Synthesis, Structure and Biological Activity of Dicarboxylate Phosphahetaines

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of Dicarboxylate Phosphabetaines

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Abstract

New stable dicarboxylate phosphabetaines were synthesized by the phosphorylation of a series of
unsaturated carboxylic acids. Interaction of 3-(diphenylphosphonio)propionic acid with
unsaturated monocarboxylic acids leads to formation of stable dicarboxylate phosphabetaines 1-7. The structure of the isolated compounds was determined by IR and NMR spectroscopy, X-ray
single crystal diffraction studies and elemental analysis. Their thermal stability was studied by
simultaneous thermogravimetry and differential scanning calorimetry. All of the synthesized
compounds were tested for their antibacterial and anti-Candida activity.
GRAPHICAL ABSTRACT

R = R₁= R² = H (1)
R = CH₃, R₁= R² = H (2)
R = R₁= H, R² = CH₃ (3)
R = Ph, R₁= R² = H (4)
R = 3-ClC₆H₄, R₁= R² = H (5)
R = 2-Thienyl, R₁= R² = H (6)
R = 3,5-di-ct-Bu-4-Oh-C₆H₄, R₁= R² = H (7)

Keywords

Dicarboxylate phosphobetaines; organophosphorus compounds; antimicrobial activity
INTRODUCTION

Organophosphorus compounds are one of the most important groups of modern antimicrobial agents, due to their high antifungal and antibacterial activity\(^1\text{-}^3\). Various types of organophosphorus compounds have been synthesized and their biological activities have been tested\(^4\text{-}^6\). Herewith we report on the synthesis, structure and biological activity of new stable dicarboxylate phosphabetaines.

RESULTS AND DISCUSSION

We previously described the syntheses of various phosphabetaines from tertiary phosphines and unsaturated mono- and dicarboxylic acids and the results of their structural assessment and reactivity studies\(^7\text{-}^{16}\).

\[
R^1R^2R^3P + R^4CH=\tilde{C}OH \xrightarrow{R^5} R^1R^2R^3P\tilde{C}CHCOO
\]

\(R^1 = R^2 = R^3 = \text{Ph, Bu, } C_6H_{11}^+; \)
\(R^4 = \text{H, CH}_3, \text{Ph, COOH}; \)
\(R^5 = \text{H, CH}_3\)

In the present work we synthesized new stable dicarboxylate phosphabetaines on the basis of unsaturated monocarboxylic acids. As a phosphorylating agent we used 3-(diphenyl-phosphonio)propanoic acid because it contains not only a tertiary phosphorus atom, but also a carboxylic group. Interaction of 3-(diphenylphosphonio)propionic acid with unsaturated monocarboxylic acids leads to formation of stable dicarboxylate phosphabetaines 1-7.
The reactions of 3-(diphenylphosphonio)propionic acid with unsaturated monocarboxylic acids in ethylacetate or acetonitrile are complete within 1 day and form the target betaines 1-7 as white crystals in 67-80\% yields. All of the synthesized compounds were characterized by $^{31}$P NMR and IR spectroscopy as well as by their melting point and elemental analysis (Tables 1 and 2). Their thermal stability was studied by simultaneous thermogravimetry and differential scanning calorimetry (Figure 1).

Thermogravimetry and differential scanning calorimetry of phosphabetaine 1 revealed a high thermal stability. The TG-DSC curve (Figure 1) shows a well-defined endothermic effect with its maximum at 236 °C, which is associated with a weight loss. The decomposition of phosphabetaine 1 involves water and CO$_2$ release. The absence of weight loss in the range 30-226 °C is indicative of a high thermal stability of this compound.

The structure of the dicarboxylate phosphabetaines obtained has been confirmed by physical methods, including X-ray single crystal diffraction for two compounds 2 and 5 (Figures 2 and 3). X-ray data show that these betaine structures are stabilized in the crystalline phase by intermolecular hydrogen bonding.
The biological activity of dicarboxylate phosphabetaaines has been studied (Table 3).

The antibacterial and antifungal activity of a series of dicarboxylate phosphabetaaines were investigated *in vitro* against several pathogenic representative Gram-negative bacteria (*Pseudomonas aeruginosa* ATCC 27853 and *Escherichia coli* ATCC 25922), Gram-positive bacteria (*Staphylococcus aureus* ATCC 29213 and *Bacillus cereus* ATCC 11778), and pathogenic fungi *Candida albicans* ATCC 885-653. The results are summarized in Table 3.

Cup-plate Agar method was used for evaluation of antibacterial activity. The nutrient agar medium was used. The medium with bacteria was poured into sterilized Petri dishes under aseptic conditions. Standard drugs were Chlorhexidine (50 µg/0.1 mL) and test compounds at concentration of 50 µg/0.1 mL. The solvent used was a mixture of water and isopropanol at different ratios (1:10). Plates were incubated at 37 °C for 24 hours. The antifungal activity was carried out by using cup-plate method using Sabouraud’s agar medium. The standard drug used was Griseofulvin (50 µg/0.1 mL) and the test compounds at concentration of 50 µg/0.1 mL by using of the mixture of the solvents ethanol and water at different ratios (1:10). After incubation the average of inhibition was recorded in mm.

The synthesized compounds exhibited moderate antimicrobial activities *in vitro*. Especially, compounds 6 and 7 showed the most potent antibacterial and antifungal activities.

**CONCLUSIONS**

New dicarboxylate phosphabetaaines were synthesized and their structures were determined by IR, NMR, TG-DSC and X-ray single crystal diffraction. The antimicrobial activity was measured. We have also reported the first crystal structures of these compounds.
EXPERIMENTAL

All chemicals purchased from Sigma-Aldrich were reagent grade and used without purification. All organic solvents were dried and freshly distilled before use.

The $^{31}$P NMR spectra ($\text{CDCl}_3$) were registrated with a Bruker Avance-400 instrument. The IR spectra were obtained on an IR Prestige-21 instrument in the range 400-3700 cm$^{-1}$ in mineral oil or in thin film between KBr plates. Thermal stability was studied using a Netzsch Jupiter STA 449C microthermoanalyzer for simultaneous thermogravimetric analysis and differential scanning calorimetry, coupled with a Netzsch QMS 403C Aeolos mass spectrometer; the samples were heated at a rate of 10 deg/min in an argon atmosphere. Microanalytical data were provided by the Microanalytical Laboratory, A.E. Arbuzov Institute of Organic and Physical Chemistry, Russian Academy of Sciences, Kazan.

General Procedure for the Synthesis of Dicarboxylate Phosphabetaines 1-7

A mixture of equimolar amounts of 3-((diphenylphosphonio)propionic acid and unsaturated monocarboxylic acids in dry ethyl acetate or acetonitrile was stirred at room temperature for 6 h, when the solid precipitated after the reduction of the volume of the solvent. The separated precipitate was filtered off, washed several times with diethyl ether and dried in vacuum over CaCl$_2$.

Single Crystal X-ray Diffraction Studies

A data set for a single crystal of compound 2 was collected with a Bruker AXS Kappa APEX Duo diffractometer with graphite-monochromated Mo-K$_\alpha$ radiation ($\lambda = 0.71073$ Å). Programs used: data collection APEX2$^{17}$, data reduction SAINT$^{18}$, absorption correction SADABS version 2.10$^{19}$, structure solution SHELXT$^{19}$, structure
refinement by full-matrix least-squares against \( F^2 \) using SHELXL\textsuperscript{20}. Hydrogen atoms were placed into calculated positions and refined as riding atoms, except the hydrogen of the carboxyl group which was located from a difference Fourier map and refined isotropically. The figures were generated using Mercury 3.1 programs\textsuperscript{21}. The hydrogen atom is disordered over two carboxyl groups and was refined with an occupancy ratio of 0.5.

Crystal data for \( \text{2} \): formula \( \text{C}_{19}\text{H}_{21}\text{O}_4\text{P} \), crystal size \( 0.27 \times 0.18 \times 0.12 \text{ mm}^3 \), \( M_r = 344.33 \), monoclinic, space group \( \text{C}2/c \), \( a = 16.323(4) \), \( b = 9.162(2) \), \( c = 23.005(6) \text{ Å} \), \( \beta = 91.327(6)^\circ \), \( V = 3439.5(15) \text{ Å}^3 \), \( Z = 8 \), \( \rho_c = 1.330 \text{ g/cm}^3 \), \( \mu = 0.179 \text{ mm}^{-1} \), \( T = 150(2) \text{ K} \), \( \theta \) range = 1.771\(^\circ\) to 30.526\(^\circ\), reflections collected 38918; independent: 5244 (\( R_{\text{int}} = 0.0637 \)) and 3631 observed reflections [\( I > 2 \sigma(I) \)], 227 refined parameters, \( R_1 = 0.0500 \), \( wR_2 = 0.0621 \) [\( I > 2\sigma(I) \)]; maximal residual electron density: 0.73/-0.59 e Å\(^{-3}\).

Crystallographic data for the structural analysis of compound \( \text{2} \) has been deposited at the Cambridge Crystallographic Data Center (CCDC number 1485737). Copies of the information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK (Fax: + 44-1223-336033; email: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk).

A data set for a single crystal of \( \text{C}_{24}\text{H}_{22}\text{ClO}_4\text{P} \) \( \text{5} \) were obtained with an automatic Bruker Smart APEX II CCD diffractometer [\( \lambda(\text{MoK}\alpha) = 0.71073 \text{ Å}, \omega\)-scanning]. Programs used: data collection APEX2\textsuperscript{17}, data reduction SAINT\textsuperscript{18}, structure solution SHELXS97\textsuperscript{19}, structure refinement by full-matrix least-squares against \( F^2 \) using SHELXL-97\textsuperscript{19}.

Crystal data for \( \text{C}_{24}\text{H}_{22}\text{ClO}_4\text{P} \), \( M = 440.84 \text{ g/mol} \), monoclinic, space group \( \text{P}2_1/n \) (No. 14), \( Z = 4 \), \( a = 10.024(6) \), \( b = 16.711(10) \), \( c = 16.279(10) \text{ Å} \), \( \beta = 104.850(6)^\circ \), \( V = 2636(3) \text{ Å}^3 \), \( \rho_{\text{calc}} = \)}
1.111 g·cm$^{-3}$, $\mu = 0.229$ mm$^{-1}$, multi-scan absorption correction was applied using SADABS$^{20}$, 21148 reflections collected ($\pm h, \pm k, \pm l$), $\theta$ range = 1.8$^0$ to 27.0$^0$, 5739 independent ($R_{int} = 0.094$) and 2589 observed reflections [$I \geq 2 \sigma(I)$], 279 refined parameters, $R = 0.1177$, $wR^2 = 0.3849$, max. residual electron density 0.86 (-0.71) e Å$^{-3}$. R-factors are high because of the weakly diffracting small crystal.

Crystallographic data for the structural analysis of compound 2 has been deposited at the Cambridge Crystallographic Data Center (CCDC number 1487431). Copies of the information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK (Fax: + 44-1223-336033; email: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk).

ACKNOWLEDGEMENTS

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REFERENCES


17. Bruker. APEX2 Software Suite for Crystallographic Programs, Bruker AXS, Inc., Madison, WI, USA, **2009**.


Table 1. Selected IR data, $^{31}$P NMR chemical shifts and melting points for the dicarboxylate phosphabetaines 1-7

<table>
<thead>
<tr>
<th></th>
<th>Compound</th>
<th>Selected IR data (cm$^{-1}$) $\nu$(COO') / $\nu$(COOH)</th>
<th>$\delta^{31}$P (ppm)</th>
<th>m.p. (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-((2-carboxyethyl)-diphenylphosphonio)propanoate</td>
<td>1680</td>
<td>28.4</td>
<td>221</td>
</tr>
<tr>
<td>2</td>
<td>3-((2-carboxyethyl)-diphenylphosphonio)butanoate</td>
<td>1630/1710</td>
<td>35.0</td>
<td>176</td>
</tr>
<tr>
<td>3</td>
<td>3-((2-carboxyethyl)-diphenylphosphonio)-2-methylpropanoate</td>
<td>1620/1680</td>
<td>27.1</td>
<td>79</td>
</tr>
<tr>
<td>4</td>
<td>3-((2-carboxyethyl)-diphenylphosphonio)-3-phenylpropanoate</td>
<td>1590/1700</td>
<td>31.2</td>
<td>193</td>
</tr>
<tr>
<td>5</td>
<td>3-((2-carboxyethyl)diphenylphosphonio)-3-(4-chlorophenyl)propanoate</td>
<td>1540/1620</td>
<td>30.3</td>
<td>157.3</td>
</tr>
<tr>
<td>6</td>
<td>3-((2-carboxyethyl)diphenylphosphonio)-3-(3,5-tert-butyl-4-hydroxyphenyl)propanoate</td>
<td>1550/1680</td>
<td>32.4</td>
<td>196.7</td>
</tr>
<tr>
<td>7</td>
<td>3-((2-carboxyethyl)diphenylphosphonio)-3-(thiophen-2-yl)propanoate</td>
<td>1660/1700</td>
<td>35.0</td>
<td>182.4</td>
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</table>
Table 2. Physical data for the dicarboxylate phosphabetaines 1-7

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mw (g/mol)</th>
<th>Yield (%)</th>
<th>Empirical formula</th>
<th>Found (Calcd) (%)</th>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>1</td>
<td>330</td>
<td>81</td>
<td>C_{18}H_{19}PO_4</td>
<td>66.27 (65.45)</td>
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<tr>
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<td>344</td>
<td>74</td>
<td>C_{19}H_{21}PO_4</td>
<td>65.43 (65.30)</td>
</tr>
<tr>
<td>3</td>
<td>344</td>
<td>67</td>
<td>C_{19}H_{21}PO_4</td>
<td>69.48 (69.70)</td>
</tr>
<tr>
<td>4</td>
<td>406</td>
<td>76</td>
<td>C_{24}H_{23}PO_4</td>
<td>70.10 (70.40)</td>
</tr>
<tr>
<td>5</td>
<td>440.5</td>
<td>65</td>
<td>C_{24}H_{22}PO_4Cl</td>
<td>64.50 (65.38)</td>
</tr>
<tr>
<td>6</td>
<td>412</td>
<td>70</td>
<td>C_{22}H_{21}PO_4S</td>
<td>63.96 (64.88)</td>
</tr>
<tr>
<td>7</td>
<td>534</td>
<td>49</td>
<td>C_{32}H_{39}PO_5</td>
<td>71.80 (71.91)</td>
</tr>
</tbody>
</table>
Table 3. Antifungal and bactericidal activity of dicarboxylate phosphabetaines 6 and 7

(growth inhibition zone, mm) of compounds (c = 50 µg/0.1 mL)

<table>
<thead>
<tr>
<th>Compound</th>
<th>E. coli</th>
<th>Bacillus cereus</th>
<th>Ps. aeruginosa</th>
<th>S. aureus</th>
<th>Candida albicans</th>
</tr>
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<tbody>
<tr>
<td>6</td>
<td>12</td>
<td>9</td>
<td>7</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>6</td>
<td>6</td>
<td>11</td>
<td>15</td>
</tr>
<tr>
<td>Chlorohexidine</td>
<td>11</td>
<td>8</td>
<td>9</td>
<td>17</td>
<td>15</td>
</tr>
</tbody>
</table>
Figure 1. TG/DSC analysis data phosphabetaine 1
Figure 2. Molecular structure of 2,3-((1-carboxypropan-2-

\text{yl})diphenylphosphonio)propanoate in the crystal
Figure 3. Molecular structure of 5,3-((2-carboxy-1-(4-chlorophenyl)ethyl)diphenylphosphonio)propanoate in the crystal