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MCR V:[1] the Seven-Component Reaction

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Dedicated to Professor Lennart Eberson on the occasion of his 65th birthday

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The following paper describes the reaction of seven different starting materials for the formation of one product. This reaction is a union of two multicomponent reactions (MCR): the Asinger and the Ugi reaction. The number of possible, highly diverse products of unions of such MCRs is immense.

By definition multicomponent reactions (MCRs) are reactions of more than two starting materials that form a product which contains the essential parts of all of the starting materials.[2] Historically, the Strecker reaction in 1850 was the first MCR described.[3] Nowadays many MCRs are known and routinely used in organic syntheses. There are three basic types of MCR that can be distinguished.

In the MCRs of type I all starting materials, intermediates and final products equilibrate and their reactions are reversible. The classical 3CRs are generally α-aminoalkylations, as realized by Hellmann and Opitz.[4]

In the MCRs of type II all, or at least part, of the starting materials and intermediates equilibrate, but the final product-forming step proceeds practically irreversibly.[5] Most of such MCRs are either α-aminoalkylations, whose intermediate products react with bifunctional materials and irreversibly form heterocyclic products, or MCRs of isocyanides.

In the few MCRs of type III the products are formed by sequences of practically irreversible chemical reactions. Some phosphorus-related MCRs correspond to sequences of irreversible reactions.[1]

For a long time MCRs have been considered as exotic variants of organic reactions. In recent years they have become very popular in the context of combinatorial chemistry.[6] It can be shown that they are extremely useful in producing a variety of highly diverse libraries of small drug-like organic compounds.[7] Furthermore with only a handful of starting materials, myriad compounds can be generated.[8]

Apart from their usefulness in preparative chemistry, MCRs can also be considered as major players in prebiotic chemistry. It has been proposed that, e.g., adenine, a purine base of DNA and RNA, was formed under prebiotic conditions by the reaction of five hydrogen cyanide molecules.[9] It is interesting to compare the biochemical formation of IMP, the precursor of adenosine 5′-monophosphate and guanosine 5′-monophosphate (Fig. 1) with the prebiotic synthesis of adenine. In the latter all five HCN molecules react in different ways to give this product, whereas the biochemical formation of IMP corresponds to an MCR of type III as defined above. Each step is driven to the right-hand side through enzymatic reactions.

Certainly complex molecules have been formed from simple starting materials under prebiotic conditions. The fact that isocyanides can be synthesised under prebiotic conditions and that they comprise an important class of natural products[10] points to the possibility that isocyanide-driven MCRs may have played an important role in prebiotic times.

One of the most general MCRs is the four-component reaction also called Ugi reaction or U-4CR.[5] Oxo compounds (aldehydes or ketones), isocyanides, amines and acid components react and form a variety of different scaffolds, depending mainly on the class of acid component used, e.g., hydroazoic acid as the acid component reacts smoothly to form α-aminotetrazoles. Similarly 13 different types of acid component can be transformed during the U-4CR to give a wide variety of different products.[11] Each of them can easily be diversified by varying the other components.

During our studies on isocyanide chemistry we asked ourselves how many different starting materials can be combined to give a product. We found that at least seven different starting materials can react together.[12] In this communication we report some further examples of the 7-CR going beyond the thiazoline scaffold.

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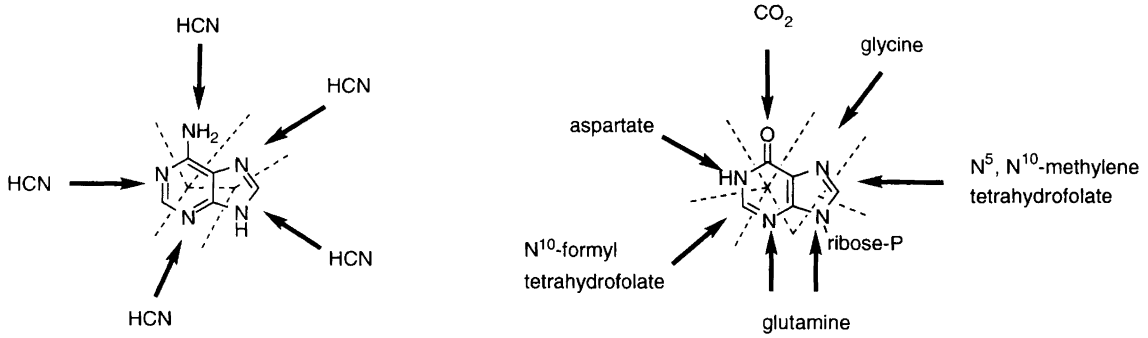


Fig. 1. Comparison of the synthesis of adenine from five hydrogen cyanide molecules under prebiotic conditions with the formation of IMP, the precursor of ATP and GTP under biochemical conditions.

The 7-CR starts with the Asinger four-component reaction (A-4CR) followed by the U-4CR (Fig. 2). During the A-4CR, sodium hydrogensulfide reacts with an α- or β-bromo aldehyde or ketone forming an α- or β-mercapto aldehyde or ketone. These intermediates react with ammonia and a second carbonyl component to form a thiazolidine or thiazine derivative. The Asinger reaction corresponds to a very general reaction with a great variety of starting materials and has good compatibility with different functional groups. Recently it has been shown that α-hydroxy[14] as well as β-hydroxy aldehydes[15] react equally well in an A-MCR to form oxazoles and oxazines, respectively. Therefore the A-MCR is a powerful reaction to produce five- and six-membered 2,5-dihydro-1,3-thiazoles, 2,5-dihydro-1,3-oxazoles, 5,6-dihydro-*2H*-1,3-oxazines or 5,6-dihydro-*2H*-1,3-thiazines. The imine group of the Asinger heterocycles produces the starting material for the following U-4CR. In order to increase the number of starting materials we composed an acid component in the U-4CR. Carbon dioxide and an alcohol forms carbonic acid monoesters which are known to react like acids in the U-4CR.[16] The carbonic acid monoesters react with the Asinger imine and the isocyanide to form the unstable α-adduct. This

Asinger ∪ Ugi ≡ 7 component reaction

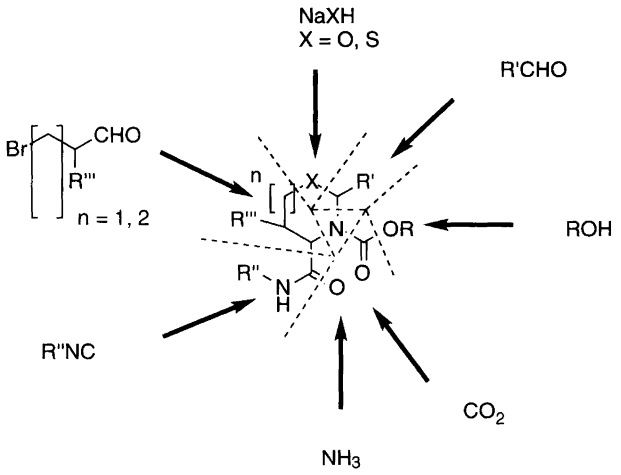
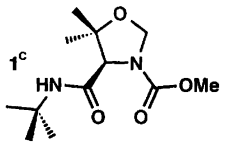
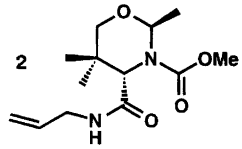
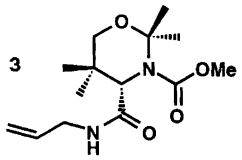
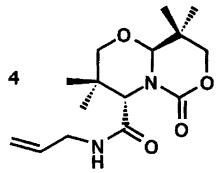
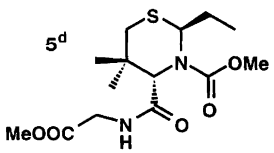


Fig. 2. Sketch of the seven-component reaction showing the origination of the product atoms relative to the starting materials. Note that during the 7-CR a double bond of carbon dioxide is broken.

Table 1.

7 CR product[a]	Yield (%)[b]
1[c] 	8
2 	19
3 	21
4 	40
5[d] 	30

[a]All compounds are racemic. All compounds were characterized by ^1H NMR, ^{13}C NMR, GC–MS and TLC. [b]Yields after chromatographic work-up. [c]Paraformaldehyde as the carbonyl component. [d]3-Chloro-1,1-dimethylpropionaldehyde was used as a β-halogeno aldehyde. It can be conveniently prepared by PCC-oxidation of commercially available 3-chloro-2,2-dimethylpropanol.

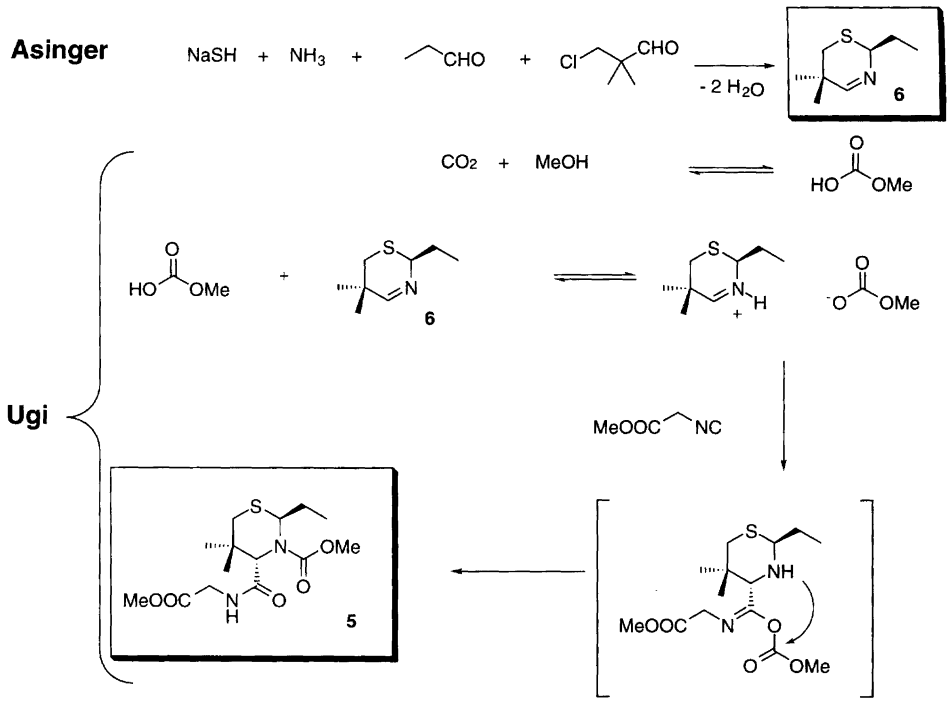


Fig. 3. Mechanism of the seven-component reaction examplified by the formation of **5**.

intermediate rearranges into the stable seven component product.

In Table 1 several different products of the 7-CR are depicted. The intermediate heterocycle **6** of A-MCR can be isolated in 50% yield as a colourless liquid. It is noteworthy that this reaction seems to be an S_N2 reaction of a neopentylic system.

In order to obtain the six-membered oxazine derivatives **2**, **3** and **4**, the bifunctional hydroxy carbonyl compound, β-hydroxypivalinaldehyde was used as a component. During the formation of the monocycles **2** and **3**, bicyclic **4** was always observed as a by-product. The major product is **4** if no other oxo component is used. We have been able to grow crystals for X-ray structure analysis of the intermediate Asinger heterocycle as well as the final bicyclic 7-CR product **4**. In contrast with the five-membered heterocycles where the diastereoselectivities are not high, in the case of the six-membered product only one diastereomer was observed (Fig. 4). NOESY experiments and the X-ray structure of **4** show that the single diastereomer is the thermodynamically disfavoured 2,4-trans isomer.

The major competing side-reaction in all cases of the 7-CR is the 5-CR of the carbonyl component, ammonia, isocyanide, carbondioxide and the alcohol (Fig. 5). This observation indicates that the incomplete formation of the Asinger intermediate accounts for the unsatisfactory yield of the 7-CR.

Despite the low and unsatisfactory yields of the 7-CR the idea of combining several MCRs to give new MCRs with higher numbers of starting material will be a very fruitful way to develop the diversity of pharmaceutical research. Preliminary experiments have shown that the yields of the 7-CR can be enhanced by performing the reaction on a resin.[17]

In conclusion, several new heterocyclic scaffolds prepared by 7-CR are described. The general principle behind these might be very useful for practical applications in combinatorial chemistry as well as for a better theoretical understanding of prebiotic chemistry.

Experimental

General procedure for seven component product **1**, **5**. A saturated methanolic solution of ammonia (10 ml), NaOH or NaSH (10 mmol), oxo compound and α- or β-halogen aldehyde (10 mmol) were stirred at 0 °C for 30 min. Isocyanide (10 mmol) was added to this solution. The resulting solution was stirred with CO_2 (40 bar) in a pressure vessel for 4 days. After chromatographic (ethyl acetate–hexane; silica gel) work-up, the products were obtained in the yields listed in Table 1.

General procedure for seven component product **2**, **3**. A saturated methanolic solution of ammonia (10 ml), oxo compound (10 mmol) and β-hydroxypivalinaldehyde (10 mmol) were stirred at 0 °C for 30 min. Isocyanide (10 mmol) was added to this solution. The resulting solution was stirred with CO_2 (40 bar) in a pressure vessel for 4 days. After chromatographic work-up (ethylacetate–hexane; silica gel) the products were obtained in the yields listed in Table 1.

General procedure for seven-component product **4**. A saturated methanolic solution of ammonia (10 ml) and

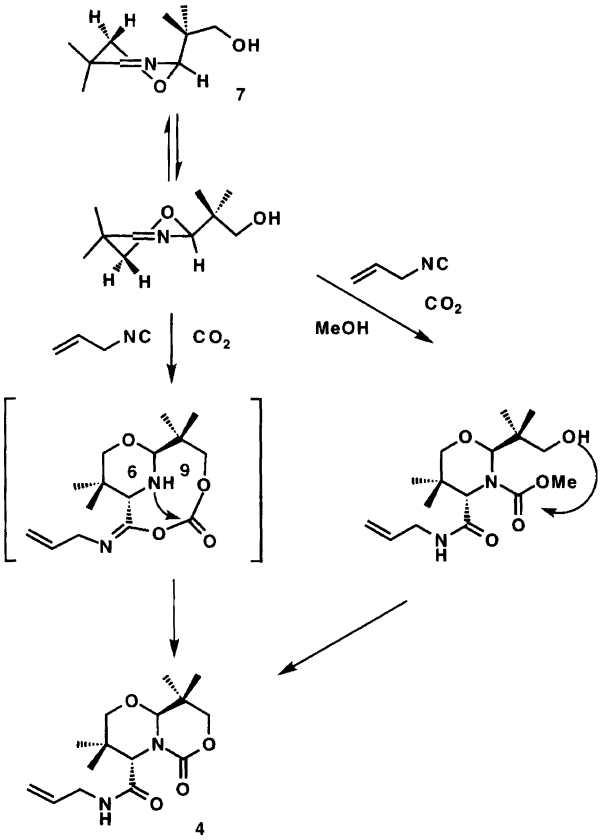


Fig. 4. Formation of the Asinger intermediate **7** and the bicyclic 7-CR product **4**. Temperature-dependent NMR experiments as well as the examination of the diastereoselctivity of the addition of nucleophiles to the imine double bond show that the Asinger heterocycle **7** exists predominantly in one conformation in solution. The same conformation exists in the crystal. In this conformation the steric repulsion between the R group in position 2 and the proton in position 6 is minimized. The addition of the conformationally rigid iminium ion and the carbonic acid monoester to the isocyanide followed by the irreversible rearrangement leads to only one diasteromer **4**. Note in the α-adduct a nine-membered ring is smoothly formed, which collapses to a six-membered ring in the final product. An alternative mechanism could be as shown on the right-hand branch. Asinger compound **7** undergoes a reaction between isocyanide, methanol and carbon dioxide without the involvement of the hydroxy group of the side-chain. After the 7-CR, the side-chain hydroxy group displaces methanol, forming bicyclic **4**. This would involve five- and six-membered rings only. Since the Ugi reaction resulting in β-lactams and cyclic hexapeptides proceeds through uncommon ring sizes of 7 and 21, respectively, none of these mechanisms can be excluded.

β-hydroxypivalinaldehyde (20 mmol) were stirred at 0 °C for 30 min. Allyl isocyanide (10 mmol) was added to this solution. The resulting solution was stirred with CO_2 (40 bar) in a pressure vessel for 4 days. After chromatographic work-up (ethylacetate–hexane; silica gel) the product was obtained in the yields listed in Table 1.

Analytical data for 5,5,9,9-tetramethyl-10-prop-2-enylcarbamoyl-3,7-dioxa-1-azabicyclo[440]decane **4**: $C_{15}H_{24}N_2O_4 = 296.37$ g mol^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$, 22 °C, Me_3Si): δ 0.95 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3), 1.08 (s, 3 H, CH_3), 1.14 (s, 3 H, CH_3), 3.38 (d, 1 H, $^2J = 10.86$ Hz), 3.83, (m, 2 H, 2 × CH), 3.90 (s, 2 H, CH_2), 4.15 (d, 1 H, $^2J = 11{,}06$ Hz, CH), 4.53 (s, 1 H, CH), 5.22 (s, 1 H, CH), 5.73–5.84 (m, 1 H, CH_2), 7.08 (t, 1 H, $^3J = 5.01$ Hz, NH). ^{13}C NMR (90 MHz): δ 17.4, 21.4, 25.6, 32.2, 32.7, 41.3, 61.9, 72.5, 86.7, 116.2, 133.5, 153.5, 169.9. IR (KBr, cm^{-1}): 1275 (m), 1430 (m), 1490 (m), 1552 (m, br), 1662br (s), 2970 (m), 3330br (m). M.p. 143 °C. GC–MS (CI, *m/z*): 297 MH^+, R_f (ethylacetate–hexane): 0.46.

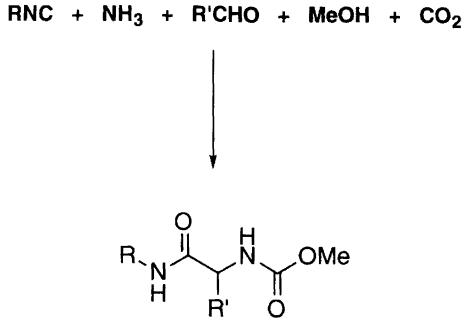


Fig. 5. The major side reaction of the 7-CR is a 5-CR.

Procedure for Asinger heterocycle **6**. Ammonia was bubbled over 2 h through a solution of 2 g NaSH, 4.2 g (35 mmol) 3-chloro-2,2-dimethylpropanal and 2.53 ml (35 mmol) propionaldehyde in methanol at 0 °C. After evaporation of the solvent, the residual oil was distilled at 14 Torr. The fraction boiling at 86–95 °C yielded 2.9 g (53%) of the yellow oil **6**. $C_8H_{15}NS = 157.28$ g mol^{-1}. ^{1}H NMR (360 MHz, $CDCl_3$, 22 °C, Me_3Si): δ 0.93 (dt, 3 H, $^3J = 7.4$ Hz, $^3J = 7.4$ Hz), 1.14 (s, 3 H), 1.20 (s, 3 H), 1.72–1.79 (m, 1 H), 1.88–1.94 (m, 1 H), 2.54 (dd, 1 H, $^4J = 1.5$ Hz, $^2J = 13.5$ Hz), 4.45–4.49 (m, 1 H), 7.45 (m, 1 H). ^{13}C NMR (90 MHz): δ 10.6, 25.3, 26.3, 30.0, 32.3, 35.5, 61.9, 168.2. IR (film, cm^{-1}): 1656, 2885, 2930, 2960. GC–MS (CI mode) *m/z*: MH^+ 158.

The analytical data for **7** are described in Ref. 13.

Crystallographic data collection and structure determination (Figs. 6 and 7). A single crystal of **7** was selected and mounted on an Enraf–Nonius CAD4 four-circle

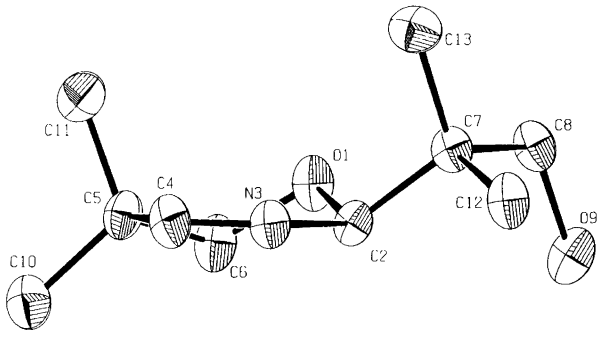


Fig. 6. ORTEP plot of molecule **7**.

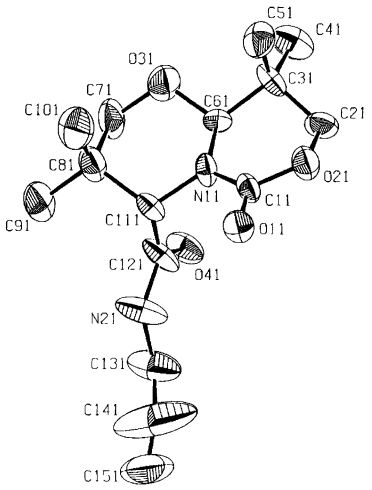


Fig. 7. ORTEP plot of molecule **4**.

diffractometer. Accurate cell dimensions were determined from 25 automatically centered high angle reflections ($31<2\theta<40°$) and refined by a least-squares routine.[18] Intensity data collection was carried out at 163 K using graphite monochromatized Mo Kα radiation and operating in the θ/2θ scan mode. 4281 intensity data were recorded, corrected for LP-effects but no correction for decay and absorption was applied. The atomic scattering factors and anomalous dispersion factors were taken from *International Tables*.[19] The structure was solved by a combination of direct methods, difference Fourier calculations and full-matrix least-squares analysis using the programs SIR-92, SHELXL-93, and STRUX-V.[20] After refinement of positional and anisotropic thermal parameters, the hydrogen positions were located and refined isotropically. Refinements were carried out by minimizing $\Sigma w(F_o^2-F_c^2)^2$ and stopped at shift/err <0.001, $wR_2=0.104$, and $R_1=0.045$. The final difference Fourier map showed no percularities. Crystallographic details are listed in Table 2. Final atomic parameters are given in Table 3.

A single crystal of **4** was selected and mounted on a STOE & Co. imaging plate diffraction system (IPDS). Accurate cell dimensions were determined from a maximum of 2000 reflections selected from 180 images and refined by a least-squares routine.[21] Intensity data collection was carried out at 213 K using graphite monochromatized Mo Kα radiation using rotation mode.[22] 14828 intensity data were recorded, corrected for LP effects, but no correction for decay and absorption was applied. The atomic scattering factors and anomalous dispersion factors were taken from Ref. 19. The structure was solved by a combination of direct methods, difference Fourier calculations and full-matrix least-squares analysis using the programs SHELXS-86, SDP, and STRUX-V. After refinement of positional and anisotropic thermal parameters the hydrogen positions were calculated in ideal positions ($d_{C-H}=0.95$ Å, $B_{C-H}=1.3B_C$) except for those bonded to the disordered allyl group C132 to

Table 2. Crystal data, intensity collection and structure refinement for $C_{10}H_{19}NO_2$ **7** and $C_{15}H_{24}N_2O_4\cdot CHCl_3$ **4**.

	7	**4**
Chemical formula	$C_{10}H_{19}NO_2$	$C_{16}H_{25}Cl_3N_2O_4$
M_w	185.27	415.75
Color	Colorless	Colorless
Crystal size (mm)	1.02 × 0.38 × 0.36	0.39 × 0.39 × 0.34
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/c$
a/Å	6.143(1)	20.082(7)
b/Å	17.592(2)	10.290(2)
c/Å	9.974(2)	21.451(8)
β/°	97.49(1)	114.10(2)
V/Å^3	1068.7(3)	4046(2)
Z	4	8
T/K	163	213
ρ_{calcd}/g cm^{-3}	1.151	1.365
μ/cm^{-1}	0.8	4.7
F_{000}	408	1744
λ/Å	0.71073	0.71073
Scan range/°	$1\leqslant\theta\leqslant25$	$3\leqslant\theta\leqslant25$
Scan width/°	$\Delta\theta=1.50+0.25\tan\theta$	Imaging plate
Data collected (h, k, l)	+7, ±20, ±11	±22, ±11, ±24
No. of rflns. collected	4281	14828
No. of indep. rflns.	1884	5973
No. of obsd. rflns. (N)	1884 (all data)	3869 [$I>2\sigma(I)$]
No. of variables (M)	195	450
R_{int}	0.026	0.053
R_1[a]	0.045	0.127
wR_2[b]	0.104	
$R\omega$[c]		0.036
GOF[d]	1.024	Not available
Extinction correction[e]	ε refined to ε=0.014(4)	
$\Delta\rho_{max/min}$/e Å^{-3}	+0.27, −0.22	+0.73, −0.69

[a] $R_1=(\||F_o|-|F_c\||)/\Sigma|F_o|$. [b] $wR_2=[\Sigma w(F_o^2-F_c^2)^2/\Sigma w(F_o^2)^2]^{1/2}$. [c] $R\omega=[\Sigma\omega(|F_o|-|F_c|)^2/\Sigma\omega F_o^2]^{1/2}$. [d] $GOF=[\Sigma w(F_o^2-F_c^2)^2/(N-M)]^{1/2}$. w: SHELX-93 weights. ω: SDP weights. [e] $F_c(corr.)=kF_c[1+0.001\times\varepsilon F_c^2\lambda^3/\sin(2\theta)]^{-1/4}$.

Table 3. Final coordinates and equivalent isotropic thermal parameters of the non-hydrogen atoms for **7**.

Atom	x	y	z	U_{eq}/Å^{2a}
O(1)	0.09381(13)	0.35802(5)	0.10665(9)	0.0299(3)
O(9)	−0.17174(15)	0.50472(5)	0.20141(10)	0.0338(3)
N(3)	0.4432(2)	0.42127(6)	0.11306(10)	0.0261(3)
C(2)	0.2112(2)	0.42730(7)	0.13237(12)	0.0230(4)
C(4)	0.5029(2)	0.36634(8)	0.04443(13)	0.0304(4)
C(5)	0.3606(2)	0.30338(7)	−0.02275(13)	0.0285(4)
C(6)	0.1233(2)	0.32845(8)	−0.02257(15)	0.0324(4)
C(7)	0.1899(2)	0.45236(7)	0.27741(12)	0.0251(4)
C(8)	−0.0549(2)	0.45375(8)	0.29493(13)	0.0291(4)
C(10)	0.4108(3)	0.29309(9)	−0.16775(15)	0.0379(5)
C(11)	0.4068(3)	0.23010(9)	0.0579(2)	0.0423(5)
C(12)	0.2846(2)	0.53238(8)	0.30111(15)	0.0315(4)
C(13)	0.3081(2)	0.39684(9)	0.38001(14)	0.0357(5)

[a] U_{eq} is defined as 1/3 of the trace of the orthogonalized U_{ij} tensor.

Table 4. Final coordinates and equivalent isotropic thermal parameters of the non-hydrogen atoms for **4**.

Atom	*x*	*y*	*z*	B_{eq}/Å$^{2\,a}$
C(1)	0.16770(19)	0.5058(7)	0.4341(3)	4.5(2)
Cl(1)	0.18034(10)	0.3504(3)	0.41305(12)	10.18(8)
Cl(2)	0.08829(5)	0.5227(3)	0.44200(10)	9.98(9)
Cl(3)	0.24024(6)	0.5548(3)	0.50733(12)	10.25(9)
C(2)	0.32327(19)	0.4798(7)	0.0651(3)	4.6(2)
Cl(4)	0.33067(11)	0.6348(3)	0.09636(13)	10.33(9)
Cl(5)	0.25010(6)	0.4645(3)	−0.01110(12)	9.41(8)
Cl(6)	0.40282(6)	0.4444(4)	0.05672(10)	13.3(1)
N(11)	0.40788(12)	0.5652(5)	0.2967(2)	3.0(1)
C(11)	0.38932(15)	0.4768(6)	0.2480(3)	3.1(1)
O(11)	0.32855(11)	0.4255(4)	0.22252(19)	3.8(1)
O(21)	0.43828(10)	0.4350(4)	0.22422(18)	4.0(1)
C(21)	0.50626(17)	0.5127(6)	0.2447(3)	4.1(2)
C(31)	0.53849(15)	0.5353(6)	0.3194(3)	3.6(2)
C(41)	0.60919(17)	0.6152(7)	0.3359(3)	5.2(2)
C(51)	0.55296(19)	0.4130(7)	0.3577(3)	4.4(2)
C(61)	0.48288(15)	0.6239(7)	0.3295(3)	3.2(2)
O(31)	0.50193(11)	0.6345(5)	0.40056(19)	5.1(1)
C(71)	0.45174(19)	0.7179(8)	0.4130(3)	5.6(2)
C(81)	0.37618(16)	0.6529(7)	0.3892(3)	4.2(2)
C(91)	0.3254(2)	0.7469(8)	0.4012(3)	6.1(2)
C(101)	0.3827(2)	0.5256(9)	0.4269(3)	6.3(2)
C(111)	0.34884(14)	0.6239(6)	0.3100(3)	3.1(2)
C(121)	0.32133(16)	0.7392(6)	0.2659(3)	4.3(2)
O(41)	0.36008(10)	0.8247(5)	0.25615(19)	4.7(1)
N(21)	0.24792(16)	0.7469(6)	0.2353(3)	5.8(2)
C(131)	0.21067(19)	0.8457(8)	0.1836(3)	6.9(2)
C(141)	0.1432(3)	0.8194(12)	0.1386(5)	14.9(4)
C(151)	0.0833(2)	0.8279(12)	0.1054(4)	10.7(4)
N(12)	0.09299(12)	0.4098(5)	0.2061(2)	3.1(1)
C(12)	0.11024(14)	0.4993(6)	0.2531(3)	2.9(1)
O(12)	0.16990(11)	0.5530(4)	0.2810(2)	4.3(1)
O(22)	0.06000(10)	0.5407(4)	0.27511(18)	4.1(1)
C(22)	−0.00895(16)	0.4665(6)	0.2523(3)	3.8(2)
C(32)	−0.03801(16)	0.4361(6)	0.1786(3)	3.1(2)
C(42)	−0.10704(16)	0.3580(7)	0.1617(3)	4.9(2)
C(52)	−0.05215(16)	0.5569(8)	0.1363(3)	5.2(2)
C(62)	0.01988(15)	0.3460(7)	0.1711(3)	3.9(2)
O(32)	0.00346(11)	0.3290(5)	0.10260(18)	5.7(1)
C(72)	0.05522(18)	0.2436(8)	0.0932(3)	6.9(2)
C(82)	0.12962(18)	0.3136(7)	0.1184(3)	4.3(2)
C(92)	0.1867(2)	0.2183(9)	0.1113(3)	6.5(2)
C(102)	0.1212(2)	0.4367(10)	0.0791(3)	6.9(2)
C(112)	0.15285(15)	0.3477(6)	0.1944(3)	3.0(1)
C(122)	0.18309(16)	0.2354(6)	0.2432(3)	4.1(2)
O(42)	0.14393(10)	0.1540(5)	0.2532(2)	5.7(1)
N(22)	0.25699(15)	0.2302(5)	0.2758(3)	5.2(2)
C(132)	0.2948(2)	0.1307(8)	0.3263(4)	8.1(3)
C(142)	0.3620(4)	0.1702(16)	0.3809(7)	5.7(3)*
C(143)	0.3658(3)	0.1205(14)	0.3410(6)	4.0(2)*
C(152)	0.4248(2)	0.1382(9)	0.3924(4)	7.6(3)

[a]Starred atoms were refined isotropically. B_{eq} is defined as $(4/3)*[a^2*\beta(1,1)+b^2*\beta(2,2)+c^2*\beta(3,3)+ac(\cos\beta)*\beta(1,3)]$.

C152, which were included in the structure factor calculation but not refined. Refinements were carried out by minimizing $\Sigma w(|F_o|-|F_c|)^2$ and stopped at shift/err <0.001, $R_w=0.036$, and $R_1=0.127$. In the final difference Fourier map the largest peaks $+0.73$ and -0.69 e Å^{-3} were located around the solvent molecules $CHCl_3$.

Crystallographic details are listed in Table 2. Final atomic parameters are given in Table 4.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC-100414. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44 (0)1223 336033; e-mail: teched@chemcrys.cam.ac.uk].

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