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ORIGINAL PAPER

Tetraphenylborate Salt of Bambuterol (Bambec®): Synthesis, Characterization and X-ray Structure of *N*-(2-(3,5-bis((dimethylcarbamoyl)oxy)phenyl)-2-hydroxyethyl)-2-methylpropan-2-aminium tetraphenylborate

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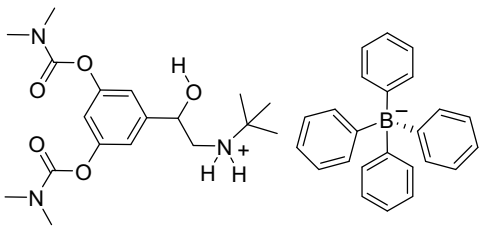
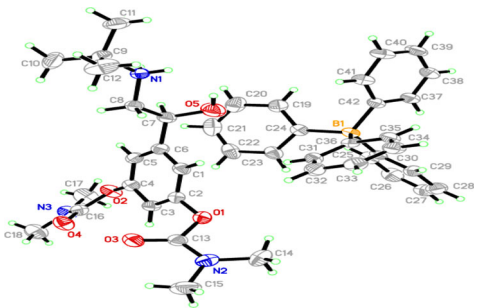
Abstract The title compound tetraphenylborate salt of bambuterol (Bambec®), *N*-(2-(3,5-bis((dimethylcarbamoyl)oxy)phenyl)-2-hydroxyethyl)-2-methylpropan-2-aminium tetraphenylborate (**4**), was prepared in 73 % yield by the reaction of 5-(2-(*tert*-butylamino)-1-hydroxyethyl)-1,3-phenylene bis(dimethylcarbamate) hydrochloride (bambuterol hydrochloride) (**2**) with sodium tetraphenylborate (**3**) in deionized water, at ambient temperature, through anion exchange reaction. The structure of the title borate salt was characterized by IR, mass and ^{1}H NMR analyses. Colorless crystals of **4** suitable for an X-ray structural analysis were obtained by slow evaporation from acetonitrile. Compound 4 crystallizes in the monoclinic, space group $P2_1/c$, with $a = 8.8931$ (2) Å, $b = 20.4639$ (6) Å, $c = 21.4393$ (6) Å, $\beta = 93.640$ (2)°, $V = 3893.81$ (18) Å^3, Z = 4.

Graphical Abstract Synthesis, characterization and X-ray structure of tetraphenylborate salt of bambuterol (Bambec®), the drug for the treatment of asthma, bronchospasm, emphysema, and chronic obstructive pulmonary disease.

Keywords Bambuterol · (Bambec®) · Anion exchange · Tetraphenylborate salt · Crystal structure · X-ray analysis





Introduction

Bambuterol hydrochloride is an oral a long acting beta-adrenoceptor agonist (LABA), it has been approved for the treatment for once-daily treatment of the symptoms of asthma, bronchospasm, emphysema, and chronic obstructive pulmonary disease in 28 countries. It is produced in marketing by AstraZeneca pharmaceutical company as Bambec®. Bambuterol, a biscarbamate ester prodrug of the β_2 adrenergic agonist terbutaline, is available in 10 and

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20 mg (25 and 50 μmol) tablets as the hydrochloride salt [1, 2]. It has been demonstrated that both of bambuterol enantiomers are potent in the treatment of asthma [3].

QueryOn the other hand, sodium tetraphenylborate is the organic compound with the formula $NaB(C_6H_5)_4$. It is a salt, wherein the anion consists of four phenyl rings bonded to boron. This white crystalline solid is used to prepare other tetraphenylborate salts, which are often highly soluble in organic solvents. The compound is used in inorganic and organometallic chemistry as a precipitating agent. Furthermore, tetraphenylborate recently was used as a precipitating agent for radioactive ion extraction [4]. It is also used as precipitating agent for formation of new active materials which were used as ion sensing material for some drug [5–9].

Many pharmaceutical salts are not chemically equivalent and such chemical differences causes differences in their therapeutic prosperities and increase their chemical stability. Salt selection is now a common standard operation in drug development and in most cases the drug salts show preferential properties as compared with the parent agent. Consequently, there has been a huge interest in the production of drug salts. Almost half of the clinically used drugs are salts and many drugs are now produced in more than one salt form [10].

In this study we hope to report herein the synthesis, characterization and X-structure of tetraphenylborate salt of bambuterol (Bambec®).

Experimental

Chemistry

General

Melting point was determined on a Gallenkamp melting point apparatus and it is uncorrected. Infrared (IR) Spectrum was recorded as KBr disks using the Perkin Elmer FT-IR Spectrum BX apparatus. NMR Spectra were scanned in DMSO-d_6 on a Brucker NMR spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C. Chemical shifts are expressed in δ-values (ppm) relative to TMS as an internal standard. Coupling constants (J) are expressed in Hz. D_2O was added to confirm the exchangeable protons. Mass spectrum was measured on an Agilent Triple Quadrupole 6410 QQQ LC/MS equipped with an ESI (electrospray ionization) source.

*N-(2-(3,5-bis((dimethylcarbamoyl)oxy)phenyl)-2-hydroxyethyl)-2-methylpropan-2-aminium tetraphenylborate (**4**)*

To a solution of 5-(2-(*tert*-butylamino)-1-hydroxyethyl)-1,3-phenylene bis(dimethylcarbamate) hydrochloride (bambuterol hydrochloride) (**2**) (0.4039 g, 1 mmol) in deionized water (10 mL) a solution of sodium tetraphenylborate (**3**) (0.3422 g, 1 mmol) in deionized water (10 mL) was added. The formed white precipitate was filtered off, washed with cold deionized water. The precipitate was dried under vacuum to give the title ion-pairs complex. Recrystallization from methanol the title compound in 73 %; m.p. 198–200 °C; IR ν 3502–3045 (2NH+OH), 1670–1654 (2C=O) cm^{-1}; ^{1}H NMR (DMSO–d_6, 500 MHz) δ 1.30 (s, 9H, –C(C$\underline{H_3}$)$_3$, 2.92, 3.05 (s, 12H, 2 –N(C$\underline{H_3}$)$_2$), 3.10–3.13 (m, 2 H, CH_2), 4.84–4.87 (m, 1H, CH), 6.33 (bs, D_2O exchangeable, 1H, OH), 6.79–6.82 (m, 4H, 4H4 of tetraphenyl borate), 6.92–6.95 (m, 9H, H4 of benzene ring of bambuterol, 4H3 and 4H5 of tetraphenyl borate), 7.11 (d, 2H, J = 3.0 Hz, H2 and H6 of benzene ring of bambuterol), 7.18–7.20 (m, 8, 4H3 and 4H5 of tetraphenyl borate), 8.50 (2bs, D_2O exchangeable, 2H, 2NH); ^{13}C NMR (DSMO-d_6, 125 MHz) δ 25.55 (3C, –C($\underline{C}$H$_3$)$_3$, 36.16 (2C, –N($\underline{C}H_3$)$_2$), 39.58 (2C, –N($\underline{C}H_3$)$_2$), 47.71 ($\underline{C}$H$_2$), 56.97 (–$\underline{C}$(CH$_3$)$_3$), 68.92 (–C(OH)–), 115.90 (C4 of benzene ring of bambuterol), 116.83 (C2 and C6 of benzene ring of bambuterol), 121.98 (4$\underline{C}$4 of tetraphenyl borate), 125.73, 125.75, 125.77, 125.79 (4$\underline{C}$3 and 4$\underline{C}$5 of tetraphenyl borate), 136.00 (4$\underline{C}$2 and 4$\underline{C}$6 of tetraphenyl borate), 144.21 (C1 of benzene ring of bambuterol), 152.09 (C=O), 154.11 (C=O), 163.25, 163.64, 164.03, 164.42 (4$\underline{C}$1 of tetraphenyl borate); ESI-MS (+ve) m/z: 368.1 (M$^+$–(Ph)$_4$B), 294.0.

X-ray Crystallography

General

Single crystals of **4** were obtained by slow evaporation from acetonitrile. A good crystal of a suitable size was selected for X-ray diffraction analysis. Data were collected on a Bruker APEX-II CCD diffractometer equipped with graphite monochromatic CuK\α radiation (λ = 1.54178) at 296 (2) K. Cell refinement and data reduction were done by Bruker SAINT; program used to solve structure and refine structure is SHELXS-97 [11]. The final refinement was performed by full- matrix least-squares techniques with anisotropic thermal data for non-hydrogen atoms on F^2. All the hydrogen atoms were placed in calculated positions and constrained to ride on their parent atoms. Multi-scan absorption correction was applied by use of SADABS software. The crystal and refinement data are given in Table 1, selected geometric parameters are listed in Table 2, and selected torsion angles are given in Table 3 and hydrogen-bond geometry are listed in Table 4.[1]

[1] Crystallographic data for the structure **4** has been deposited with the Cambridge Crystallographic Data Center (CCDC) under the numbers CCDC 1037897-1037898. Copies of the data can be obtained, free of charge, on application to CCDC 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk/ http://www.ccdc.cam.ac.uk].

Table 1 Summary of X-ray crystallographic data for compound **4**

Crystal data	
Chemical formula	$C_{18}H_{30}N_3O_5{\cdot}C_{24}H_{20}B$
M_r	687.66
Crystal system, space group	Monoclinic, $P2_1/c$
Temperature (K)	296 (2)
a, b, c (Å)	8.8931 (2), 20.4639 (6), 21.4393 (6)
β (°)	93.640 (2)
V (Å^3)	3893.81 (18)
Z	4
Radiation type	Cu $K\alpha$
μ (mm^{-1})	0.61
Crystal size (mm)	0.31 × 0.18 × 0.15
Data collection	
Diffractometer	Bruker *APEX*-II CCD diffractometer
Absorption correction	Multi-scan *SADABS* Bruker 2014
T_{min}, T_{max}	0.827, 0.910
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	26859, 7277, 5221
R_{int}	0.049
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.062, 0.191, 1.04
No. of reflections	7277
No. of parameters	478
No. of restraints	0
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	0.83, −0.41

Table 2 Selected bond lengths (Å) and angles (°) for compound **4**

Bond lengths (Å)			
O1–C2	1.39 (3)	N2–C14	1.45 (4)
O3–C13	1.21 (3)	N3–C16	1.33 (3)
O4–C16	1.20 (3)	C24–B1	1.64 (4)
O5–C7	1.40 (4)	N1–C8	1.49 (2)
N2–C13	1.32 (3)		
Bond angles (°)			
C2–O1–C13	117.85 (19)	O1–C13–O3	121.90 (2)
C4–O2–C16	121.02 (18)	O3–C13–N2	126.10 (2)
C8–N1–C9	117.37 (17)	O4–C16–N3	125.60 (2)
C13–N2–C15	118.50 (3)	O2–C16–O4	123.40 (2)
C13–N2–C14	123.40 (2)	O2–C16–N3	111.00 (2)
C16–N3–C18	119.60 (2)	C19–C24–B1	124.43 (19)
C17–N3–C18	117.10 (3)	O5–C7–C6	113.30 (2)
C16–N3–C17	123.30 (2)	O5–C7–C8	107.61 (19)
O1–C2–C3	120.60 (2)	N1–C8–C7	110.65 (16)
O1–C2–C1	117.20 (2)	N1–C9–C12	108.90 (2)
O2–C4–C3	121.67 (17)	O1–C13–N2	111.90 (2)

Results and Discussion

Chemistry

The reaction of 5-(2-(*tert*-butylamino)-1-hydroxyethyl)-1,3-phenylene bis(dimethylcarbamate) hydrochloride (bambuterol hydrochloride) (**2**) with sodium tetraphenylborate (**3**) in deionized water, at ambient temperature, afforded the title compound tetraphenylborate salt of bambuterol (Bambec®), *N*-(2-(3,5-bis((dimethylcarbamoyl)oxy)phenyl)-2-hydroxyethyl)-2-methylpropan-2-aminium tetraphenylborate (**4**) in 73 % yield through anion exchange reaction (Scheme 1).

The IR of compound **4** showed the absorption bands of two carbonyl functions in the ring 1670–1654 cm^{-1} while the absorption bands of –OH and 2 –NH appeared in the ring 3502–3045 cm^{-1}.

The ^{1}HNMR (DSMO-d_6, 500 MHz) of **4** revealed the singlet signal of *tert*-butylamino protons at δ 1.30 in addition to the singlet signals of dimethylcarbamate protons which appeared at δ 2.92 and 3.05. Th multiplet signals of CH_2 and CH protons appeared in the region δ 3.10–3.13

Table 3 Selected torsion angles (°) for compound **4**

Torsion angle	(°)	Torsion angle	(°)
C6–C1–C2–O1	175.10 (2)	C32–C31–C36–B1	176.20 (2)
C13–O1–C2–C3	−62.30 (3)	C38–C37–C42–B1	177.00 (3)
C13–O1–C2–C1	123.80 (2)	C40–C41–C42–C37	1.50 (4)
C2–C3–C4–O2	172.90 (2)	C40–C41–C42–B1	−176.60 (3)
C16–O2–C4–C5	−132.90 (2)	C37–C42–B1–C24	−110.80 (3)
C16–O2–C4–C3	55.00 (3)	C41–C42–B1–C24	67.20 (3)
C2–C1–C6–C5	0.80 (3)	C37–C42–B1–C30	9.90 (3)
C5–C6–C7–O5	−136.70 (2)	C41–C42–B1–C30	−172.20 (2)
C1–C6–C7–C8	−79.70 (3)	C37–C42–B1–C36	128.50 (3)
C5–C6–C7–C8	102.00 (3)	C41–C42–B1–C36	−53.50 (3)
C9–N1–C8–C7	168.20 (2)	C19–C24–B1–C42	−12.20 (3)
O5–C7–C8–N1	57.20 (3)	C23–C24–B1–C42	168.20 (2)
C6–C7–C8–N1	−178.20 (2)	C19–C24–B1–C30	−132.20 (2)
C8–N1–C9–C12	60.80 (3)	C23–C24–B1–C30	48.30 (3)
C8–N1–C9–C10	−62.10 (3)	C19–C24–B1–C36	107.90 (2)
C8–N1–C9–C11	179.60 (2)	C23–C24–B1–C36	−71.70 (3)
C15–N2–C13–O1	−177.30 (3)	C29–C30–B1–C42	90.00 (2)
C2–O1–C13–O3	−8.40 (3)	C25–C30–B1–C42	−86.50 (2)
C2–O1–C13–N2	173.60 (2)	C29–C30–B1–C24	−149.60 (2)
C18–N3–C16–O4	−3.00 (4)	C25–C30–B1–C24	33.90 (3)
C17–N3–C16–O4	178.00 (3)	C29–C30–B1–C36	−28.80 (3)
C18–N3–C16–O2	177.80 (3)	C25–C30–B1–C36	154.70 (2)
C17–N3–C16–O2	−1.30 (4)	C31–C36–B1–C42	145.80 (2)
C4–O2–C16–O4	2.40 (4)	C4–O2–C16–N3	−178.30 (2)

Table 4 Hydrogen-bond geometry (Å, °), Cg_3 is (C25–C30)

D–H···*A*	*D*–H	H···*A*	*D*···*A*	*D*–H···*A*
N1–H1B···O4^{i}	0.90	2.00	2.88 (3)	170.00
N1–H1C···O3^{i}	0.90	1.91	2.79 (3)	166.00
O5–H5B···O3^{i}	0.82	2.48	3.28 (3)	171.00
O5–H5B···N1	0.82	2.32	2.78 (3)	117.00
C39–H39A···*Cg*3	0.97	2.71	3.54 (3)	150.00

Symmetry code (i) $x + 1, y, z$

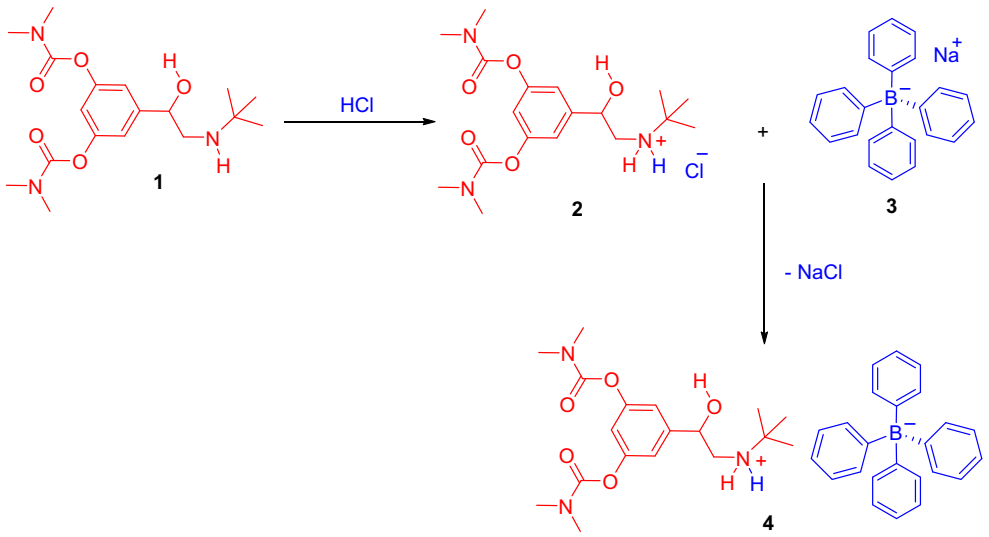
and 4.84–4.87, respectively. The protons of phenyl groups of tetraphenyl borate anion and benzene ring of *R*-bambuterol apeared in the aromatic region while the two broad D_2O exchangeable signals of OH and 2 NHs apeared at δ 6.33 and 8.50, respectively.

The ^{13}C NMR (DSMO-d_6, 125 MHz) of compound **4** exhibited the signals of aliphatic carbons at δ 25.55 (3*C*, –C($\underline{C}H_3$)$_3$, 36.16 (2*C*, –N($\underline{C}H_3$)$_2$), 39.58 (2*C*, –N($\underline{C}H_3$)$_2$), 47.71 ($\underline{C}H_2$), 56.97 (–$\underline{C}$(CH$_3$)$_3$) and 68.92 (–*C*(OH)–), respectively. Furthermore, ^{13}C NMR of **4** showed the signals of benzene ring of bambuterol at δ 115.90 (*C*4), 116.83 (*C*2 and *C*6), 144.21 (*C*1), respectively, while it showed the signals due to the carbons of four phenyl rings of tetraphenyl borate at δ 121.98 (4$\underline{C}$4), 125.73, 125.75, 125.77, 125.79 (4$\underline{C}$3 and 4$\underline{C}$5), 136.00 (4$\underline{C}$2 and 4$\underline{C}$6), 163.25, 163.64, 164.03, 164.42 (4$\underline{C}$1), respectively. Finally, the signals of carbamate carbons appeared at δ 152.09 and 154.11, respectively.

The ESI-MS (+ve) of compound **4** revealed a peak at *m*/*z* 368.1 equal to (M^+– (Ph)$_4$B) in addition to the peak at *m*/*z* 294.0.

X-ray crystallography

The title compound crystallizes with one cation and anion in the asymmetric unit (Figs. 1, 2), that is a *N*-(2-(3,5-bis((dimethylcarbamoyl)oxy)phenyl)-2-hydroxyethyl)-2-methylpropan-2-aminium cation and a tetraphenylborate anion. As typical for tetraphenylborate, the tetraphenylborate anion is in a tetrahedral geometry around the B atom [C–B–C angles of 108.80 (19)°–110.13 (18)°]. Regarding the bambuterol cation, the structure has chiral center in C7 and the absolute configuration around this carbon is *S*, all side substitutions attached to the phenyl ring (C1–C6) were located in same direction and this crystal structure seems to be the same of bambuterol hydrochloride which published in 2008 by Gao Cao et al. [2]. The crystal structure is stabilized by N–H···O and O–H···O



Scheme 1 Synthesis of tetraphenylborate salt of bambuterol (Bambec®) **4**

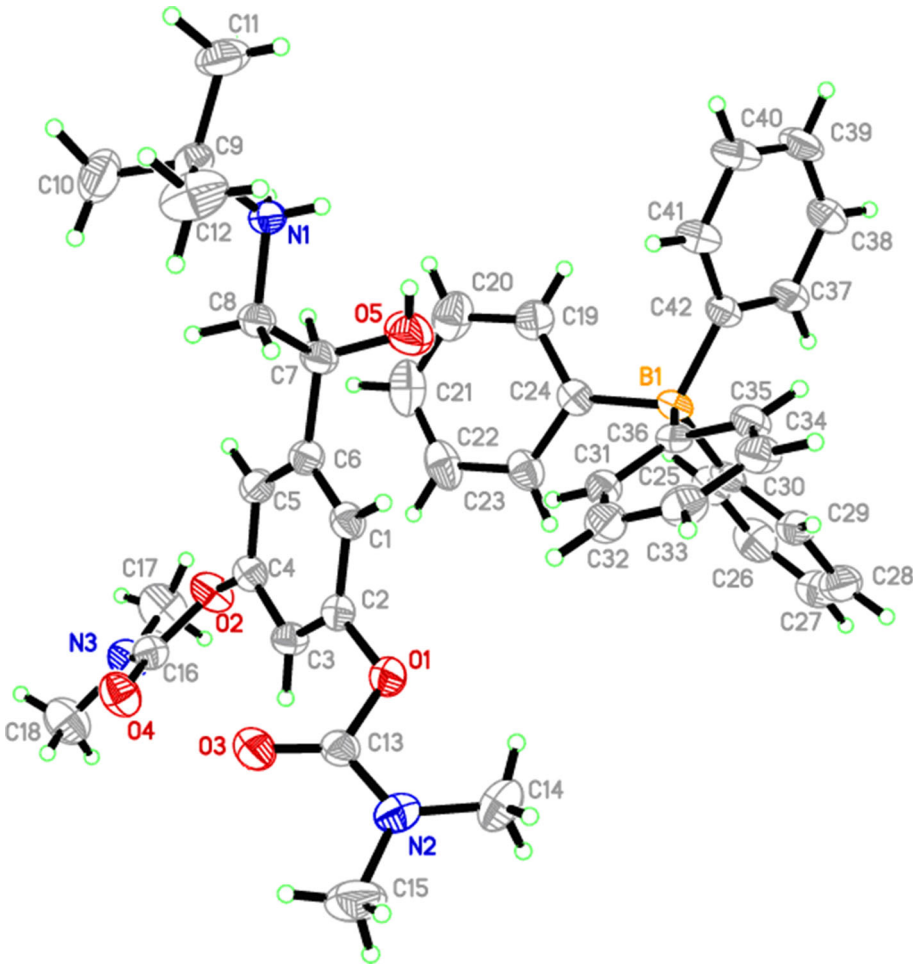


Fig. 1 View of the two ions of **4** in the asymmetric unit showing the atom-labelling scheme. *Ellipsoids* are drawn at the 50 % probability level with H atoms represented by circles of arbitrary size

hydrogen bonds into a three-dimensional framework structure forming the chain extending along along the *a* axis direction. The crystal packing is further stabilized by weak C–H···π (phenyl) interactions (Table 4) that links the adjacent chains into a two dimensional structure along the *bc* plane.

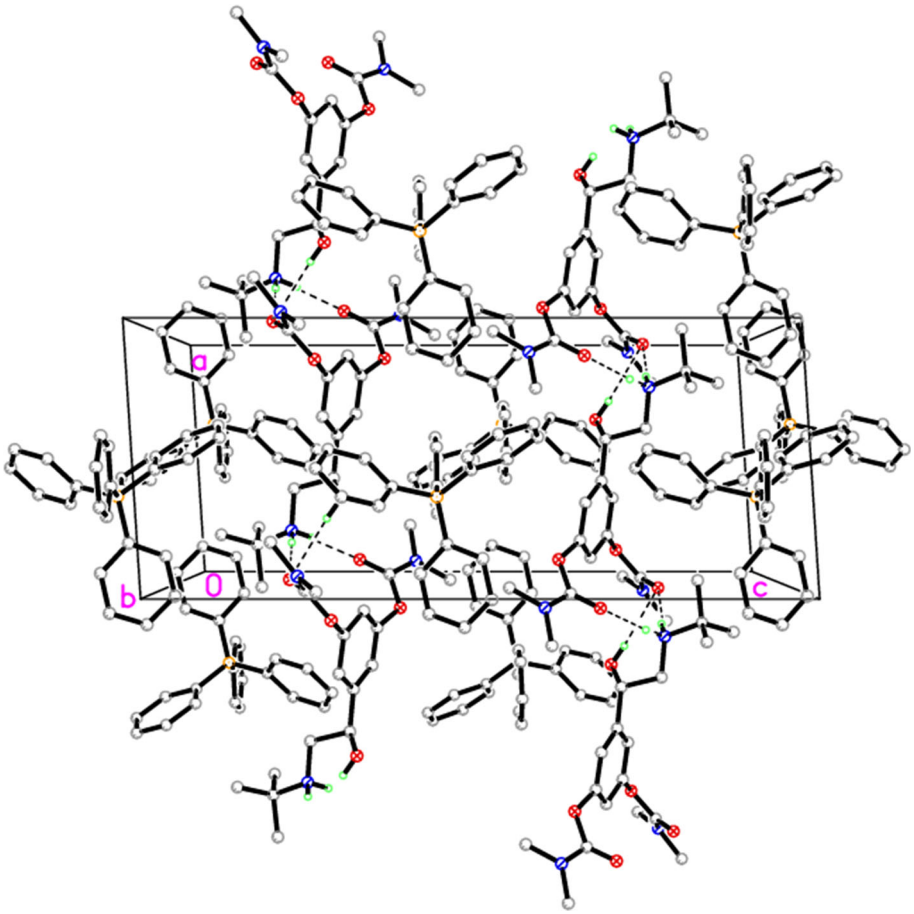


Fig. 2 Crystal packing of **4** showing intermolecular N–H···O and O–H···O hydrogen bonds as dashed lines (H atoms not involved in hydrogen bonding are omitted for clarity)

Conclusion

In conclusion, the title compound **4** was prepared efficiently by the reaction of bambuterol hydrochloride **2** with sodium tetraphenylborate (**3**) in deionized water at ambient temperature. The structure of **4** was established under the basis of its X-ray single crystal analysis.

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Conflict of interest The authors have declared that there is no conflict of interest.

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