.7 (5)
C(7)–C(8)–C(9)	124.6 (5)	C(13)–C(12)–C(17)	117.3 (5)
O(4)–C(9)–O(3)	122.6 (5)	C(17)–C(12)–C(11)	121.0 (5)

Table 4. Hydrogen-Bonding Geometry (Å, °)

D–H···A	D–H	H···A	D···A	D–H···A
O_1–H_{1a}···O_4^i	0.66 (0.05)	2.03 (0.05)	2.69 (0.01)	171.66 (6.37)
O_2–H_{2a}···O_1^{ii}	0.80 (0.05)	2.07 (0.05)	2.82 (0.01)	155.97 (5.64)

Symmetry codes: (i) $2-x$, $1-y$, $1-z$; (ii) $1-x$, $-y$, $1-z$.

for carbonyl group (s, 1685 cm^{-1}), peaks for C=C stretch (m, 1610—1640 cm^{-1}) and a peak for C–O stretch (1100 cm^{-1}) consistent with structure I. However, the one dimensional ^{1}H-NMR spectrum was not of sufficient quality to allow reliable assignment of proton signals to distinguish between structures I, II, and III. X-ray analysis showed that the reaction product had structure I corresponding to CAPE.

A perspective view of compound (I) with atomic numbering is shown in Fig. 1. The X-ray crystallographic data and the selected geometric patterns are shown in Tables 1—4. The structure of compound (I) has two rings, A and B. Both rings are planar within experimental observations. Ring B makes an angle of 42.21 (0.15)° to the linker (C7–C8–C9–O3–C10). The linker makes an angle of 10.75 (0.21)° to ring A. This ring makes an angle of 52.96 (0.13)° with the best plane through B. The bond C7–C8 is a *trans*-double bond. The molecules are linked in unit cell by two types of intermolecular hydrogen bonds $O_1H\cdots O_4$ (2.69 Å) and $O_1\cdots HO_2$ (2.82 Å) (Fig. 2, Table 3). X-ray data has also shown that the crystal of I (recrystallized from benzene) contains one-half molecule of solvent benzene for each molecule of CAPE giving a molecular formula of $C_{17}H_{16}O_4 \cdot 1/2C_6H_6$.

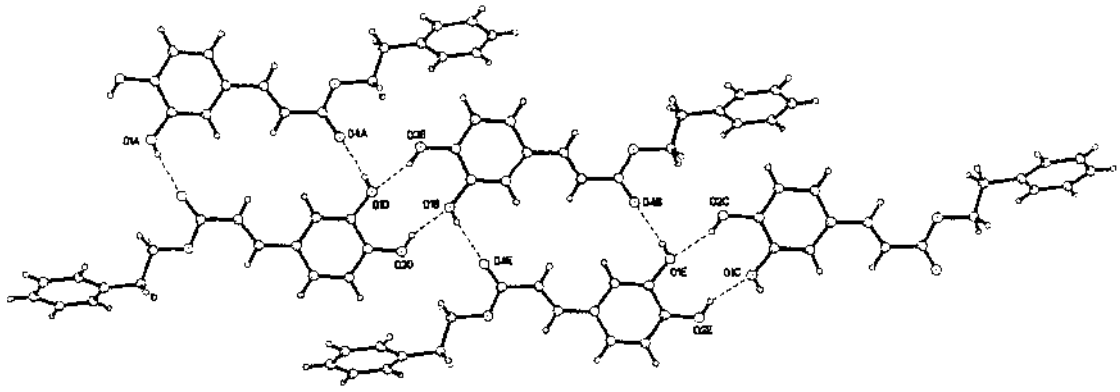

Fig. 2. A View of the Molecular Packing and H-Bonding Interactions of I

Symmetry codes are given in Table 4. For clarity the molecule of solvent benzene per two molecules of CAPE in the crystal structure has been omitted from the Figure.

Thus, we have confirmed by single crystal X-ray diffraction that the major product of the reaction of caffeic acid salt with β-bromoethylbenzene in HMPA solvent is CAPE and not the two ethers II and III.

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