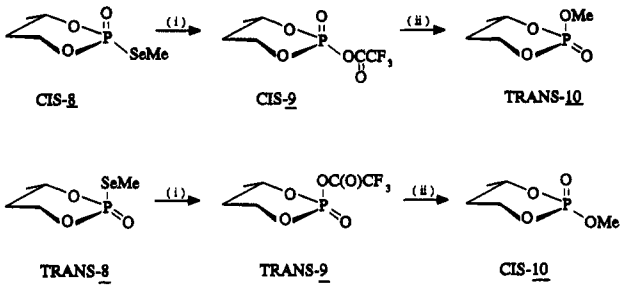
Scheme I[a]



[a] Reaction conditions: (i) mercuric trifluoroacetate (1 equiv), MeCN, rt, t = 5 min; (ii) methanol (4–10 equiv), rt, t = 5 min.

Co-injection of **5** and a genuine sample of **5**, prepared independently, additionally confirmed its identity (GC HP-1, t_R 8.7 min).

3. Synthesis of *O,O*-Diethyl *O*-Trifluoroacetyl Phosphate (6). Into a stirred solution of **2** (0.245 g, 1 mmol) in acetonitrile (5 mL) was added dropwise a solution of **1** (0.426 g, 1 mmol) in acetonitrile (1 mL) at room temperature. After 5 min dry hexane (5 mL) was poured into the reaction mixture, and a precipitate was filtered off under nitrogen. Solvents were carefully removed under reduced pressure. A residue was distilled under reduced pressure. The fraction boiling at 30–35 °C (0.1 mmHg) was collected and identified as **6** (^{31}P NMR δ −10.29 ppm C_6C_6/MeCN) [lit.[20] bp 25 °C (0.01 mmHg); ^{31}P NMR δ −9.6 ppm]: MS m/z 250 ($M^{\bullet+}$); yield 0.2 g (80%).

The reaction of **6** with an excess of ethanol in MeCN yielded **3** (^{31}P NMR δ −0.81 ppm), whereas aniline provided anilinium *O,O*-diethyl phosphate (^{31}P NMR δ −0.23 ppm) and trifluoroacetanilide, quantatively: MS m/z 189 ($M^{\bullet+}$) (100), 77 $(C_6H_5)^+$, 120 $(C_6H_5NHCO)^{\bullet+}$.

4. Reaction of *O,Se*-Dimethyl *N*-Phenylphosphoramidoselenoate (4) with $Hg(OCOCF_3)_2$. Into a solution of **4** (0.027 g, 0.1 mmol) in dry acetonitrile (0.5 mL) cooled to −40 °C was added a solution of **1** (0.043 g, 0.1 mmol) in acetonitrile (0.1 mL). The white precipitate of $MeSeHgOCOCF_3$ appeared instantly. The NMR spectrum of the filtrate indicated the formation of a single product **7** (^{31}P NMR δ −2.7 ppm). The spectrum recorded after addition of dry methanol (0.05 mL) confirmed a formation of **5**, as compared with a genuine sample (^{31}P NMR δ 5.54 ppm): MS m/z 201 ($M^{\bullet+}$), 169 (M − MeOH)$^{\bullet+}$.

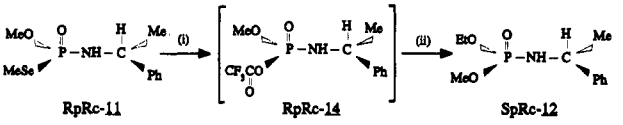
5. Synthesis of 2-(Trifluoroacetoxy)-2-oxo-4-methyl-1,3,2-dioxaphosphorinane (*cis*-9). Into a stirred solution of *cis*-**8** (0.230 g, 1 mmol) in dry acetonitrile (5 mL) was added a solution of **1** (0.426 g, 1 mmol) in dry acetonitrile in one portion at room temperature. After 5 min dry hexane (10 mL) was poured into the reaction mixture and a white precipitate was filtered off. Solvents were removed under reduced pressure, and the oily residue was distilled. The fraction distilling at 50–55 °C (0.1 mmHg) was collected and identified as *cis*-**9** (^{31}P NMR δ −12 ppm/C_6D_6): MS m/z 249 ($M^{\bullet+}$), 54 (100) $(C_4H_6)^{\bullet+}$, 55 (C_4H_7), 99 $(PO_4H_4)^+$, 136 (M − $CF_3COOH)^{\bullet+}$; yield 0.160 g (65%).

6. Methanolysis of 2-(Methylseleno)-2-oxo-4-methyl-1,3,2-dioxaphosphorinane (*cis*-8 and *trans*-8). Into a solution of *cis*-**8** (0.046 g, 0.2 mmol) and dry methanol (0.04 mL) was added a solution of **1** (0.08 g, 0.19 mmol) in dry acetonitrile (0.1 mL). After filtering off the precipitate, the reaction mixture was concentrated and analyzed. Beside the main product *trans*-**10**, unreacted *cis*-**8** was present in reaction mixture (10%).

trans-**10**: ^{31}P NMR δ −6.5 ppm [lit.[3] δ −6.4 ppm]; MS[21] m/z 166 ($M^{\bullet+}$), 54 (100) $(C_4H_6)^{\bullet+}$, 113 (M − $C_4H_5)^+$, 139 (M − $C_2H_3)^+$. In an analogous experiment with *trans*-**8** used as a substrate, the product *cis*-**10** was formed almost exclusively (^{31}P NMR δ −5.2 ppm; lit.[3] δ −5.1 ppm) with traces of pyrophosphates (δ −18.87 ppm, −19.87 ppm).

cis-**10**: MS m/z 166 ($M^{\bullet+}$), 113 (100) (M − $C_4H_5)^{\bullet+}$, 139 (M − $C_2H_3)^+$. Compound $MeSeHgOCOCF_3$ precipitating during the reaction course, formed a hygroscopic white powder. It was washed with dry diethyl ether, dried on vacuum line [50 °C (0.01 mm Hg)], and analyzed: ^{19}F NMR δ −69.15 ppm (pyridine-d_5). Elemental analysis confirmed the structure (Calcd: H, 0.74; C, 8.84. Found: H, 0.88; C, 8.89).

Scheme II[a]



[a] Reaction conditions: methanol (4–10 equiv), mercuric trifluoroacetate (1 equiv), MeCN, rt.

7. Reaction of 2-(Trifluoroacetoxy)-2-oxo-4-methyl-1,3,2-dioxaphosphorinane (*trans*-9) with Aniline. Into a solution of *trans*-**8** (0.046 g, 0.2 mmol) and **1** (0.08 g, 0.2 mmol) in acetonitrile (0.5 mL), resulting in the in situ formation of *trans*-**9**, as confirmed by means of ^{31}P NMR (δ −16.44 ppm), was added freshly distilled aniline (0.1 g, 0.11 mmol) in acetonitrile (0.1 mL). The precipitate was filtered off, and the filtrate containing anilinium salt of 2-hydroxy-2-oxo-4-methyl-1,3,2-dioxaphosphorinane was concentrated and its mass spectrum, after silylation with BSA, corresponded to 2-[(trimethylsilyl)oxy]-2-oxo-4-methyl-1,3,2-dioxaphosphorinane: m/z 224 ($M^{\bullet+}$). The identity of the second product presented in solution, namely trifluoroacetanilide, has been proved by GC–MS analysis (yield 100%): MS m/z 189 (100) ($M^{\bullet+}$); 77 $(C_6H_5)^+$; 120 $(C_6H_5NHCO)^{\bullet+}$; GC (HP-1) t_R 5.76 min.

Ethanolysis of *O,Se*-Dimethyl *N*-(α-Methylbenzyl)-phosphoramidoselenoates (11) in the Presence of 1. Into a solution of (R_p,R_c)-**11** (0.029 g, 0.1 mmol) in dry acetonitrile (0.5 mL) was added dropwise ethanol (0.04 mL), followed by a solution of **1** (0.043 g, 0.1 mmol), and then the mixture was stirred at ambient temperature for 0.5 h. The precipitate was filtered off, and the filtrate was concentrated and dissolved in $CDCl_3$. The ^{31}P NMR spectrum of resulting material contained only one signal at δ 9.32 ppm ($CDCl_3$), characteristic for (S_p,R_c)-**12** [lit.[1] ^{31}P NMR δ 9.38 ppm]: ^{1}H NMR δ 1.09 (t, 3 H, $^3J_{HH}$ = 6.8 Hz, CH_3CH_2O), 1.46, 1.50 (2 d, 3 H, $^3J_{HH}$ = 6.8 Hz, CH_3CH), 3.68 (d, 3 H, $^3J_{P\text{-}H}$ = 11.3 Hz, CH_3O), 3.80–3.90 (m, 2 H, CH_2O), 4.28 (m, 1 H, CH_3CH), 7.2–7.9 ppm (5 H_{arom}).

In the same way ethanolysis of mixture of (R_p,R_c)-**11** and (S_p,R_c)-**11** (1:2.7, respectively, ^{31}P NMR assay δ 27.0 and 26.4 ppm) was performed. Two signals in ^{31}P NMR spectrum in $CDCl_3$ were observed, δ 9.35 and 9.42 ppm in the ratio ca. 3:1, corresponding to (R_p,R_c)-**12** and (S_p,R_c)-**12**, respectively. Addition of pure (S_p,R_c)-**12** (0.01 g) gave rise to the expected change of ratio of diastereoisomers.

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Li$^+$ and Ca^{2+} Ions as Complementary Regulatory Elements for the Formation of Propeller-like Conformations

Izac Dayan, Yitzhak Tor, Jacqueline Libman, and Abraham Shanzer*

Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel

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Regulation of molecular conformations is a key element in biochemical processes such as enzyme activity[1] or oxygen transport.[2] Conformational changes affect the structure

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Scheme I

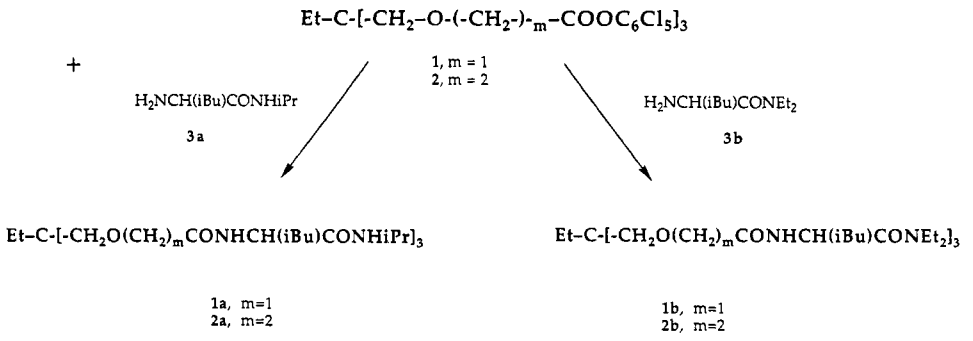

Table I. IR and NMR Data of Free Ligands and Their Li^+ and Ca^{2+} Complexes[a]

	frequencies ν, cm^{-1} ($\Delta\nu$)						chemical shifts δ, ppm ($\Delta\delta$)					
	NH		CONH, int		CON, ext		CCH_2O		OCH_2		CH_2CO	
compound	$CDCl_3$	CD_3CN	$CDCl_3$	CD_3CN	$CDCl_3$	CD_3CN	$CDCl_3$	CD_3CN	$CDCl_3$	CD_3CN	$CDCl_3$	CD_3CN
1a	3415[b] 3353[b]	3301	1662[b]	1667	1662[b]	1667	3.45 (s)	3.43 (d) 3.48 (d)			3.98 (s)	3.89 (d) 3.97 (d)
1a + 1 equiv of Li^+	(−63[b]) (−1[b])		(1[b])	(−2)	(1[b])	(−2)	(0.08) (0.29)	(−0.02) (0.31)			(0.09) (0.22)	(0.10) (0.18)
1a + 1 equiv of Ca^+	(−63[b]) (−1[b])		(−5[b])	(−12)	(−5[b])	(−12)	(0.3)	(0.24) (0.28)			(0.35)	(0.35) (0.37)
1b	3400[b]		1674[b]	1678	1636[b]	1640	3.50 (s)[b]	3.49 (s)			3.98 (d)[b] 4.04 (d)	3.93 (s)
1b + 1 equiv of Li^+	(−63[b])		(−3[b])	(−9)	(1[b])	(3)	(−0.11[b]) (0.34[b])	(0.14) (0.37)			(0.11[b]) (0.15[b])	(0.08) (0.19)
1b + 1 equiv of Ca^+			(−16)	(−33)	(−1)	(−19)		(0.20)				(0.32)
2a	3304[b]	3358	1652[b]	1661	1652[b]	1661	3.16 (d) 3.20 (d)	3.18 (s)	3.63 (m)	3.59 (m)	2.42 (m) 2.56 (m)	2.36 (m) 2.41 (m)
2a + 1 equiv of Li^+	(+46[b])		(−4[b])	(−6)	(−4[b])	(−6)	(0.30) (0.32)	(0.15)	(0.01)	(0.01)	(0.06) (0.19)	(0.05) (0.07)
2a + 1 equiv of Ca^+	(+214[b]) (+50[b,c])		(−10.5[b,c])	(−16.5)	(−10.5[b,c])	(−16.5)	(0.42[b,c]) (0.45[b,c])	(0.44)	(0.18[b,c])		(0.17[b,c]) (0.31[b,c])	
2b	3427[b] 3362[b] 3310[b]	3376 3353 3295	1658[b]	1668	1633[b]	1641	3.28 (s)	3.18 (s)	3.65 (t)	3.59 (m)	2.48 (m)	2.33 (m) 2.45 (m)
2b + 1 equiv of Li^+	(−65[b]) (0) (+52[b])		(0[b])	(−1)	(−2[b])	(2)	(0.11[b])	(0.13)	(0.01[b])		(0.05[b])	
2b + 1 equiv of Ca^+	(−122[b]) (−57[b]) (−5[b])		(−28[b])	(−35)	(−4[b])	(−8)	(0.54[b]) (0.12[b])	(0.51) (0.31)	(0.02[b])	(0.01) (0.26)	(0.05[b]) (0.27[b])	(0.15) (0.23)

[a] 10 mM solutions; the numbers in parentheses are the shifts induced upon binding; all spectra have been recorded at ambient temperatures. [b] $CDCl_3$–CD_3CN, 95:5. [c] 2 equiv of Ca^{2+}.

of allosteric enzymes and may either stimulate or inhibit their activity.[3,4] Recently, we introduced C_3 symmetric trispeptides whose conformations may be controlled by the nature of the solvent: in apolar solvents these compounds adopt propeller-like conformations by virtue of a network of H bonds, and in protic solvents they collapse to form random arrangements.[8] Complementary to these findings, we demonstrated that C_3 symmetric ligands of type 2b form propeller-like complexes when binding Ca^{2+} ions, while the free ligands adopt random conformations.[9] In this article we show that Li^+ ions act complementary to Ca^{2+} ions in forming chiral complexes with type 1, rather than type 2 ligands, and thereby introduce synthetic receptors whose helicity may selectively be regulated by exogenous means.

The chiral ligands are characterized by four elements: (i) C_3 symmetric, tripodal topology which is inherently fit to accomodate hexacoordinating metal ions in octahedral geometries, (ii) oxa amide groups as binding sites (one ether oxygen and one amide carbonyl at close proximity on each arm) for alkali and alkaline earth metal ions,[9-11] (iii) asymmetric centers to generate complexes of preferred chiral sense, either clockwise or counterclockwise, and (iv) secondary amide groups CONHiPr at their termini to optionally support helicity in the free ligands by H bonding.[8] The corresponding trisamides **1b** and **2b**[9] with tertiary amide groups $CONEt_2$ at their termini served as reference compounds to establish the contribution of the external amide NH groups to H-bonded structures.

Ligands **1a** and **2a** were prepared by condensation of trisphenolates **1** and **2**[9] with the corresponding amino acid derivatives, **3a** and **3b** (Scheme I). The trisamides **1a** and

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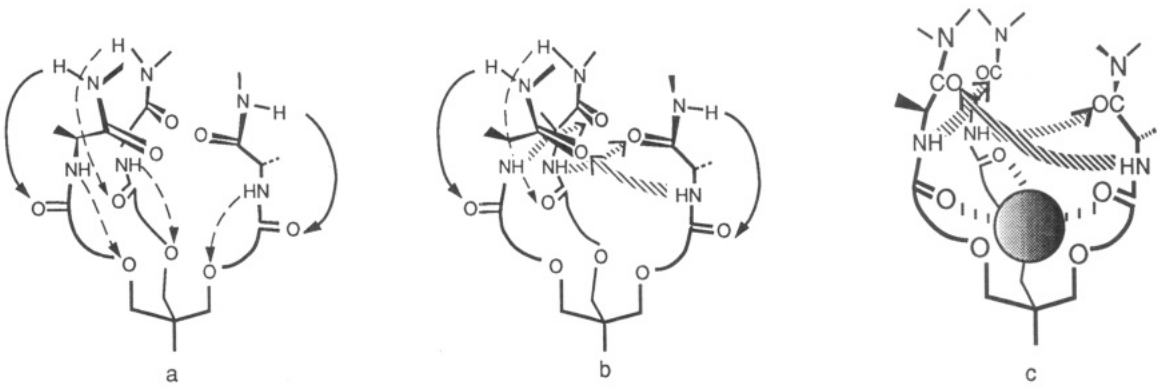

Figure 1. Possible H-bond networks in chiral ligands[12] and their metal complexes (intrastrand (a) and interstrand (b) H bonds in the free ligands; H-bonded complex (c)).

2a showed in the IR spectra lower amide CO absorptions for the internal amides than the reference trisamides **1b** and **2b** and mostly lower NH frequencies (Table I), demonstrating the involvement of the terminal CONHiPr groups in H-bonded conformations. ^{1}H-NMR spectra allowed us to distinguish between inter- and intrastrand H bonds. Interstrand H bonds restrict the conformational freedom of the molecule and thereby enhance the nonequivalence of the diastereotopic protons,[8] while intrastrand H bonds fail to do so. **1a** showed distinct chemical shifts for its diastereotopic methylene protons $C(CH_2O-)_3$ in acetonitrile, but practically identical chemical shifts in chloroform. The opposite solvent effect was observed for **2a** (Table I). On the other hand, both reference molecules **1b** and **2b**, which lack terminal amide NH groups, showed practically identical chemical shifts for the diastereotopic protons in both solvents. These observations demonstrate that interstrand H bonds can occur in **1a** and **2a**, although under different conditions: in **1a** when using acetonitrile as solvent, in **2a** when using chloroform.

Exclusively low frequency amide CO and NH absorptions coupled with anisotropy of the diastereotopic protons implies the presence of fully H-bonded conformations with interstrand H bonds (Figure 1b) for **1a** in acetonitrile and for **2a** in chloroform. Low-frequency NH absorptions and lack of anisotropy is in compliance with intrastrand H bonds, as expressed by **1a** in chloroform and **2a** in acetonitrile (Figure 1a).[13]

The configurations of both types of ligands after binding of Li^+ or Ca^{2+} ions were screened by IR and NMR spectroscopy (Na^+ and K^+ failed to bind to any of the ligands). Negligible or moderate red shifts of the amide carbonyls were recorded in the Li^+ complexes, but significant shifts were recorded in the Ca^{2+} complexes (Table I), suggesting variable involvement of the carbonyl groups in binding. The amide NH frequencies of the Li^+ and Ca^{2+} complexes showed red shifts relative to those of the free ligands, (except for **2a**), indicating weakening of the N–H bonds upon binding. This may be due to enhanced polarization of the carbonyl group, or strengthening of the H-bond network (Figure 1c).

NMR titration with $LiClO_4$ established 1:1 binding stoichiometry for all ligands and demonstrated induced or enhanced anisotropy for the diastereotopic protons in type 1, but not type 2 binders. Ca^{2+} binding, on the other hand, induced anisotropy in ligand **2b**, but not in type 1 ligands, quite complementary to Li^+.

Since ligand exchange is fast on the NMR time scale for both the Li^+ and Ca^{2+} complexes, the occurrence of anisotropy is strongly suggestive of (i) inherently chiral complexes such as octahedral complexes and (ii) chiral preference of either of the two possible diastereomeric arrangements.[14] That binding of Li^+ generates a chiral arrangement in type 1, but not type 2 ligands, while the opposite is true for binding of Ca^{2+}, was confirmed by CD spectroscopy. Thus the CD spectrum of **1b**–Li^+ showed a bathochromically displaced and somewhat enhanced Cotton effect relative to the free ligand (**1b**, $\Delta\epsilon = +8.75$ at 194 nm; **1b**–Li^+, $\Delta\epsilon = +12.5$ at 200 nm), indicating exciton coupling between the amide groups as a result of organization through metal binding. No such effect was observed for **2b**–Li^+. With Ca^{2+}, on the other hand, excition coupling was observed upon binding to **2b**, but not to **1b**,[9] in full agreement with the NMR data.

The lack of anisotropy of the diastereotopic protons in type 2 Li^+ complexes, and type 1 Ca^{2+} complexes is in accord with either (i) mixtures of diastereomeric, octahedral complexes[15] or (ii) complexes possessing geometries with σ symmetry, or pseudo-σ symmetry, as occurring in hexacoordinating prismatic complexes or triscoordinating trigonal complexes. Although the former possibility can at this moment not be excluded, the observed findings can well be rationalized by the latter possibilities when considering the differences in the ionic radii of Li^+ (0.68 Å) and Ca^{2+} (0.99 Å) and the differences in the sizes of the respective chelate rings that are five-membered in type 1 and six-membered in type 2 ligands. Ions of Li^+ are thus fit to form octahedral complexes with type 1 ligands, as recently demonstrated by X-ray diffraction of related complexes,[11] but likely to be too small to generate octahedral complexes with type 2 ligands. Ions of Ca^{2+}, on the other hand, well match the octahedral cavities of type 2 ligands, but are too large for type 1 ligands, as indicated

(12) The possibility of intrastrand H bonds between the internal amide NH and external amide CO to form a five-membered H-bond ring is energetically less favored than the alternative intrastrand H bonds between the internal amide CO and external amide NH to give a seven-membered H-bond ring.[8]

(13) Such conformations might possibly be supported by intrastrand H bonds between the internal amide NH and ether oxygen to form six-membered H-bond rings in type 2 ligands in acetonitrile. In type 1 ligands such H bonds are less favorable, as they would provide five-membered H-bonded rings.

(14) Octahedral complexes may either adopt a right-handed configuration, termed Δ, or a left-handed configuration, termed Λ. In the absence of asymmetric centers in the ligating molecules, the two configurations are enantiomeric, energetically identical, and therefore equally populated. However, in the presence of asymmetric centers in the ligating molecules, the two possible configurations become diastereomeric and energetically nonequivalent, such that either of the two forms may be preferentially formed.

(15) Time averaging due to fast interconversion between diastereomeric, octahedral complexes could a priori give rise to identical chemical shifts for the diastereotopic protons in the NMR spectra. Similarly, equal populations of the diastereomeric complexes would result in small Cottom effects in the CD spectra, since signals derived from exciton coupling of opposite chirality would cancel each other.

by EFF calculations.[9] Experiments to extend these structures to create artificial receptors suitable for chiral discrimination between molecular substrates are in progress.

Experimental Section

Gereral. ^{1}H NMR spectra were measured on the Bruker WH-270 spectrometer, or on the Varian FT-80 spectrometer, at concentrations of (1–2) × 10^{-2} mol L^{-1}. Chemical shifts are reported in ppm on the δ scale relative to tetramethylsilane (TMS) as internal standard.

Infrared spectra were measured using the Nicolet-510 FTIR spectrometer at concentrations of (1–2) × 10^{-2} mol L^{-1}. Absorption frequencies are given in cm^{-1}. UV–vis and circular dichroism (CD) spectra were measured using a Hewlett-Packard diode array spectrophotometer Model 8450A and a JASCO J-500C spectropolarimeter, respectively.

Chromatographic purifications were performed by column chromatography, using aluminum oxide, silica gel 60 (70–230-mesh ASTM), or flash chromatography using silica gel 60 (230–400-mesh ASTM). The homogeneity of the compounds was examined by thin-layer chromatography (mostly silica-coated plates, Merck), using at least two different solvent systems and two visualization methods (i.e. fluorescence quenching, iodine, ninhydrine). Solvents and commercially available reagents were of analytical grade. Protected amino acids were purchased from Sigma.

Preparation of $H_2NCH(i\text{-Bu})CONH\text{-}i\text{-Pr}$, 3a. *N,N*-Dicyclohexylcarbodiimide (2.56 g, 12.4 mmol), and 4-(dimethylamino)pyridine (50 mg) were added to a solution of Cbz-L-leucine (3 g, 11.3 mmol) and (1.302 g, 11.3 mmol) *N*-hydroxysuccinimide in dry THF (50 mL) at 0 °C. The reaction mixture was allowed to stand at 4 °C overnight. The formed dicyclohexylurea was filtered and washed with THF. Isopropylamine (0.974 mL, 11.3 mmol) was added to the combined active ester solutions, and the reaction mixture was stirred at room temperature for 2 days. The THF was then evaporated, and the crude mixture was chromatographed on neutral alumina ($CHCl_3$) to afford $CbzNHCH(i\text{-Bu})CONH\text{-}i\text{-Pr}$ in 63% yield as an oil. IR (nujol): 1686 (OCONH), 1643 cm^{-1} (CONH). ^{1}H NMR (80 MHz, $CDCl_3$): 7.33 (m, 5 H, Ar H), 7.0 (d, 1 H, J = 5.8 Hz, CONH-*i*-Pr) 5.10 (s, 2 H, $ArCH_2$), 5.8 (m, 1 H, OCONH), 4.86–3.98 (m, 2 H, CH of Leu and CH of *i*-Pr), 1.71–1.32 (m, 3 H, CH_2 and CH of *i*-Bu), 1.11 (d, 6 H, J = 6.5 Hz, CH_3 of *i*-Pr), 0.92 ppm (d, 6 H, J = 5.4 Hz, CH_3 of *i*-Bu).

A solution of protected $CbzNHCH(i\text{-Bu})CONH\text{-}i\text{-Pr}$ (2.3 g, 7.53 mmol) in ethanol was added to a suspension of Pd/C (5%) (0.576 g) in ethanol (50 mL). The mixture was hydrogenated at atmospheric pressure for 1 h, filtered, and evaporated to dryness to provide **3a** as an oil in 92% yield. IR ($CDCl_3$): 1657 cm^{-1} (CONH). ^{1}H NMR (80 MHz, $CDCl_3$): 7.01 (bs, 1 H, CONH-*i*-Pr), 4.18–3.91 (m, 1 H, CH of *i*-Pr), 3.32 (dd, J = 3.6 and 10 Hz, 1 H, CH of Leu), 1.82–1.57 (m, 3 H, CH_2 and CH of *i*-Bu), 1.14 (d, 6 H, J = 6.4 Hz, CH_3 of *i*-Pr), 0.94 ppm (m signals, 6 H, CH_3 of *i*-Bu).

Preparation of $EtC\{CH_2OCH_2CONHCH(i\text{-Bu})CONH\text{-}i\text{-Pr}\}_3$, 1a. The same procedure as used earlier for compound **1b**[9] was employed for synthesizing the derivative **1a** using L-$NH_2CH(i\text{-Bu})CONH\text{-}i\text{-Pr}$ (**3a**) as amine. The crude mixture was purified by rapid chromatography on neutral aluminum oxide ($CHCl_3$–MeOH, 98:2 and 95:5) to remove pentachlorophenol and then by flash chromatography on silica gel ($CHCl_3$–MeOH, 98:2, 97:3, 95:5, and 90:10) to provide **1a** in 17% yield as a solid, mp 73–76 °C. IR (10 mM, $CDCl_3$): 3427 and 3317 (NH), 1664 cm^{-1} (CONH). ^{1}H NMR (270 MHz, $CDCl_3$): 7.20 (d, 3 H, J = 8.6 Hz, CONH-Leu), 6.35 (d, 3 H, J = 7.7 Hz, CONH-*i*-Pr), 4.44 (m, 3 H, CH of Leu), 4.02 (m, 3 H, CH of *i*-Pr), 3.98 (s, 6 H, CH_2CO), 3.45 (s, 6 H, CCH_2O), 1.69–1.48 (m, 9 H, CH_2 and CH of *i*-Bu), 1.15–1.10 (m, 18 H, CH_3 of *i*-Pr), 0.95–0.91 (m, 18 H, CH_3 of *i*-Bu), 0.87 ppm (t, 3 H, CH_3 of Et).

Preparation of $EtC\{CH_2OCH_2CH_2CONHCH(i\text{-Bu})CONH\text{-}i\text{-Pr}\}_3$, 2a. The same procedure as employed earlier[9] for compound **2b** was employed for synthesizing compound **2a**, using trisphenolate **2** and amine L-$NH_2CH(i\text{-Bu})CONH\text{-}i\text{-Pr}$, **3a**. The crude mixture was purified by rapid chromatography on neutral aluminum oxide ($CHCl_3$–MeOH, 98:2, 95:5, and 90:10) to remove pentachlorophenol and then by chromatography on silica gel (CH_2Cl_2–MeOH, 98:2 and 95:5) and afforded a white glassy solid, **2a**, in 57% yield, mp 203–5 °C (after precipitation from acetonitrile). FAB MS (3-nitrobenzyl alcohol): 813 $(M + H)^+$. IR (10 mM, $CDCl_3/CD_3CN$): 3304 (NH), 1652 cm^{-1} (CONH). ^{1}H NMR (270 MHz, $CDCl_3$): 7.70 (d, 3 H, J = 8.4 Hz, CONH-Leu), 6.68 (d, 3 H, J = 7.9 Hz, CONH-*i*-Pr), 4.45 (m, 3 H, CH-Leu), 4.01 (m, 3 H, CH-*i*-Pr), 3.63 (m, 6 H, OCH_2), 3.18 (AB q, 6 H, CCH_2O), 2.56 and 2.42 (2 m, 6 H, CH_2CO), 1.65 (m, 9 H, CH_2 and CH of *i*-Bu), 1.32 (q, 2 H, CH_2 of Et), 1.14 (m, 18 H, CH_3 of *i*-Pr), 0.93 (m, 18 H, CH_3 of *i*-Bu), 0.79 ppm (t, 3 H, J = 7.5 Hz, CH_3 of Et).

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Supplementary Material Available: ^{1}H NMR spectra of title compounds **3a** and **4a** (2 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Reactions of Molecules with Two Equivalent Functional Groups. 4. Selective Mono-oxidation in the Heterogeneous Reaction of Bis(hydroxymethyl)benzene Isomers with Manganese Dioxide

Ioannis Constantinides and Roger S. Macomber*

Department of Chemistry, University of Cincinnati, Cincinnati, Ohio 45221-0172

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Introduction

We have recently reported studies[1-3] on reactions of molecules with two equivalent functional groups (X), where reagent R converts X to product functional group P as depicted in Scheme I. We demonstrated that when the functional groups in X_2, XP, and P_2 operate independently, and the reactions are irreversible, the fraction of each compound in the final product mixture can be accurately predicted by a system of simple equations.[1,2] One important consequence of the independence of the groups is that X_2 is exactly twice as reactive as XP (i.e., $k_2/k_1 \equiv \kappa = 0.5$). Deviations from this behavior ($k_2/k_1 \neq 0.5$) give a quantitative measure of intramolecular interactions between the functional groups in X_2 and XP. Such deviations have been detected in several reactions such as acetylation of the ortho isomer of bis(hydroxymethyl) benzene ($\kappa = 0.61$),[2a] substitution reaction of several α,ω-dibromoalkanes with KCN (κ = 0.61 to 1.15),[3] and nucleophilic addition reaction of 1,10-cyclooctadecanedione with several nucleophiles.[4] By contrast, the acetylation of *m*- and *p*-bis(hydroxymethyl)benzene[2a] as well as of 1,6-hexanediol[2b] gave results in complete agreement with the independent group model ($k_2/k_1 \approx 0.5$).

The new results reported herein demonstrate other important aspects of this study, including their applicability

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