Organic and Biological Chemistry
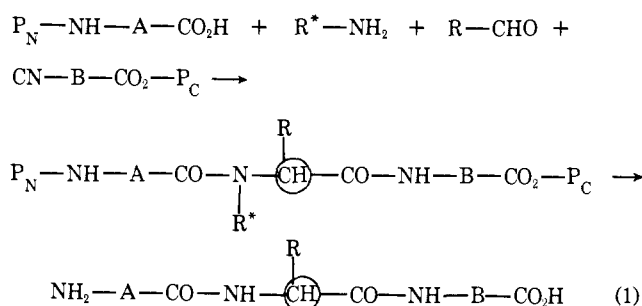
Stereoselective Four-Component Condensations of α-Ferrocenylethylamine and Its Absolute Configuration[1]

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Abstract: (+)-α-Ferrocenylethylamine, benzoic acid, isobutyraldehyde, and *t*-butyl isocyanide undergo stereoselective four component condensations; the diastereomeric products, V_n and V_p, are dealkylated by formic acid to the (*R*)- and (*S*)-N-benzoylvaline-N'-*t*-butylamides, VI. The influence of the reaction conditions upon the ratio of the diastereomeric products and also their nmr spectra leads to a reassignment of the absolute configuration of (+)-α-ferrocenylethylamine.

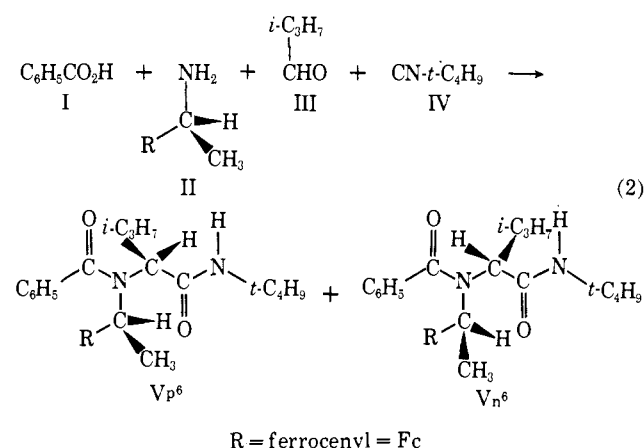The four-component condensations of isonitriles[4] provide a basis for a novel method for the synthesis of peptides according to eq 1; P_N and P_C are N- and C-terminal protecting groups.

$$P_N—NH—A—CO_2H \ + \ R^*—NH_2 \ + \ R—CHO \ +$$

$$CN—B—CO_2—P_C \longrightarrow$$

$$NH_2—A—CO—NH—\overset{R}{\underset{}{\text{(CH)}}}—CO—NH—B—CO_2H \qquad (1)$$

By this synthetic approach a new amino acid unit is produced and with it a new (encircled) center of chirality. In order to use this approach to best advantage an optically active amine must be employed whose asymmetric inducing power is high under conditions where the overall yield of the four component condensations is good, so that the desired stereoisomer is produced preferentially. The amine residue must also be subject to facile cleavage so that the actual peptide derivative can be obtained. Furthermore the group R* of the inducing primary amine component must, after the condensation, be replaceable by hydrogen under mild conditions.

The easy formation of α-ferrocenylalkyl carbonium ions[5] led us to investigate stereoselective four com-

ponent condensations of α-ferrocenylalkylamines like (2), and dealkylations like (4) as model reactions for (1).

$$C_6H_5CO_2H \ + \ \underset{\text{II}}{\underset{R}{\text{NH}_2}} \ + \ \underset{\text{III}}{CHO} \ + \ \underset{\text{IV}}{CN\text{-}t\text{-}C_4H_9} \longrightarrow$$

(2)

R = ferrocenyl = Fc

(1) Stereoselective Syntheses, V, and Isonitriles, XXIV. For the preceding report in these series, see ref 2.

(2) I. Ugi and G. Kaufhold, *Ann. Chem.*, **709**, 11 (1967).

(3) Research Associates in the Department of Chemistry of the University of Southern California in (a) 1969–1970 and (b) 1968–1969.

(4) Review articles: I. Ugi, *Angew. Chem.*, **74**, 9 (1962); *Angew. Chem. Intern. Ed. Engl.*, **1**, 8 (1962); *Jahrb. Akad. Wiss. Göttingen*, 21 (1965); "Neuere Methoden der präparativen Organischen Chemie," Vol. IV, W. Foerst, Ed., Verlag Chemie, Weinheim, Germany, 1966, p 1; "Isonitrile Chemistry," I. Ugi, Ed., Academic Press, New York, N. Y., 1970, Chapters 8 and 9; K. Sjøberg, *Svensk. Kem. Tidskr.*, **75**, 493 (1963); R. Oda and T. Shono, *J. Soc. Org. Syn. Chem. Jap.*, **22**, 695 (1964); N. P. Gambarjan, *Zh. Vses. Khim. Obshch.*, **12**, 65 (1967).

(5) J. H. Richards and E. A. Hill, *J. Amer. Chem. Soc.*, **81**, 3484 (1959); D. S. Trifan, R. Bacskai, *Tetrahedron Lett.*, 1 (1960); D. S.

Trifan and R. Bacskai, *J. Amer. Chem. Soc.*, **82**, 5010 (1960); E. A. Hill and J. H. Richards, *ibid.*, **83**, 3840, 4216 (1961); G. R. Buell, W. E. McEwen, and J. Kleinberg, *ibid.*, **84**, 40 (1962); E. A. Hill *J. Org. Chem.*, **28**, 3586 (1963); J. C. Ware and T. G. Traylor, *Tetrahedron Lett.*, 1295 (1965); M. Rosenblum, "Chemistry of the Iron Group Metallocenes," Part I, John Wiley & Sons, Inc., New York, N. Y., 1965, p 129; M. Cais, J. J. Dannenberg, A. Eisenstadt, M. J. Levenberg, and J. H. Richards, *Tetrahedron Lett.*, 1695 (1966); M. Cais, *Organometal. Chem. Rev.*, **1**, 435 (1966); J. D. Fitzpatrick, L. Watts, and R. Pettit, *Tetrahedron Lett.*, 1299 (1966); M. Rosenblum and F. W. Abbate, Advances in Chemistry Series, No. 62, American Chemical Society, Washington, D. C., 1966, p 532; T. T. Tidwell and T. G. Traylor, *J. Amer. Chem. Soc.*, **88**, 3442 (1966); T. G. Traylor and J. C. Ware, *ibid.*, **89**, 2304 (1967); J. Feinberg and M. Rosenblum, *ibid.*, **91**, 4325 (1969); G. Gokel, P. Hoffmann, D. Marquarding, E. Ruch, and I. Ugi, *Angew. Chem.*, **82**, 77 (1970).

(6) The compounds Va and b are the (*S*)(*S*) = *p* isomers[7] (VIa and b, (*R*)(*S*) = *n*[7]).

(7) The use of a nomenclature which refers to configurational relationships rather than configurations and is independent of antipodicity is desirable for diastereomers. The classical *threo–erythro* nomenclature for diastereomers with two elements of chirality refers to configurational relationships, but is not well enough defined to be generally useful. A simple nomenclature that meets all the requirements and is consistent with (*R*)(*S*) nomenclature is the *p–n* nomenclature[8] [with positive (*p*) = ( )(*R*) or (*S*)(*S*) and negative (*n*) = (*R*)(*S*) or (*S*)(*R*)].

(8) (a) I. Ugi, *Z. Naturforsch., B*, **20**, 405 (1965); (b) E. Ruch and I. Ugi, *Theor. Chim. Acta*, **4**, 287 (1966); (c) E. Ruch and I. Ugi, "Topics in Stereochemistry," Vol. IV, N. L. Allinger and E. L. Eliel, Ed., Interscience Publishers, New York, N. Y., 1969, p 99.

Experimental Section

N-Benzoyl-N[(S)-α-ferrocenylethyl]-(R)- and -(S)-valine-t-butyl-amides (V$_n$ and V$_p$). At 20° 1.66 g (20 mmoles) of t-butyl iso-cyanide[9] was added to a 1 m solution of 4.58 g (20 mmoles) of (+)-α-ferrocenylethylamine[10] (IIa) ([α]²⁰D +21.0° (c 4, ethanol)), 2.44 g (20 mmoles) of benzoic acid, and 1.44 g (20 mmoles) of isobutyr-aldehyde in 11.5 g of methanol. After 4 hr the reaction mixture was diluted with water and extracted with chloroform. After washing with 1 N sodium hydroxide and water, the chloroform solution was evaporated in vacuo to give 9.0 g (92%) of a crude mixture, 5 g of which was separated by column chromatography (silica gel Merck, 0.05–0.20 mm; eluent, petroleum ether (bp 60–80°)-acetone (10:1)) to yield 2.93 g of V$_n$ and 2.03 g of V$_p$ (V$_n$, mp 147–148° (from cyclohexane), [α]²⁰D 116.1°, [α]²⁰₅₄₆ 210.5° (c 2.4, methanol), tlc R$_f$ 0.33 (same solvent system as above) (Anal. Calcd for C₂₈H₃₆FeN₂O₂ (488): N, 5.75. Found: N, 5.65; mass spectrum molecular ion at 488); V$_p$, mp 144–145° (from cyclo-hexane), [α]²⁰D 454°, [α]²⁰₅₄₆ 658° (c 2.4, methanol), tlc R$_f$ 0.16 (same as above) (Anal. Calcd for C₂₈H₃₆FeN₂O₂ (488): N, 5.75. Found: N, 6.15; mass spectrum molecular ion at 488)).

N-Benzoyl-(R)- and- (S)-valine-N'-t-butylamide[11] (VII). V$_n$ (500 mg) was dissolved in 5 ml of 98% formic acid. After 45 min at 20°, ice was added and the acid was neutralized with solid sodium carbonate. The ether extract was dried over sodium sulfate and evaporated. The residue was boiled with petroleum ether and fil-tered: yield 250 mg (88%) of (R)-VI, mp 218–219°, [α]²⁰D +61.4° (c 2.1, acetic acid–chloroform, 1:1) (lit.[11] [α]²⁰D +60.9°). On analogous treatment, 240 mg (84%) of (S)-VI was obtained from 500 mg of V$_p$; [α]²⁰D −59.3° (same as above).

Results and Discussion

The observed product ratio $Q_{pn} = c_{Vp}:c_{Vn}$ of the model reaction (2, R = phenyl = Ph) which had been investigated earlier varies from 21:79 to 79:21[12] as a function of the reaction conditions, and the steric course of reaction 2 (R = Fc) shows a similar varia-tion (see Table I). Therefore, the product ratios of stereoselective four component condensations can only be compared if they refer to reaction conditions under which analogous pairs of corresponding reactions[8] predominate.

Table I. The Product Ratio $Q_{pn} = c_p/c_n = c_{Vp}/c_{Vn}$ of Reaction 2 (R = Fc and R = Ph) in Methanol

Expt no.	Temp, °C	Concn of I–III, m	Q$_{pn}$ for (2) R = Fc	R = Ph
1	20	1.00	41:59	40:60
2	−60	1.00	38:62	33:67
3	0	0.0375	79:21	78:22

The concept of pairs of corresponding reactions is useful for the theoretical treatment[8] of stereoselective reactions like asymmetrically induced syntheses,[13]

(9) I. Ugi, U. Fetzer, U. Eholzer, H. Knupfer, and K. Offermann, Angew. Chem., 77, 492 (1965); Angew. Chem. Intern. Ed. Engl., 4, 472 (1965); "Neuere Methoden der Präparativen Organischen Chemie," Vol. IV, W. Foerst, Ed., Verlag Chemie, Weinheim, Germany, 1966, p 37.

(10) K. Schlögl and M. Fried, Monatsh. Chem., 95, 558 (1964); see also H. Falk, C. Krasa, and K Schlögl, ibid., 100, 254 (1969).

(11) I. Ugi and K. Offermann, Chem. Ber., 97, 2996 (1964).

(12) H. Herlinger, H. Kleimann, K. Offermann, D. Rücker, and I. Ugi, Ann. Chem., 692, 94 (1966); I. Ugi, K. Offermann, H. Herlinger, and D. Marquarding, ibid., 709, 1 (1967).

(13) Review Articles: A. McKenzie, Angew. Chem., 45, 59 (1932); E. E. Turner and M. M. Harris, Quart. Rev. (London), 1, 299 (1947); V. Prelog, Bull. Soc. Chim. Fr., 987 (1956); E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill Book Co., Inc., New York, N. Y., 1962; J. J. Klabunowski, "Asymmetrische Synthese," VEB Deutscher Verlag der Wissenschaften, Berlin, 1963; K. Mislow, "Introduction to Stereochemistry," W. A. Benjamin, Inc., New York, N. Y., 1966; H. Pracejus, Fortsch. Chem. Forsch., 8, 493 (1967); D. R. Boyd and M. H. McKervey, Quart. Rev. (London), 22, 95 (1968); J. Mathieu and J. Weill-Raynal, Bull. Soc. Chim. Fr., 1211 (1968).

i.e., steroselective reactions by which new elements of chirality are formed under the influence of a chiral reference system.

We may call stereoselective reactions corresponding reactions if the reaction products are stereoisomers in thermodynamic equilibrium or are formed by kinetically controlled reactions via a set of corresponding transition complexes which are stereoisomers in thermodynamic equilibrium. In both cases the relative amounts of reaction products are independent of the initial con-centrations of the starting materials and, by this very property, corresponding reactions stand out from other stereoselective reactions.[8c] Pairs of corresponding reactions are described by eq 3a, which may even be

$$\ln c_p/c_n = -(F_p - F_n)/RT \qquad (3a)$$

$$= \rho \chi \chi' \qquad (3b)$$

used as a criterion for determining whether a stereo-selective reaction is a pair of corresponding reactions. In (3a) c_p and c_n represent the observed concentration of the p and n isomers;[8] for thermodynamically con-trolled reactions, the (Gibbs) free energies, F, refer to the stereoisomeric products; for kinetically controlled reactions the $F (= F^{\mp})$ refer to transition states.

Most of the known stereoselective reactions are probably pairs of corresponding reactions and therefore directly subject to theoretical discussion. The reactions which are described by Cram's[14] and Prelog's[15] rules are, for example, within the range of validity of these rules, simple pairs of corresponding reactions. These rules state that in those diastereomeric products which are formed preferentially in certain classes of asym-metrically induced syntheses, there is a specific con-figurational relationship between the initial and newly formed centers of chirality.

The stereoselective four component condensations are complex systems of four competing pairs of corre-sponding reactions which differ in kinetic order and product ratio. Hence the ratio of the diastereomeric products of stereoselective four component con-densations is a function of the initial concentrations of the reactants and other reaction conditions.[2,12]

The results shown in Table I, in combination with the assumption that under similar extreme conditions[2] reaction 2 (R = Ph and R = Fc) proceeds predom-inantly by analogous mechanisms, i.e., analogous combinations of pairs of corresponding reactions, and that with regard to reaction 2, the phenyl and ferrocenyl groups contribute in an analogous manner to the asymmetrically inducing power of the initial chiroids (i.e., in II $\lambda_{C_6H_5}$, $\lambda_{C_{10}H_9Fe} > \lambda_{CH_3} > \lambda_H$)[8] leads with regard to the products of 2 (R = Fc) to the conclusion that the assumed stereochemical assignment of V$_n$ and V$_p$ (R = Fc) is correct.

The fact that the nmr signals of the isopropyl and t-butyl groups of the p and n diastereomers V (R = phenyl and ferrocenyl) are remarkably different (last two rows of Table II) but are similar for the nonisomeric V$_p$ (R = Ph and Fc) as well as V$_n$ (R = Ph and Fc) lends further support to our above assignment.

On treatment with formic or trifluoroacetic acid, V$_p$ yields (S)-N-benzoylvaline-N'-t-butylamide

(14) D. J. Cram and F. A. Abd Elhafez, J. Amer. Chem. Soc., 74, 5828 (1952).

(15) V. Prelog, Helv. Chim. Acta, 36, 308 (1953).

Table II. The Nmr Spectra of V (Varian A-60, TMS, CDCl₃)

Assignment of protons	Rel area	Multiplicity	V_p τ	V_p J, Hz	V_n τ	V_n J, Hz	V_p τ	V_p J, Hz	V_n τ	V_n J, Hz
			R = Fc				R = Ph			
C_6H_5CO	5	Pseudo s	2.53		2.54		2.52		2.55	
$C_6H_5CH(CH_3)$	5	Pseudo s					2.79		2.72	
$C_6H_5CH(CH_3)$	1	q					4.90	7.0	4.92	7.0
$-CH(CH_3)$	1	q	5.04	7.0	5.12	7.0				
$C_5H_4(Fe)C$	4	m	~5.8		~5.7					
			~5.95		~5.85					
$C_5H_5(Fe)$	5	s	6.17		6.09					
$-CHCH(CH_3)_2$	2	m	~7.1		7.0		~6.95		~7.0	
$-CH(CH_3)-$	3	d	8.50	7.0	8.49	7.0	8.39	7.0	8.40	7.0
$-C(CH_3)_3$	9	s	8.83		8.64		8.86		8.61	
$-CH(CH_3)_2$	6	m	~9.05		9.18	6.0	8.93	6.5	9.20	6.0
					9.50	6.0	9.01	6.5	9.66	6.0

((S)-VI), and V_n the corresponding (R) antipode. This result implies that V_p is the (S)(S) diastereomer and V_n is the (S)(R) diastereomer.

$$V_p \xrightarrow{H^+} (S)\text{-VI} \tag{4}$$
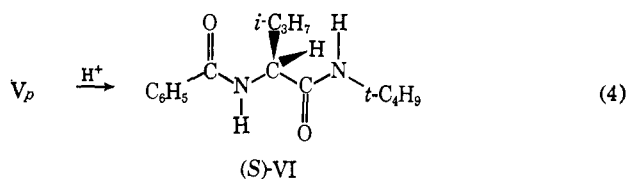
Hence (+)-α-ferrocenylethylamine, one of the key compounds in the stereochemistry of ferrocene de-

rivatives,[16] has the (S) configuration, in contrast to a previous assignment,[10] which was based on optical rotation data.

(16) The present authors will report in the near future on the synthesis and assignment of the absolute configurations of optically active ferrocene derivatives with planar chirality[17] by highly stereoselective metalation of (S)-N-dimethyl-α-ferrocenylethylamine and subsequent reactions with electrophiles, which is followed by further transformations of the primary products.
(17) K. Schlögl, "Topics in Stereochemistry," Vol. I, N. L. Allinger and E. L. Eliel, Ed., Interscience Publishers, New York, N. Y., 1967 p 39.

A Study of Competitive R₂O-3 and Homoallylic Participation in a Medium-Sized Ring. Acetolysis of Oxocan-3-yl and 3,4,7,8-Tetrahydro-2H-oxocin-3-yl Brosylates[1]

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Abstract: The products of acetolysis of oxocan-3-yl brosylate and 3,4,7,8-tetrahydro-2H-oxocin-3-yl brosylate were studied. First-order rate constants for the solvolysis of these oxygen-containing medium-sized ring compounds were determined and compared with values previously reported for cyclooctyl, 4-cycloocten-1-yl, and 3-cycloocten-1-yl brosylates. Oxocan-3-yl brosylate yielded products which arise exclusively from an intermediate bicyclic oxonium ion, while 3,4,7,8-tetrahydro-2H-oxocin-3-yl brosylate afforded products explicable on the basis of the derived homoallylic cation. Oxocin-3-yl brosylate exhibits a 70-fold rate retardation relative to cyclooctyl brosylate. Analysis of the significance of this result is shown to be complex, chiefly because of the unknown rate acceleration anticipated because of steric decompressions introduced by the hetero atom. The rate of solvolysis of 3,4,7,8-tetrahydro-2H-oxocin-3-yl brosylate was only 45 times slower than that of its carbocyclic congener (the expected rate retardation was approximately 10^2), indicating the lesser steric requirements of ether oxygen when compared to a ring methylene group. Additional aspects of the R₂O-3 participation question in these systems are discussed. One of the significant conclusions concerns the fact that homoallylic participation overwhelms R₂O-3 neighboring group assistance in a medium-sized ring.

The solvolyses of several oxygenated molecules related structurally to 4-methoxy-1-butyl (1) and 5-methoxy-1-pentyl brosylates (2) have provided

(1) Unsaturated Heterocyclic Systems. LVII. For the previous paper, see L. A. Paquette and R. W. Begland, J. Org. Chem., 34, 2896 (1969).

a fund of information concerning the nature of RO-5 and RO-6 neighboring group participation.[2,3] Struc-

(2) For a recent review of this subject, see B. Capon, Quart. Rev. (London), 18, 45 (1964).
(3) (a) R. Heck, J. Corse, E. Grunwald, and S. Winstein, J. Amer. Chem. Soc., 79, 3278 (1957); (b) S. Winstein, E. Allred, R. Heck, and