Synthesis and Crystal Structure of 2,2'-[(Allylimino)diethane-2,1-diyl]bisphthalimide

Laurent LATXAGUE,[†] Christel CHANSEAU,* Marie-Christine DURRIEU,* Stéphane MASSIP,** and Jean-Michel LEGER**

*INSERM U577, Bordeaux and Université Victor Segalen Bordeaux 2, UMR-577, Bordeaux, F-33076, France

**EA 4138 Pharmacochimie, Université Victor Segalen Bordeaux 2, Bordeaux, F-33076, France

The structure of 2,2'-[(allylimino)diethane-2,1-diyl]bisphthalimide was determined by X-ray crystallography. The symmetry operation $(-x+2, -y+1, -z)$ generates the whole molecule. The compound crystallized in a monoclinic system, and was characterized thus: $P2_1/n$, $a = 8.013(6)\text{\AA}$, $b = 32.731(7)\text{\AA}$, $c = 8.485(2)\text{\AA}$, $\beta = 113.50(4)^\circ$, $Z = 4$, $V = 2040.8(17)\text{\AA}^3$. The crystal structure was solved by direct methods and refined by full-matrix least-squares on F^2 to final values of $R1 = 0.0654$ and $wR2 = 0.1665$.

(Received September 24, 2008; Accepted February 9, 2009; Published on web May 10, 2009)

In biomaterial research, surface functionalization is of crucial importance.¹ Therefore, undertaking chemical modifications by grafting small active peptides, like the bio-adhesive arginine-glycine-aspartic acid (RGD) sequence on a material surface, may account for a better biocompatibility of the implant.² Organosilicon compounds may be used for this purpose *via* the commercially available 3-aminopropyl(triethoxy)silane (APTES). Thus, small RGD peptides have been introduced on the surface of APTES-silanized materials, resulting in a better adhesion of human osteoprogenitor cells.³ Assuming that cell attachment is RGD density-dependant⁴ and the rate of organosilicon grafting on the material is constant, a way to increase the final RGD density implies that (at least) a diaminosilane linker (or better, a polyaminosilane) should be used instead of the monofunctional APTES. From this perspective, *N,N*-dialkylamines may be considered as key intermediates in the synthesis of more complex polyaminosilyl linkers. Therefore, the synthesis of a basic set of such amines, possessing at first two amino end groups and a versatile allylic moiety, was undertaken. We expect from the two amino groups to bind twice as much oligopeptides, or any other molecule of interest, the allylic moiety acting like a potential anchoring group on the biomaterial surface by means of a hydrosilylation reaction with triethoxysilane. During the synthesis of *N*-allyl

dialkylamines, the already known 2,2'-[(allylimino)diethane-2,1-diyl]bisphthalimide⁵ was synthesized according to a new pathway. Thus, commercial diethanolamine was first alkylated with allyl bromide ($\text{Na}_2\text{CO}_3/\text{MeCN}$, 80°C) and the resulting allylic diol (80%) was reacted with thionyl chloride in dichloromethane to give *N,N*-bis(2-chloroethyl)allylamine

Table 1 Crystal and experimental data

Chemical formula: $\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_4$
Formula weight = 403.43
$T = 293(2)\text{K}$
Crystal system: monoclinic
Space group: $P2_1/n$
$a = 8.013(6)\text{\AA}$
$b = 32.731(7)\text{\AA}$
$c = 8.485(2)\text{\AA}$
$\beta = 113.50(4)^\circ$
$V = 2040.8(17)\text{\AA}^3$
$Z = 4$
$D_x = 1.313\text{ mg/m}^3$
Radiation: Cu $K\alpha$ ($\lambda = 1.54178\text{\AA}$)
$\mu = 0.748\text{ mm}^{-1}$
$F(0\ 0\ 0) = 848$
Crystal size = $0.15 \times 0.10 \times 0.10\text{ mm}$
No. of reflections collected = 3671
No. of independent reflexions = 3671
θ range for data collection: 2.70 to 69.96°
Data/Restraints/Parameters = 3676/0/272
Goodness-of-fit on $F^2 = 1.043$
R indices [$I > 2\sigma(I)$]: $R1 = 0.0654$, $wR2 = 0.1665$
R indices (all data): $R1 = 0.1257$, $wR2 = 0.2251$
$(\Delta/\sigma)_{\text{max}} = 0.000$
$(\Delta\rho)_{\text{max}} = 0.241\text{ e}\text{\AA}^{-3}$
$(\Delta\rho)_{\text{min}} = -0.242\text{ e}\text{\AA}^{-3}$
Measurement: Enraf-Nonius CAD4
Program system: SHELXL ⁷
Structure determination: SHELXS-97 ⁸
Refinement: Full matrix least squares on F^2
CCDC deposition number: 688311

Fig. 1 Chemical diagram of the title compound.

[†] To whom correspondence should be addressed.
E-mail: laurent.latxague@biophys.u-bordeaux2.fr

Table 2 Selected bond angles (°)

C(15)-N(14)-C(13)	112.2(3)
C(15)-N(14)-C(28)	113.1(3)
C(13)-N(14)-C(28)	110.7(3)

Table 3 Selected torsion angles (°)

C(9)-N(8)-C(12)-C(13)	88.0(5)
C(12)-C(13)-N(14)-C(15)	71.6(4)
C(13)-N(14)-C(15)-C(16)	-161.1(4)
N(14)-C(15)-C(16)-N(17)	174.1(3)
C(15)-C(16)-N(17)-C(18)	-84.1(5)

Table 4 Hydrogen-bonding geometry (Å, °)

C-H...Y	C-H	C-Y	C-H...Y
C(3)-H(3)...O(10,II)	0.93	3.357(6)	169.0
C(4)-H(4)...N(14,II)	0.93	3.519(6)	166.2
C(26)-H(26)...O(11,III)	0.93	3.424(6)	176.0

Symmetry codes: II ($x, y, 1+z$); III ($x-1/2, 1/2-y, z-1/2$).

(95%). To this compound (5.04 g, 27 mmol) in dry DMF (250 mL) was added potassium phthalimide (11.27 g, 61 mmol), and the mixture was heated under reflux in a nitrogen atmosphere for 24 h. After the usual work-up followed by column chromatography, the title compound was obtained in 63% yield (Fig. 1).

Single crystals suitable for X-ray structure analysis could be obtained by crystallization from isopropyl alcohol, which afforded white crystals. The crystal and structure-refinement data are summarized in Table 1. The hydrogen atoms were included as fixed contributions in idealized positions with isotropic displacement parameters 20% larger than those of the attached carbon atoms.

The crystallized molecule (Fig. 2) exhibits standard angles and bond distances.⁶ As expected, the central nitrogen atom N(14) imposes an overall tetrahedral shape with mean angles of 112° (Table 2). Dihedral angles (Table 3) indicate that each aminoethyl chain is almost perpendicular to the phthalimide rings. The torsion angles C(13)-N(14)-C(15)-C(16) and N(14)-C(15)-C(16)-N(17) close to 180°, indicate an open chain from C(13) to C(18). On the other hand, the C(12)-C(13)-N(14)-C(15) angle is 71.6(4)° revealing a different conformation for the second phthalimidomethyl moiety, nearly perpendicular to the remaining open chain. The phthalimido rings are twisted like the blades of a propeller with an interplanar angle of 74.5(1)°. Additionally, the molecules in the crystal packing, are linked *via* two C-H...O and one C-H...N intermolecular hydrogen bonds (Table 4).

Crystal X-ray analyses of several related molecules have already been reported in the literature. Among them, a great

Fig. 2 ORTEP structure of 2,2'-(allylimino)diethane-2,1-diyl]bis-phthalimide with atom labeling, showing 30% probability ellipsoids..

diversity of the spatial conformation can be observed. For instance, 2,2'-(formamidedi-1,2-ethanediyl)bis[1-*H*-isoindole-1,3-(2*H*)-dione], although apparently closer to our molecule, adopts a pyramidal shape, the two phthalimido rings facing each other.⁹ On the other hand, the presence of a third phthalimido ring, as in the *N,N,N'*-(nitrotriethylene)-trisphthalimide,⁶ doesn't exhibit a fully extended propeller shape as would be expected from our own results; instead, the third ring system is "folded back" on the remaining part of the molecule, a feature that is explained by an essentially electrostatic interaction between atoms of the pyrrolic moiety and the lone pair of electrons on the amine nitrogen of the neighboring aminoethyl chain. Finally, our phthalimide derivative may be favorably compared with the more flexible *N,N*-bis-(phthalimidopropyl)-*N*-propylamine,¹⁰ which exhibits a comparable shape and similar intermolecular hydrogen C-H...O bonds, but additionally, an intramolecular interaction favored by longer propyl chains.

References

1. D. G. Castner and B. D. Ratner, *Surf. Sci.*, **2002**, 500, 28.
2. H. J. Mathieu, *Surf. Interface Anal.*, **2001**, 32, 3.
3. M.-C. Porté-Durrieu, F. Guillemot, S. Pallu, C. Labrugère, B. Brouillaud, R. Bareille, J. Amédée, N. Barthe, M. Dard, and Ch. Baquey, *Biomaterials*, **2004**, 25, 4837.
4. S. P. Massia and J. Hubbell, *J. Cell Biol.*, **1991**, 114, 1089.
5. J. Sienkiewicz, *Pol. J. Chem.*, **1990**, 64, 77.
6. G. M. Sheldrick, SHELXL 97, Program for Crystal Structure Refinement, 1997, University of Göttingen, Germany.
7. G. M. Sheldrick, SHELXS 97, Program Crystal Structure Solution, 1997, University of Göttingen, Germany.
8. D. M. Y. Barrett, I. A. Kahwa and D. J. Williams, *Acta Crystallogr.*, **1996**, C52, 2069.
9. D. M. Y. Barrett, I. A. Kahwa, J. T. Mague, and G. L. McPherson, *J. Org. Chem.*, **1995**, 60, 5946.
10. B. Brycki, I. Kowalczyk, J. Werner, T. Borowiak, and I. Wolska, *J. Mol. Struct.*, **2006**, 791, 137.