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Isopropylammonium tetrafluorohydrogenphthalate: Structural characterization and comparison to two related salts with different stoichiometric ratios

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ABSTRACT

The normal acid salt isopropylammonium tetrafluorohydrogenphthalate (**3**) was prepared and its structure was determined by X-ray crystallography. This salt is stabilized by N–H···O, O–H···O, C–H···O, and N–H···F hydrogen bonds. Compound **3** was characterized by means of solution and solid-state NMR. The *ipso*-carbons, whose signals are equivalent in solution, could be distinguished in the solid state, thus reflecting the asymmetric nature of **3**. With respect to structural features, **3** was compared with salts of different stoichiometry, i.e. the neutral salt bis(isopropylammonium) tetrafluorophthalate (**1**) and the anomalous salt isopropylammonium tetrafluorohydrogenphthalate × tetrafluorophthalic acid (**2**).

1. Introduction

The ability of covalently bound fluorine to accept hydrogen bonds has been the subject of a scientific debate [1–3]. This issue has attracted much interest in analyses of crystal structures of fluorine-containing molecules [4–7], particularly in cases of aromatic carbon-bound fluorine-mediated hydrogen bonds [8]. The introduction of fluorine is a commonly used strategy in medicinal chemistry to improve properties of bioactive compounds [9,10]. Although a hydrogen–fluorine exchange results in only minor steric changes, the high electronegativity of fluorine and the resulting polarization of the C–F bond remarkably alter the physico-chemical properties of molecules [2,8]. Therefore, the introduction of fluorine can lead to enhanced binding interactions, increased metabolic stability or selective reactivity [11]. Favorable (fluorophilic) and unfavorable (fluorophobic) environments within target proteins have been determined. Such approaches have been exploited to develop inhibitors of serine and cysteine proteases [1–3,12–15] or to design potent inhibitors of angiogenesis by fluorination of phthalic acid derivatives [16–19]. In the course of studies on salts of tetrafluorophthalic acid, one has to face limitations by the absence of aromatic protons in ^{1}H NMR, and fluorine–carbon couplings in ^{13}C NMR spectroscopy. The structural characterization is additionally complicated as a dibasic acid (H_2Y) is able to form salts with a monoacid base (R) in different stoichiometric ratios. Besides a neutral (R_2Y) and a normal acid salt (RHY), various anomalous salts (e.g. RH_3Y_2, $R_2H_4Y_3$) can be formed [20–22].

Recently, we described the neutral salt bis(isopropylammonium) tetrafluorophthalate (Fig. 1, **1**) and the anomalous salt isopropylammonium tetrafluorohydrogenphthalate × tetrafluorophthalic acid (**2**) [23]. The molecular structures of both salts could be revealed by X-ray diffraction and were supported by different spectroscopic methods. Interestingly, the solid-state NMR spectrum of **2** showed a splitting into three resonances of the carbons attached to the carboxylic groups. To further elucidate this aspect, we prepared the new normal acid salt isopropylammonium tetrafluorohydrogenphthalate (**3**). Structural data of **3** are presented herein and are discussed with regard to the related salts **1** and **2**.

2. Experimental

2.1. Materials and methods

Tetrafluorophthalic acid was obtained from Alfa Aesar (Karlsruhe, Germany) and isopropylamine was from Merck Schuchardt (Hohenbrunn, Germany). The melting point was determined on a Boëtius hot stage microscope apparatus (PHMK, VEB Wägetechnik Rapido, Radebeul, Germany). The infrared spectrum was recorded

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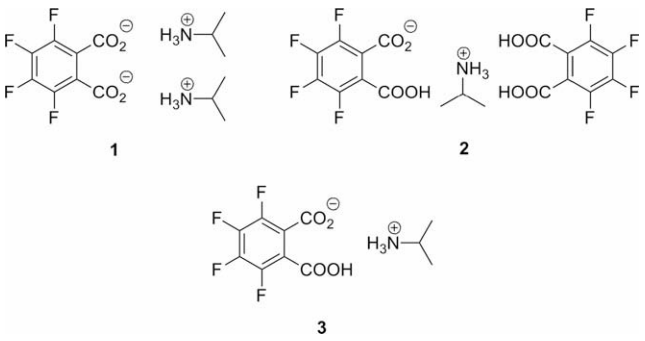

Fig. 1. Structures of isopropylammonium tetrafluorophthalates **1**–**3** with different stoichiometry.

on a Bruker Tensor 27 FT-IR instrument. Intensities of selected bands in the range of 3500–1000 cm^{-1} are indicated as s (strong), m (moderate), and w (weak). ^1H NMR (500 MHz) and ^{13}C NMR spectra (125 MHz) were recorded on a Bruker Avance DRX 500. Chemical shifts δ are given in ppm referring to the signal center using the DMSO-d_6 peaks (2.49 ppm/39.7 ppm) for reference. Spin multiplicities are indicated by the following symbols: br s (broad singlet), d (doublet), and sept (septet). Solid-state, magic-angle spinning (MAS) NMR experiments were carried out on a Varian Infinity+ spectrometer equipped with a commercial 4 mm MAS-NMR double-resonance probe. The magnetic field strength was 9.4 T corresponding to a ^{13}C and ^1H resonance frequency of 100.98 and 401.52 MHz, respectively. The ^{13}C MAS-NMR spectrum was acquired with a ramped $^{13}C\{^1H\}$ cross-polarization (CP) experiment. The spectrum shown was obtained in 1 h with a repetition delay of 5 s at room temperature. At 12 kHz spinning frequency the ^{13}C pulse lengths was 2.5 μs, 100 kHz spectral width and 800 transients. A line broadening of 50 Hz was used in data processing. The ^{13}C chemical shifts refer to tetramethylsilane (TMS). Values for the spectral parameters (integral, full width half maximum) were achieved from the least square fitting of the experimental spectrum by the spectrometer software. Elemental analysis was performed with a Vario EL apparatus.

2.2. Isopropylammonium tetrafluorohydrogenphthalate (*3*)

A solution of isopropylamine (120 mg, 2.00 mmol) in water (2.0 mL) was added to tetrafluorophthalic acid (714 mg, 2.00 mmol). After the mixture was stirred at room temperature for 10 min, the solvent was evaporated under reduced pressure. The crude product was recrystallized from MeCN to give **3** (502 mg, 84%) as colorless rhombs: m.p. 154–156 °C; IR (KBr, cm^{-1}) 3161m, 2942w, 2570w, 1917w, 1718s, 1628s, 1592s, 1475s, 1376s, 1124m, 1068s; ^1H NMR (DMSO-d_6) δ 1.16 (d, ^3J = 6.6 Hz, 6H, CH_3), 3.26 (sept, ^3J = 6.6 Hz, 1H, CH), 7.90 (br s, 3H, NH); ^{13}C NMR (DMSO-d_6) δ 20.53 (CH_3), 43.00 (CH), 122.19 (d, $^2J_{C-F}$ = 14 Hz, C1, C2), 139.60 (d, $^1J_{C-F}$ = 253 Hz, C4, C5), 143.78 (d, $^1J_{C-F}$ = 248 Hz, C3, C6), 163.13 (CO). Solid-state ^{13}C NMR δ 20.1 (CH_3), 46.6 (CH), 118.0, 122.9 (C1, C2), 134–149 (C3, C4, C5, C6), 165.4 (CO). Analytical data for $C_{11}H_{11}F_4NO_4$. Calcd: C, 44.45; H, 3.73; N, 4.71. Found: C, 44.44; H, 3.79; N, 4.65.

2.3. Crystal structure determination of *3*

Data were collected on a Nonius KappaCCD diffractometer equipped with a low-temperature device (Cryostream, Oxford Cryosystems) at 123(2) K using graphite monochromated Mo-K_α radiation (λ = 0.71073 Å). The structure was solved by direct methods (SHELXS-97) [24] and refined by full-matrix least squares on F^2 (SHELXL-97) [25]. PLATON v.230608 [26] was used for calculating dihedral angles between planes. All non-hydrogens were refined anisotropically. Hydrogen atoms were localized by difference electron density determination and were refined isotropically. CCDC-730532 contains the supplementary crystallographic data for compound **3**. It can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

3. Results and discussion

3.1. Crystal structure

The crystallographic data of compound **3**, obtained in the course of this study, are summarized in Table 1. Selected bond lengths and angles are given in Table 2, hydrogen bonding parameters are presented in Table 3. The dihedral angle between the planes of the carboxylate fragment (O1/C7/O2) and the protonated carboxyl group (O3/C8/O4) is 56.4(2)°. The angles of both groups relative to the tetrafluorobenzene ring are 50.8(2)° (O1/C7/O2), 58.6(2)° (O3/C8/O4), respectively. These two values show the same tendency compared to those observed in the tetrafluorohydrogenphthalate unit of compound **2** (30°, 76°) [23], and differ from typical orientations in hydrogenphthalates with angles between carboxylate fragments and phenyl planes in the range of 65°–85°, but smaller angles (5°–40°) between carboxyl groups and benzene rings, respectively [27].

Different types of hydrogen bonds were observed in compound **3**. Besides N–H···O, O–H···O, and C–H···O bonds, one fluorine of the aromatic ring was incorporated in a hydrogen bond of type N–H···F. All three ammonium hydrogen atoms are part of hydrogen bonds with four different tetrafluorohydrogenphthalate molecules. The hydrogen bond network is shown in Fig. 2. As in structures **1** and **2**, two hydrogens are incorporated in two-center N–H···O hydrogen bonds. In the presented structure **3**, both contacts are formed with oxygens of carboxylate fragments. For hydrogen-acceptor distances in hydrogen bonds between mono-substituted ammonium

Table 1
Crystallographic data for **3**.

Crystal data	
Empirical formula	$C_{11}H_{11}F_4NO_4$
Formula weight	297.20
Temperature (K)	123(2)
Wavelength (Å)	0.71073
Crystal size (mm)	0.34 × 0.20 × 0.10
Crystal system	Monoclinic
Space group	$P2_1/n$
a (Å)	7.8520(2)
b (Å)	16.2123(5)
c (Å)	9.2330(3)
α (°)	90
β (°)	98.026(2)
γ (°)	90
V (Å^3)	1163.84(6)
Z	4
Calculated density (g/cm^3)	1.696
Absorption coefficient (mm^{-1})	0.168
F(0 0 0)	608
θ Range for data collection (°)	2.91–30.04
Completeness to θ (%)	98.6 (θ_{max} = 30.04°)
Range of h, k, l	−10/11, −22/18, −13/12
Reflections collected/unique	15278/3345 [R(int) = 0.0479]
Absorption correction	Analytical
Max. and min. transmission	0.984 and 0.9616
Refinement method	Full-matrix least squares on F^2
Data/restraints/parameters	3345/0/225
Goodness-of-fit on F^2	0.943
Final R indices [$I > 2\sigma$ (I)]	R_1 = 0.0373, wR_2 = 0.0816
R indices (all data)	R_1 = 0.0660, wR_2 = 0.0904
Largest diff. peak and hole (e/Å^3)	0.250 and −0.352

Table 2
Selected bond lengths (Å) and angles (°) for **3.**

C7–O1	1.2636(15)
C7–O2	1.2389(15)
C8–O3	1.3104(16)
C8–O4	1.2130(16)
O1–C7–O2	128.11(12)
O3–C8–O4	125.38(12)
C6–C1–C7–O1	−52.54(16)
C6–C1–C7–O2	126.81(13)
C3–C2–C8–O3	120.54(12)
C3–C2–C8–O4	−56.65(17)

Table 3
Hydrogen bonding parameters for **3.**

D–H···A	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)
O3–HO3···O1[a]	0.99(2)	1.62(2)	2.5512(13)	155.2(19)
N1–HN1A···O1[b]	0.906(16)	2.023(16)	2.9287(14)	177.7(13)
N1–HN1B···O2[c]	0.914(18)	1.865(19)	2.7705(15)	170.3(15)
N1–HN1C···O4[d]	0.933(19)	2.023(18)	2.8590(15)	148.2(15)
N1–HN1C···F3[e]	0.933(19)	2.423(17)	3.0292(14)	122.6(13)
C11–H11B···O3[b]	0.983(18)	2.500(19)	3.3884(17)	150.3(14)

Symmetry transformations used to generate equivalent atoms: [a] $x+1/2, -y+5/2, z+1/2$; [b] $-x+1/2, y-1/2, -z+3/2$; [c] $-x, -y+2, -z+2$; [d] $-x+1/2, y-1/2, -z+5/2$; [e] $x+1/2, -y+3/2, z+1/2$.

groups and carboxylate oxygens, a mean value of 1.84 Å was reported [28]. Thus, the HN1B···O2 distance (1.87 Å) is in accordance therewith, but the HN1A···O1 bond is somewhat longer (2.02 Å).

In contrast to **1** and **2**, a fluorine atom, i.e. F3 in *para*-position to the protonated carboxyl group, is involved in the hydrogen bonding network of structure **3**. The hydrogen atom HN1C is forming a three-center (bifurcated) hydrogen bond to acceptors fluorine F3 and oxygen O4 from two different tetrafluorohydrogenphthalate molecules. The major component of this unsymmetrical bifurcated hydrogen bond is directed to the oxygen, as it is more linear (148° vs. 123°) and has a shorter hydrogen-acceptor distance in comparison to the minor one directed to the fluorine (2.02 Å vs. 2.43 Å). There are structures reported with bifurcated hydrogen bonds to fluorine and oxygen, but the donors/acceptors do not belong to three different molecules in such cases [5,29].

The protonated oxygen O3 of the carboxyl group is part of an intermolecular O–H···O bond to oxygen O1 of the carboxylate fragment. Such strong contacts (O···O distance 2.55 Å) were also observed in **2** as well as crystals of other hydrogenphthalates [23,27,30–32]. Moreover, the carboxyl oxygen O3 accepts a C–H···O hydrogen bond from a methyl group of the isopropyl ammonium molecule.

In total four N–H···O hydrogen bonds are directed toward the carboxylate oxygens of **1**, the carboxylate fragment of **2** accepts four hydrogen bonds from N–H or C–H donors, whereas three hydrogen bonds from O–H or N–H are directed toward the

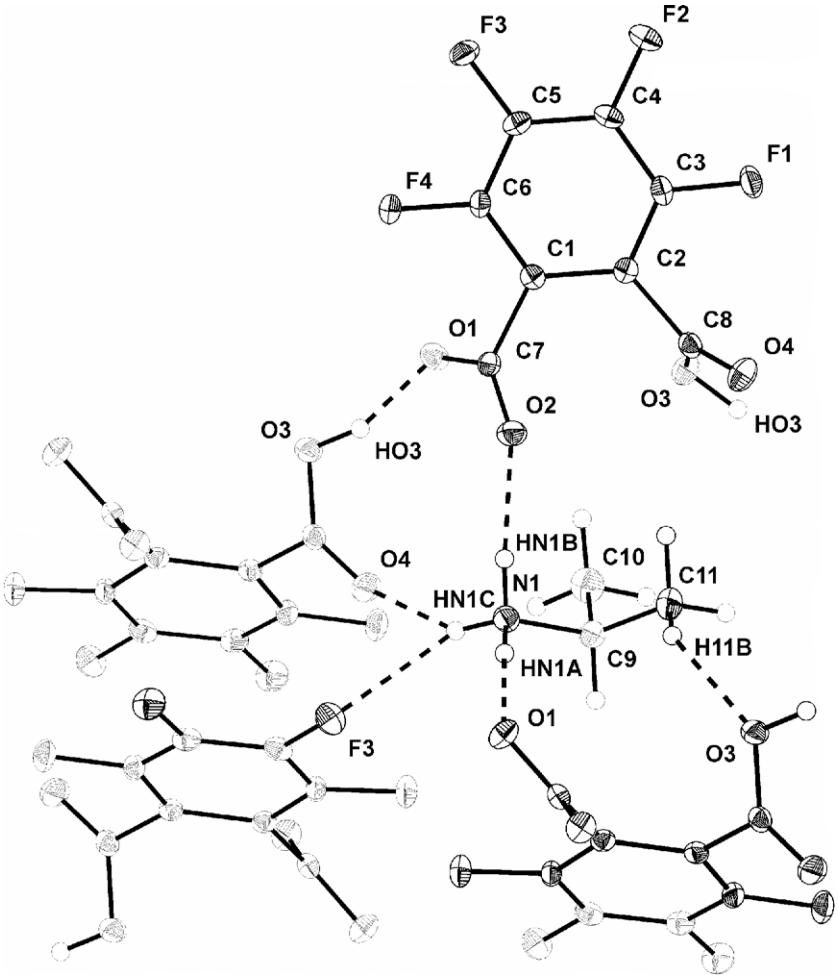

Fig. 2. Molecular plot of **3** showing the atom-labelling scheme and displacement ellipsoids at the 30% probability level for the non-H atoms. H atoms are depicted as small circles of arbitrary radii and dashed lines represent hydrogen bonds.

carboxylate oxygens of **3**. Taken together the three crystal structures of **1**, **2** and **3** show different binding geometries and hydrogen bonding arrangements. Only in the structure of **3**, a fluorine atom acts as a hydrogen bond acceptor.

3.2. Spectroscopic characteristics

^{1}H NMR and ^{13}C NMR spectra of compound **3** were recorded in DMSO-d_6. The shifts for the aromatic carbons were assigned on the basis of ^{13}C–^{19}F coupling constants and substituent increments [33]. $^{1}J_{C-F}$ and $^{2}J_{C-F}$ coupling constants were around 250 Hz and 14 Hz, respectively. Only four different signals for the carbons of the tetrafluorohydrophthalate molecule appear in the spectrum of **3**, thus different positions relative to the protonated or deprotonated carboxyl moiety were not reflected. This can be attributed to a rapid proton migration in solution. Similar observations have been made for compound **2** [23], as well as related proton transfers in 1,3-dicarbonyl compounds [34] and dicarboxylic acids [35].

When comparing the salts **1**–**3**, we noticed substantially different ^{13}C chemical shifts for the CO carbons and for those bearing the COO(H) groups (*ipso*-C). The values correlate with the ratio of carboxylate fragments to carboxyl groups. The neutral salt **1** with exclusively carboxylate fragments provides shifts of 164.5 ppm (CO) and 125.9 ppm (*ipso*-C), respectively. The values of the normal acid salt **3** with COO^- and COOH in equal amounts are 163.1 ppm (CO) and 122.2 ppm (*ipso*-C). A COO/COOH ratio of 1:3 in the anomalous salt **2** yields 162.9 ppm (CO) and 120.3 ppm (*ipso*-C). In particular, the value for the *ipso*-position (substituent increment for COONa: 8.4, for COOH: 2.1 [33]) indicates the stoichiometric ratio, whereas the shifts of the other benzene carbons are inappropriate because of carbon–fluorine couplings.

To further characterize the structure of compound **3**, a solid-state ^{13}C NMR spectrum was recorded (Fig. 3). Chemical shifts of fluorine-substituted carbons appear together as a broad signal between 134 ppm and 149 ppm. This was also observed in the solid-state spectra of the two tetrafluorophthalate-derived salts **1** and **2** [23]. The asymmetry of structure **3**, induced by the different protonation, is reflected by two signals for the *ipso*-carbons. Integration of the corresponding peak areas gave similar values (3.1 vs. 3.6). Accordingly, when recording the solid-state spectrum of the anomalous salt **2**, we observed three distinct resonances with AUC ratios of 1:1:2 [23]. Vila et al. studied 1,3-diphenyl-propane-1,3-dione and also noticed splitting of the *ipso*-carbon and carbonyl carbon signals [34]. The solid-state ^{13}C NMR spectra of **2** (and **3**) do not reveal a dissimilarity of the CO carbons, since their signals are not separated. The occurrence of one common signal for COO^- and COOH carbons is in agreement with the relatively low sensitivity of the ^{13}C isotropic chemical shift to protonation, as can be explained by relations between main components δ_{22} and δ_{11} of the ^{13}C chemical shift tensor [36]. However, as a matter of principle, such a differentiation is possible. Ilczyszyn et al. have determined the structure of a sarcosine–maleic acid (1:1) complex by X-ray diffraction and distinguished the charged and uncharged carboxyl(ate) groups by means of solid-state ^{13}C NMR spectroscopy [37]. Barry et al. characterized normal and anomalous tetramethylammonium salts of dicarboxylic acids and observed different ^{13}C NMR shifts for nonequivalent carboxyl(ate) carbons in solid state [38]. In the cases of **2** and **3**, crystal and bonding forces which influence bond angles and distances and thus the resulting ^{13}C chemical shift [21] might be responsible for a coalescence of the CO signals.

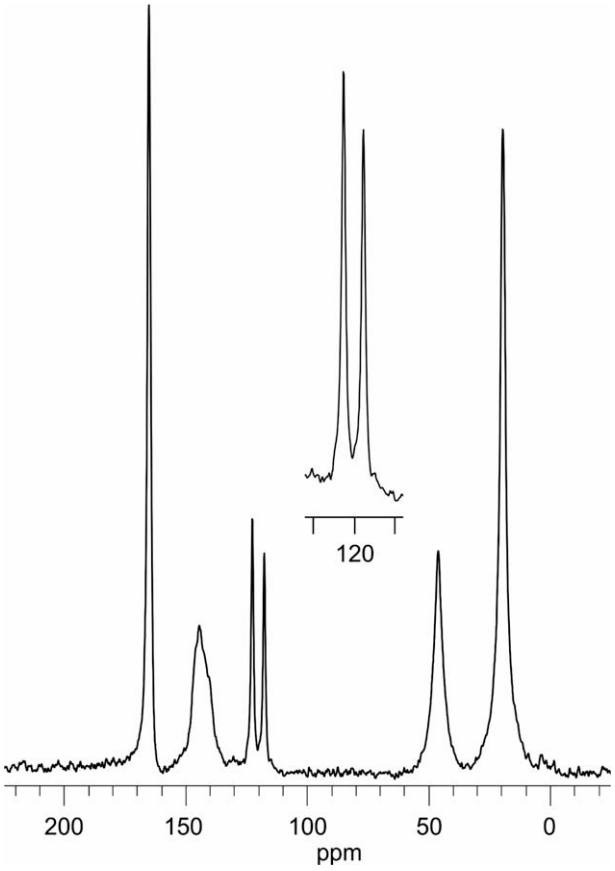

Fig. 3. ^{13}C CP-MAS spectrum of **3** with (inset) an expansion of the *ipso*-carbon region.

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References

[1] J.D. Dunitz, ChemBioChem 5 (2004) 614.
[2] H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, ChemBioChem 5 (2004) 637.
[3] J.A. Olsen, D.W. Banner, P. Seiler, B. Wagner, T. Tschopp, U. Obst-Sander, M. Kansy, K. Müller, F. Diederich, ChemBioChem 5 (2004) 666.
[4] T. Steiner, Angew. Chem. Int. Ed. Engl. 41 (2002) 48.
[5] L. Shimoni, J.P. Glusker, Struct. Chem. 5 (1994) 383.
[6] Z. Sun, L.W. McLaughlin, J. Am. Chem. Soc. 41 (2007) 12531.
[7] M. Pham, M. Gdaniec, T. Połoński, J. Org. Chem. 63 (1998) 3731.
[8] A.V. Razgulin, S. Mecozzi, J. Med. Chem. 49 (2006) 7902.
[9] K. Müller, C. Faeh, F. Diederich, Science 317 (2007) 1881.
[10] S. Fustero, M. Sánchez-Roselló, V. Rodrigo, J.F. Sanz-Cervera, J. Piera, A. Simón-Fuentes, C. del Pozo, Chem. Eur. J. 14 (2008) 7019.
[11] W.K. Hagmann, J. Med. Chem. 51 (2008) 4359.
[12] A. Hofmann-Röder, E. Schweizer, J. Egger, P. Seiler, U. Obst-Sander, B. Wagner, M. Kansy, D.W. Banner, F. Diederich, ChemMedChem 1 (2006) 1205.
[13] A. Eilfeld, C.M. Gonzalez Tanarro, M. Frizler, J. Sieler, B. Schulze, M. Gütschow, Bioorg. Med. Chem. 16 (2008) 8127.
[14] R. Löser, K. Schilling, E. Dimmig, M. Gütschow, J. Med. Chem. 48 (2005) 7688.
[15] D. Kim, L. Wang, M. Beconi, G.J. Eiermann, M.H. Fisher, H. He, G.J. Hickey, J.E. Kowalchick, B. Leiting, K. Lyons, F. Marsilio, M.E. McCann, R.A. Patel, A. Petrov, G. Scapin, S.B. Patel, R.S. Roy, J.K. Wu, M.J. Wyvratt, B.B. Zhang, L. Zhu, N.A. Thornberry, A.E. Weber, J. Med. Chem. 48 (2005) 141.
[16] S.S. Ng, M. Gütschow, M. Weiss, S. Hauschildt, U. Teubert, T.K. Hecker, F.A. Luzzio, E.A. Kruger, K. Eger, W.D. Figg, Cancer Res. 63 (2003) 3189.
[17] S.S. Ng, G.R. MacPherson, M. Gütschow, K. Eger, W.D. Figg, Clin. Cancer Res. 10 (2004) 4192.
[18] E.R. Lepper, S.S. Ng, M. Gütschow, M. Weiss, S. Hauschildt, T.K. Hecker, F.A. Luzzio, K. Eger, W.D. Figg, J. Med. Chem. 47 (2004) 2219.
[19] S.M. Capitosti, T.P. Hansen, M.L. Brown, Bioorg. Med. Chem. 12 (2004) 327.
[20] J.E. Barry, M. Finkelstein, S.D. Ross, J. Org. Chem. 47 (1982) 64.
[21] L.H. Merwin, S.D. Ross, Magn. Reson. Chem. 30 (1992) 440.
[22] R. Chitra, P. Roussel, F. Capet, C. Murli, R.R. Choudhury, J. Mol. Struct. 923 (2009) 45.

[23] M. Pietsch, H.-G. Häcker, G. Schnakenburg, W. Hoffbauer, M. Nieger, M. Gütschow, J. Mol. Struct. 878 (2008) 131.
[24] G.M. Sheldrick, Acta Cryst. A46 (1990) 467.
[25] G.M. Sheldrick, SHELXL-97, Program for Crystal Structure Analysis, University of Göttingen, Göttingen, Germany, 1997.
[26] A.L. Spek, J. Appl. Cryst. 36 (2003) 7.
[27] A. Langkilde, D. Madsen, S. Larsen, Acta Cryst. B60 (2004) 502.
[28] R. Taylor, O. Kennard, W. Versichel, Acta Cryst. B40 (1984) 280.
[29] J.P. Jasinski, R.J. Butcher, L. Mallesha, K.N. Mohana, H.S. Yathirajan, B. Narayana, J. Chem. Crystallogr. 39 (2009) 433.
[30] S.M. Jessen, Acta Cryst. C46 (1990) 1513.
[31] J.W. Bats, A. Kallel, H. Fuess, Acta Cryst. B34 (1978) 1505.
[32] J.W. Bats, W. Schuckmann, H. Fuess, Acta Cryst. B34 (1978) 2627.
[33] H.-O. Kalinowski, S. Berger, S. Braun, ^{13}C NMR-Spektroskopie, Thieme, Stuttgart, New York, 1984. p. 284.
[34] A.J. Vila, C.M. Lagier, A.C. Olivieri, J. Chem. Soc. Perkin Trans. 2 (1990) 1615.
[35] P.J. Choi, K.A. Petterson, J.D. Roberts, J. Phys. Org. Chem. 15 (2002) 278.
[36] M. Ilczyszyn, D. Godzisz, M.M. Ilczyszyn, K. Mierzwicki, Chem. Phys. 323 (2006) 231.
[37] M. Ilczyszyn, D. Godzisz, M.M. Ilczyszyn, Spectrochim. Acta A 59 (2003) 1815.
[38] J.E. Barry, M. Finkelstein, S.D. Ross, G.D. Mateescu, A. Valeriu, C. Svensson, J. Org. Chem. 53 (1988) 6058.