1.1 equiv), and VO(acac)₂ (1 mg) in benzene (0.25 mL) was stirred at room temperature under nitrogen for 17 h and heated at the reflux temperature for 2 h. The reaction mixture was diluted with benzene and successively washed with saturated sodium bicarbonate solution and brine. After drying and solvent removal, the crude product was purified by MPLC on silica gel (elution with 23% ethyl acetate in petroleum ether) to give 7 mg (59%) of pure **58**. The spectra of this material were identical with those reported above.

(1aR *, 4aR *, 7aR *, 7bS *) - 1, 1a, 2, 3, 4, 7, 7a, 7b - Octahydro - 3, 3, 5, 7btetramethyl-4aH-cycloprop[e]azulen-4a-ol (59). Methanesulfonyl chloride (42 µL, 2 equiv) was added dropwise to a magnetically stirredsolution of 57 (62 mg, 0.263 mmol) and triethylamine (73 µL, 2 equiv)in 3 mL of dichloromethane at -20 °C. After 2 h, water and dichloromethane were added, and the separated organic phase was washed successively with saturated sodium bicarbonate solution, water, and brine.Drying and solvent evaporation gave the epoxy mesylate as a white solid(93 mg) that was used directly in the next step.

A solution of this solid in dry tetrahydrofuran (1.5 mL) was added to liquid ammonia (30 mL), and 9.1 mg (5 equiv) of lithium wire was added in three pieces. When the reaction mixture turned colorless (ca. 2 h), another 9.1 mg of lithium wire was introduced. After 3 h, solid ammonium chloride was carefully added followed by 20 mL of hexane. Stirring was continued for 2 h, water was added, and the layers were separated. The aqueous phase was extracted with ether, and the combined ethereal solutions were washed with water and brine, dried, filtered, and concentrated. Purification by column chromatography (alumina activity III, elution with 3.8% ethyl acetate in petroleum ether) returned 41 mg of 57 and gave 12 mg of 59 (61% based on recovered starting material): IR (neat, cm⁻¹) 3600-3465, 3062, 2964, 1464, 1387, 1367, 1025, 990, 900, 820; ¹H NMR (300 MHz, C_6D_6) δ 5.21 (m, 1 H), 2.38–2.29 (m, 1 H), 2.16-2.11 (m, 1 H), 1.87 (d, J = 7.4 Hz, 1 H), 1.79-0.57 (series of m, 6 H), 1.57 (m, 3 H), 1.37 (s, 3 H), 1.03 (s, 3 H), 0.76 (z, 3 H), 0.40 (dd, J = 3.9 Hz, 1 H), 0.16 (t, J = 4.5 Hz, 1 H); MS, m/z (M⁺) calcd 220.1827, obsd 220.1833.

Africanol (1). Allylic alcohol 59 (8 mg, 0.036 mmol) in ethyl acetate (1.5 mL) containing 6 mg of platinum oxide was shaken under 50 psi of hydrogen for 3 days. The mixture was filtered, and the filtrate was evaporated. MPLC purification on silica gel (elution with 3.8% ethyl acetate in petroleum ether) gave 7 mg (88%) of 1 as a colorless solid, mp 46–47 °C (lit.¹¹ mp 47–48 °C): IR (CCl₄, cm⁻¹) 3480, 3078, 2965, 1460, 1388, 1266, 1109, 1088, 1024, 993; ¹H NMR (300 MHz, C₆D₆) δ 1.99–1.25 (series of m, 11 H), 1.22 (s, 3 H), 1.02 (s, 3 H), 0.85 (s, 3 H), 0.76 (d, J = 7.4 Hz, 3 H), 0.73–0.60 (m, 1 H), 0.45 (dd, J = 8.5, 3.9 Hz, 1 H), 0.16 (t, J = 4.4 Hz, 1 H); MS, m/z (M⁺-H₂O) calcd 204.1878, obsd 204.1862.

(1aR*,4aS*,7aR*,7bS*)-1,1a,2,3,4,7,7a,7b-Octahydro-3,3,5,7btetramethyl-4aH-cycloprop[e]azulen-4-ol (60). Methanesulfonyl chloride $(27 \ \mu\text{L}, 0.34 \text{ mmol})$ was added dropwise to a cold (-20 °C), magnetically stirred solution of **58** (40 mg, 0.169 mmol) and triethylamine (47 μ L, 0.34 mmol) in dichloromethane (2 mL). After 1.5 h, water and dichloromethane were added, and the organic phase was washed successively with saturated sodium bicarbonate solution, water, and brine. After drying and concentration, the oily epoxy mesylate (58.8 mg) was used directly in the next step.

To 20 mL of liquid ammonia was added a solution of the above material in 1 mL of dry tetrahydrofuran, followed by 5.9 mg (5 equiv) of lithium wire in three pieces. When the reaction mixture turned colorless (ca. 1 h), an additional 5.9 mg of lithium wire was introduced. After an additional hour, solid ammonium chloride was carefully added followed by 20 mL of hexane. This mixture was stirred for 2 h and treated with water. The aqueous phase was extracted with ether, and the combined organic phases were washed with water and brine, dried, filtered, and concentrated. Purification of the residue by column chromatography (alumina activity III, elution with 2.5% ethyl acetate in petroleum ether) furnished 24 mg (64.5%) of 60 as a colorless oil that crystallizes in the freezer: IR (neat, cm⁻¹) 3600-3465, 3070, 2936, 1455, 1380, 1067, 892, 824; ¹H NMR (300 MHz, C₆D₆) δ 5.30 (br, 1 H), 2.34-2.31 (m, 1 H), 2.01-0.76 (series of m, 7 H), 1.53 (d, J = 1.2 Hz, 3 H), 1.41 (s, 3 H), 1.20 (s, 3 H), 0.87 (s, 3 H), 0.51-0.42 (m, 2 H), 0.13 $(t, J = 4.2 \text{ Hz}, 1 \text{ H}); {}^{13}C \text{ NMR} (75 \text{ MHz}, C_6D_6) \text{ ppm } 146.29, 127.00,$ 86.41, 52.45, 52.30, 44.53, 35.41, 34.55, 30.72, 26.22, 25.45, 23.17, 22.27, 18.24, 11.99; MS, m/z (M⁺-H₂O) calcd 202.1721, obsd 202.1700.

(1aR*,4aR*,5R*,7aR*,7bS*)-Decahydro-3,3,5,7b-tetramethyl-4aHcycloprop[e]azulen-4a-ol (61). Allylic alcohol 60 (21 mg, 0.095 mmol) in ethyl acetate (3 mL) containing 10 mg of platinum oxide was shaken under 50 psi of hydrogen for 24 h. The mixture was filtered, and the filtrate was evaporated. MPLC purification on silica gel (elution with 4.5% ethyl acetate in petroleum ether) gave 19 mg (90%) of 61; IR (neat, cm⁻¹) 3620, 3080, 2970, 1460, 1170, 1055; ¹H NMR (300 MHz, C₆D₆) δ 2.05–0.71 (series of m, 11 H), 1.27 (s, 3 H), 1.25 (s, 3 H), 0.83 (s, 3 H), 0.76 (d, J = 6.6 Hz, 3 H), 0.54 (s, 1 H), 0.50 (dd, J = 8.3, 3.6 Hz, 1 H), 0.11 (t, J = 4.2 Hz, 1 H); ¹³C NMR (75 MHz, C₆D₆) ppm 84.22, 54.81, 52.43, 46.53, 44.16, 35.29, 34.13, 30.57, 25.50, 25.45, 23.83, 23.67, 22.97, 18.33, 12.81; MS, m/z (M⁺) calcd 222.1984, obsd 222.1973.

Acknowledgment. Financial support of this research by the National Institutes of Health (Grant GM-30827) is gratefully acknowledged. We also recognize the early contributions of Drs. David Dime and Kenneth Stevens to this project. The X-ray crystal structure analyses performed by Professor I. Bernal and Dr. James P. Springer were most instrumental in bringing the total synthesis to successful fruition. Dr. Kurt Loening of Chemical Abstracts Service is thanked for his assistance with nomenclature.

Control of Relative Stereochemistry in the Cycloadditive Route to β -Hydroxy Carbonyls. Regio- and Stereoselective Exo Alkylation of Δ^2 -Isoxazolines

Dennis P. Curran^{*1} and Jyh-Chyang Chao

Contribution from the Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260. Received October 30, 1986. Revised Manuscript Received January 12, 1987

Abstract: The regio- and stereoselective generation and subsequent alkylation of exo-lithiated Δ^2 -isoxazolines are reported. Treatment of 3-ethylisoxazoline 4 with lithium diethylamide (8 h, -80 °C), followed by benzyl bromide quench, provided 7d as a single stereoisomer. A variety of isoxazolines derived from both *cis* and *trans*-olefins undergo similar diastereoselective alkylations. A model is proposed to account for the observec selectivities based on selective (Z)-azaenolate formation followed by alkylation on the face opposite from the 4-substituent on the isoxazoline ring.

The synthetic equivalence of Δ^2 -isoxazolines (1) and aldol adducts (2, β -hydroxy ketones) has led to the emergence of a

cycloadditive strategy for formation of β -hydroxy carbonyls,^{2,3} formerly available only by carbonyl addition routes. In this

entry	starting isoxazoline	conditions ^a (alkylating agent, R'X)	products and ratios, %		isolated yield, %
	R NO			N-O H	
1	$R = CH_3$	A, CH₃I	13 (7b)	87 (8b)	76
2	R = Ph	A, CH ₃ I	13 (7e)	87 (8e)	71
3	$\mathbf{R} = \mathbf{R} = (\mathbf{CH}_{1}).$	B Ftl			52 ^b
4	$R = R = CH_3$	B, PhCH ₂ Br	96	4	40 ^c
	N-O I R R				
5	$R = CH_3$	B, EtI	86	14	72 ^d
6	$R = CH_3$	B, PhCH ₂ Br	91	9	62ª
1		B, FNCH ₂ Br			. 32
ø	-	P PLCU Pr	01	Q	520

^aConditions: A, LDEA; THF, 2 equiv of HMPA, -80 °C; 8-20 h. B, same as A except LDA base. ^bA 26% yield of the 4-alkylated product resulting from endo deprotonation was also isolated. ^cA 13% yield of the 4-alkylated product resulting from endo deprotonation was also isolated. ^d Products resulting from endo deprotonation were not detectable.

cycloadditive strategy, stereochemistry at C-4 and C-5 can often be rigidly controlled by formation of the Δ^2 -isoxazoline using a stereospecific olefin/nitrile oxide cycloaddition.⁴ To expand the general synthetic utility of the cycloadditive strategy to aldol adducts, methods for control of relative stereochemistry at the centers adjacent to the isoxazoline ring (C-3*, C-4*, C-5*) are required.⁵



Endo deprotonation and alkylation of Δ^2 -isoxazolines have been thoroughly studied by Jäger and co-workers,⁶ and the "Jäger

(1) Recipient of Sloan Foundation Fellowship, 1985-1987; Dreyfus Teacher-Scholar, 1985-1989; Eli Lilly Grantee, 1985-1987.

(2) Leading references: (a) Curran, D. P. J. Am. Chem. Soc. 1983, 105, 5826. (b) Kozikowski, A. P. Acc. Chem. Res. 1984, 17, 410. (c) Jäger, V.; Grund, H.; Buss, V.; Schwab, W.; Müeller, I.; Schole, R.; Franz, R.; Ehrier, R. Bull. Chem. Soc. Belg. 1983, 92, 1039. (d) Jäger, V. Lect. Heterocycl. Chem. 1985, 8, 79. We thank Professor Jäger for a preprint of this paper. (e) Ko, S. S.; Confalone, P. N. Tetrahedron 1985, 41, 3511. (f) Torssell, K. B. G.; Hazell, A. C.; Hazell, R. G. Tetrahedron 1985, 41, 5569.

(4) (a) Grundmann, C.; Grünhanger, P. *The Nitrile Oxides*; Springer-Verlag: New York, 1971. (b) Caramella, P. In *1,3-Dipolar Cycloaddition*; Padwa, A., Ed.; Wiley: New York, 1984; Vol. 1, pp 291-392.

(5) For other methods, see the following. C-3*: Wade, P. A.; Price, D. T.; McCauley, J. P.; Caroll, P. J. J. Org. Chem. 1985, 50, 2805. Kozikowski, A. P.; Kitagawa, Y.; Springer, J. P. J. Chem. Soc., Chem. Commun. 1983, 1460. Jones, R. H.; Robinson, G. C.; Thomas, E. J. Tetrahedron 1984, 40, 177. Larsen, K. E.; Torssell, K. B. G. Tetrahedron 1984, 40, 2985. C-5*; Jäger, V.; Müller, I. Tetrahedron 1985, 41, 3519. Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. J. Chem. Soc., Chem. Commun. 1985, 403. Annunziatta, R.; Cinquini, M.; Cozzi, F.; Raimondi, L.; Restelli, A. Helv. Chim. Acta. 1985, 68, 1217. Kozikowski, A. P.; Ghosh, A. K. J. Am. Chem. Soc. 1982, 104, 5788. Houk, K. N.; Moses, S. R.; Wu, Y.-D.; Rondan, N. G.; Jäger, V.; Schohe, R.; Fronczek, F. R. J. Am. Chem. Soc. 1984, 106, 3880. Jäger, V.; Schohe, R. Tetrahedron Lett. 1983, 24, 5501. Houk, K. N.; Duh, H.-Y.; Wu, Y.-D.; Moses, S. R. J. Am. Chem. Soc. 1986, 108, 2754. Wade, P. A.; Singh, S. M.; Krishna Pillay, M. Tetrahedron 1984, 40, 601. Curran D. P.; Kim, B. H. Synthesis 1986, 312. See also ref 2f.

Scheme I



alkylation" is a valuable method for the preparation of certain Δ^2 -isoxazolines which are not directly available from cycloaddition reactions. With the exception of the 3-methyl derivatives,⁷ useful methods for exo deprotonation of Δ^2 -isoxazolines have not been reported. We now describe the regio- and stereoselective exo deprotonation of 3,4,5-trisubstituted isoxazolines and the diastereoselective alkylation of the resulting azaenolates as a method for controlled introduction of a new stereogenic center at C-3* in the cycloadditive strategy.

As reported by Jäger,⁶ deprotonation of 3 (Scheme I) under standard conditions (LDA, THF/HMPA, 2 h, -78 °C), followed by alkylation with methyl iodide, provided 4 as the only product. The usual preference for endo deprotonation is overridden by the

⁽³⁾ Curran, D. P. Advances in Cycloaddition, in press.

^{(6) (}a) Jäger, V.; Schwab, W. Tetrahedron Lett. 1978, 3129. (b) Grund, H.; Jäger, V. Liebigs. Ann. Chem. 1980, 80. (c) Jäger, V.; Buss, V.; Schwab, W. Ibid. 1980, 122. (d) Lidor, R.; Shatzmiller, S. J. Am. Chem. Soc. 1981, 103, 5916. (e) Shatzmiller, S.; Shalom, E.; Lidor, R.; Tartkovski, E. Liebigs. Ann. Chem. 1983, 906. See also references 2c, 2d, and: Kozikowski, A. P.; Ghosh, A. K. J. Org. Chem. 1984, 49, 2762.

^{(7) (}a) Exo deprotonation of 3-methylisoxazolines: Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L. *Tetrahedron* **1986**, 42, 2129. See also ref 2b, 2c, and 6. (b) Exo deprotonation of stabilized anions: Annunziata, R.; Cinquini, M.; Cozzi, F.; Gilardi, A.; Restelli, A. J. Chem. Soc., Perkin Trans 1, **1985**, 2289, 2293.

low kinetic acidity of the endo methine hydrogen relative to the exo methyl hydrogens. However, attempted deprotonation of 4 under identical conditions led to isolation of small amounts of 5 and 6 along with a large amount of unreacted 4. It was readily ascertained that the recovery of 4 was due to its slow deprotonation under the reaction conditions.⁸ Extension of the time period for deprotonation from 2 to 24 h, followed by a methyl iodide quench as above, led to the isolation of 5 and 6 in a 3/1 ratio (60%) combined, purified yield). While 5 results from exo deprotonation, 6 must result from endo deprotonation⁹ followed by fragmentation of the resulting anion.¹⁰ A sampling of other amide bases revealed that, somewhat contraintuitively, lithium diethylamide (LDEA) was the best base for selective exo deprotonation. With the THF/HMPA solvent system, extended periods of time (8-20 h) at -80 °C were again required for complete deprotonation. Under these conditions, 5 was generated in high yield contaminated by only traces (1-3%) of **6**.

We were most excited to find that quenching of the anion generated from 4 with other alkylating agents resulted in the production of 7 and 8 with good to excellent diastereoselectivity. For example, quenching with methyl iodide- d_3 provided an 85/15 ratio of diastereoisomers 7a and 8a. Ratios increased upon progressing to ethyl iodide, *n*-butyl iodide, isopropyl iodide, and benzyl bromide (only a single isomer 7a detectable by GC) as indicated in Scheme I. The stereochemistry of 7e was assigned by reduction to the crystalline β -hydroxy ketone 9^{2a} and subsequent X-ray analysis.¹¹ The stereochemistries of 7a-d were assigned by analogy to 7e.

The stereoselective exo alkylation proved quite general, and the results of a representative selection of experiments are compiled in Table I. Several points should be noted. First, the surprising observation that LDEA is a superior base for generation of the exo anion holds only for the cyclopentyl systems (entries 1 and 2) and is not general. In all other cases (entries 3-8), best results in terms of yields and exo/endo ratios were obtained with LDA as the base. It is important to note that cis 4,5-disubstituted isoxazolines derived from olefins other than cyclopentene gave significant amounts of products derived from endo deprotonation, even under the optimum conditions.^{10b} Typical exo/endo ratios in these cases (entries 3 and 4) were 2 or 3/1. Attempts to use more hindered bases such as LTMP to increase the selectivity resulted in only modest changes in exo/endo ratios and required unreasonable time periods for complete deprotonation. On the other hand, trans 4,5-disubstituted isoxazolines suffered highly selective exo deprotonation in all cases (entries 5-8). In these systems, products arising from endo deprotonation were not detectable.

In all cases, the stereoselectivity in the alkylation of the *exo*azaenolate was good to excellent. As expected, reversing the side-chain substituent and the alkylating agent does reverse the diastereomer ratio. For example, generation of the anion from the 3-propylisoxazoline (entry 1), followed by alkylation with methyl iodide at -95 °C, again provides 7b and 8b (Scheme I), but now in a reversed ratio of 13/87. Entry 2 documents a similar reversal of stereochemistry for 7e and 8e. Furthermore, the bicyclic system is not required for stereoselectivity, and simple cis (entry 4) and trans (entries 5–9) 4,5-disubstituted isoxazolines all show similar selectivities. The stereostructure of the major product from entry 8 was determined by X-ray crystallography,¹¹ Scheme II



and the products from entries 5-8 were assigned by analogy. Comparison of the alkylation products derived from the *cis*- and *trans*- Δ^2 -isoxazolines indicates that the stereochemistry of alkylation is controlled almost exclusively by the substituent at C-4 with little or no effect by the substituent at C-5 (compare entries 4 and 6).

A working model to rationalize the above results is presented in Scheme II. As in the related alkylation of carbonyl-derived enolates,¹² we postulate that the observed selectivity is the result of diastereoface-selective alkylation of a stereochemically discrete azaenolate. It is possible that deprotonation of isoxazolines related to 11 will occur with approach of the base opposite the C-4 substituent (R) to avoid 1,3-interactions in the transition state. Assuming that the proton being removed must be nearly coplanar with the C=N π -orbitals, two conformations (13 and 14) can be advanced. Conformer 14 experiences severe 1,3-interactions between the methyl group and the C-4 substituent (R) in the transition state for deprotonation. Under kinetic control then, conformer 13 should be favored and the (Z)-azaenolate 15Z would be formed selectively after deprotonation.¹³ However, it is by no means clear that the azaenolate formation is under kinetic control. From a thermodynamic standpoint, precedent again suggests that 15Z should be favored.^{12,14}

Regardless of whether 15Z is formed under kinetic or thermodynamic control, alkylation of 15Z from the β -face, opposite the C-4 substituent (to avoid 1,3-interactions between E and R), predicts the formation of the observed major product 7. The notion that the minor diastereomer 8 arises from α -face alkylation of 15Z is supported by the general trend for increasing selectivity observed in Scheme I. The alternative for formation of 7 by alkylation on the more hindered α -face of the (E)-azaenolate 15E seems unlikely. Notice that the 4-substituent (R) controls both the enolate stereochemistry and the face selectivity in the alkylation. The nature of the 5-substituent $(R_t \text{ or } R_c)$ is of little consequence, and cis- or trans-isoxazolines provide the same type of products. However, the 5-substituent may be of importance in the selective formation of the exo-azaenolate. Trans 4,5-disubstituted isoxazolines show highly selective exo-azaenolate formation, presumably because R, hinders the approach of a base to the endo hydrogen.

In conclusion, this method should prove useful in the stereoselective elaboration of Δ^2 -isoxazolines at C-3*. Observed selectivities are generally good, and either diastereomer is available by appropriate selection of the 3-substituent and the alkylating

⁽⁸⁾ Early experiments were complicated by the apparent inability to deuteriate lithiated derivatives of 4. See: Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* 1985, 68, 1373.

⁽⁹⁾ Jäger, V.; Grund, H. Angew. Chem., Int. Ed. Engl. 1976, 15, 50. See also ref 6b.

^{(10) (}a) While most endo anions are stable at -78 °C (ref 2c and 6), the strain inherent in the bicyclooctane-like system may promote fragmentation. (b) Other endo anions (Table I, entries 3 and 4) are stable at low temperature and can be trapped by alkylation. A single endo-alkylated diastereomer is produced.

⁽¹¹⁾ Full details of the X-ray crystallographic determinations will be published in the thesis of J.-C. Chao. We thank Dr. J. Abola and J. Mandell for carrying out the structure determinations in the University of Pittsburgh X-ray Diffraction Laboratory (supported by PHS 1-S10-R02381).

⁽¹²⁾ For a review of the stereochemistry of enolate alkylation, see: Evans, D. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, Chapter 1. See also reference 14.

⁽¹³⁾ The monomeric lithioazaenolates 15 are depicted solely for the sake of convenience. No information regarding the solution structure/aggregation state is available.

⁽¹⁴⁾ For stereoselective generation and alkylation of azaenolates from oxazolines, see: Meyers, A. I. In Asymmetric Synthesis; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 3, Chapter 3. Hobbler, M. A.; Bergbreiter, D. E.; Newcomb, M. J. Am. Chem. Soc. 1978, 100, 8182. Interestingly, the opposite stereoisomer (R and N trans) is usually formed under kinetic conditions. For related acyclic azaenolates, see: Bergbreiter, D. E.; Newcomb, M. In Asymmetric Synthesis; Morrison, J. D., Ed.; Academic: New York, 1984; Vol. 2, Chapter 3, Enders, D. Ibid.; Vol. 3, Chapter 9.

agent. The model in Scheme II may be useful for application to exo-azaenolates generated from other heterocycles.¹⁴

Experimental Section

General Procedure for Exo Alkylation on Isoxazolines, Benzylation of 4. [3R*,4α,5α]-3a,5,6,6a-Tetrahydro-3-(1-methyl-2-phenylethyl)-4Hcyclopent(d lisoxazole (7e). To a solution of diethylamine (0.23 mL, 2.4 mmol) in dry THF (3 mL) at 0 °C was added n-butyllithium (1.42 mL, 2.2 mmol, 1.55 M in hexane). After 15 min, hexamethylphosphoric triamide (HMPA) was added, and the mixture was cooled to -80 °C. Isoxazoline 4 (278 mg, 2 mmol) in dry THF (2 mL) was added, and the reaction mixture was stirred for 2 h at -80 °C. Benzyl bromide (0.262 mL, 2.2 mmol) was added rapidly via syringe. The mixture was stirred 1 h at -80 °C, warmed to room temperature, then poured into dilute NH_4Cl , and extracted with $Et_2O(3\times)$. The organic phase was washed with $H_2O(4\times)$ and brine, dried over MgSO₄, and concentrated in vacuo, to give 350 mg of crude product. Flash chromatography (9% EtOAc/ hexane) of the above residue gave 278 mg (61%) of 7e: ¹H NMR (300 MHz, CDCl₃) § 7.33-7.17 (5 H, m), 4.94 (1 H, dd), 3.35 (1 H, br t), 2.97 (1 H, dd, J = 5.4, 5.0 Hz), 2.69 (2 H, m), 2.05 (1 H, m), 1.82 (1 H, m), 1.64 (3 H, m), 1.42 (1 H, br t), 1.19 (3 H, d, J = 6.6 Hz); IR (thin film) 3026, 2961, 2868, 1603, 1496, 1452, 887, 750, 700 cm⁻¹; MS, m/e calcd for C15H19NO (M⁺) 229.1467, found 229.1456.

3a,5,6,6a-Tetrahydro-3-(1-methylethyl)-4H-cyclopent[d]isoxazole (5, 7a). Alkylation was performed with methyl iodide or methyl iodide- d_3 . Purification was performed by flash chromatography (10% EtOAc/ hexane) to give **5** or **7a** in 60% yield: ¹H NMR (300 MHz, CDCl₃) δ **5.01** (1 H, dd), 3.64 (1 H, br t), 2.55 (1 H, m), 2.04 (1 H, m), 1.81 (1 H, m), 1.66 (3 H, m), 1.45 (1 H, m), 1.22 (3 H, d, J = 6.8 Hz), 1.16 (3 H, d, J = 7.0 Hz, peak reduced on quenching with CD₃I); ¹³C NMR (67 MHz, CDCl₃) δ 164.3, 86.0, 53.5, 35.7, 30.6, 27.0, 23.5, 20.8, 19.8; IR (thin film) 2965, 2870, 1468, 1448, 893, 864 cm⁻¹; MS, *m/e* calcd for C₈H₁₅NO (M⁺) 153.1154, found 153.1153.

[3*k*⁺, 4*α*, 5*α*]-3-(1-Methylpropyl)-3a, 5, 6, 6a-tetrahydro-4*H*-cyclopent-[*d*]isoxazole (7b). Purification was performed by flash chromatography (14% EtOAc/hexane), to give an inseparable mixture of diastereomers 7b and 8b (68%, 88/12 ratio): ¹H NMR (300 MHz, CDCl₃) δ 4.99 (1 H, dd), 3.59 (1 H, br t), 2.43 (1 H, m), 2.08 (1 H, m), 1.82 (1 H, m), 1.68 (4 H, m), 1.49 (2 H, m), 1.20 (3 H, d, *J* = 6.86 Hz), 0.92 (3 H, t); IR (thin film) 2963, 2872, 1462, 891 cm⁻¹; MS, *m/e* 167, 152, 139. Anal. Calcd for C₁₀H₁₇NO: C, 71.81; H, 10.24. Found: C, 71.58; H, 10.21.

[3*R*⁺,4*α*,5*α*]-3a,5,6,6a-Tetrahydro-3-(1-methylpentyl)-4*H*-cyclopent-[*d*]isoxazole (7c). Purification was performed by flash chromatography (10% EtOAc/hexane) to give an inseparable mixture of diastereomers 7c and 8c (67%, 95/5 ratio): ¹H NMR (300 MHz, CDCl₃) δ 4.98 (1 H, dd), 2.46 (1 H, br t), 2.04 (1 H, m), 1.83 (1 H, m), 1.75-1.23 (10 H, m), 1.19 (3 H, d), 0.83 (3 H, t); ¹³C NMR (67 MHz, CDCl₃) δ 163.4 (s), 85.5 (d), 53.6 (d), 35.4 (t), 34.4 (t), 32.0 (d), 30.2 (t), 28.9 (t), 23.3 (t), 22.5 (t), 17.3 (q), 13.7 (q); IR (thin film) 2957, 2932, 2870, 1458, 893 cm⁻¹; MS, *m/e* 195, 180, 166, 152. Anal. Calcd for $C_{12}H_{21}NO$: C, 73.80; H, 10.84. Found: C, 73.67; H, 10.63.

 $[3R^*,4\alpha,5\alpha]$ -3a,5,6,6a-Tetrahydro-3-(1,2-dimethylpropyl)-4H-cyclopent[d]isoxazole (7d). Purification was performed by MPLC (9% Et-OAc/hexane), to give an inseparable mixture of diastereomers 7d and

8d (62%, 97/3 ratio): ¹H NMR (300 MHz, CDCl₃) δ 4.98 (1 H, dd), 3.57 (1 H, br t), 2.31 (1 H, m), 2.05 (1 H, m), 1.94 (1 H, m), 1.83 (1 H, m), 1.70 (3 H, m), 1.47 (1 H, m), 1.12 (3 H, d, J = 6.9 Hz), 0.98 (3 H, d, J = 6.7 Hz), 0.85 (3 H, d, J = 6.8 Hz); IR (thin film) 2960, 2871, 1464, 1448, 1389, 1306, 1153, 956, 922 cm⁻¹; MS, *m/e* calcd for C₁₁H₁₉NO (M⁺) 181.1467, found 181.1467.

[3S^{*}, 4α, Sα]-3a, 5, 6, 6a-Tetrahydro-3-(1-methylpropyl)-4H-cyclopent-[d]isoxazole (8b) (Table I, Entry 1). Purification was performed by flash chromatography (10% EtOAc/hexane), to give an inseparable mixture of diasteromers 7b and 8b (76%, 13/87 ratio): ¹H NMR (300 MHz, CDCl₃) δ 4.99 (1 H, dd), 3.57 (1 H, br t), 2.35 (1 H, m), 2.06 (1 H, m), 1.90-1.4 (7 H, m), 1.15 (3 H, d, J = 1.1 Hz), 0.94 (3 H, t); IR (thin film) 2963, 2872, 1458, 954, 891 cm⁻¹; MS, m/e calcd for C₁₀H₁₇NO M - CH₃) 152.1075, found 152.1075.

 $[3S^*, 4\alpha, 5\alpha]$ -3a,5,6,6a-Tetrahydro-3-(1-methyl-2-phenylethyl)-4Hcyclopent[d]isoxazole (8e) (Table I, Entry 2). Purification was performed by MPLC (12% EtOAc/hexane), to give a mixture of diastereomers 7e and 8e (71%, 13/87 ratio): ¹H NMR (300 MHz, CDCl₃) δ 7.30-7.17 (5 H, m), 4.98 (1 H, dd), 3.57 (1 H, m), 3.15 (1 H, m), 2.69 (2 H, m), 2.04 (1 H, m), 1.70-1.2 (5 H, m), 1.15 (3 H, d, J = 6.6 Hz); IR (thin film) 2961, 2870, 1496, 1452, 956, 889, 750 cm⁻¹; MS, m/e calcd for C₁₅H₁₉NO (M⁺) 229.1467, found 229.1476. Anal. Calcd for C₁₅H₁₉NO: C, 78.56; H, 8.35. Found: C, 78.37; H, 8.48.

 $[2R^*, 1\alpha, 2\alpha]$ -2-(2-Methyl-3-phenyl-1-oxopropyl)cyclopentanol (9). For a detailed experimental procedure, see ref 2a. Recrystallization from 2% EtOAc in hexane at -4 °C gave crystals, and the structure was determined by X-ray crystallography: mp 47-48 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.3-7.15 (5 H, m), 4.27 (1 H, br s), 2.97 (3 H, m), 2.61 (2 H, m), 1.91 (3 H, m), 1.66 (3 H, m), 1.10 (3 H, d); IR (thin film) 3470, 3026, 2965, 1701, 1603, 1495, 1452, 1030 cm⁻¹; MS, *m/e* 232, 214, 147, 91, 67.

[3*R**,4α,5α]-3a,4,5,6,7,7a-Hexahydro-3-(1-methylpropyl)-1,2-benzisoxazole (Table I, Entry 3). Purification was performed by MPLC (6% EtOAc/hexane) to give a mixture of diastereomers (52%, 90/10 ratio): ¹H NMR (major diastereomer) (300 MHz, CDCl₃) δ 4.30 (1 H, dt), 2.84 (1 H, q), 2.48 (1 H, m), 2.25 (1 H, m), 2.02 (1 H, m), 1.85–1.3 (8 H, m), 1.23 (3 H, d), 0.94 (3 H, t); IR (thin film) 2965, 2934, 2860, 1458, 1379, 941, 877 cm⁻¹; MS, *m/e* calcd for C₁₁H₁₉NO (M⁺) 181.1467, found: 181.1465.

[3*R**,4 α ,5 α]-4,5-Dihydro-4,5-dimethyl-3-(1-methyl-2-phenylethyl)isoxazole (Table I, Entry 4). Purification was performed by flash chromatography (3% EtOAc/hexane), to give a partially separable mixture of diastereomers (40%) in a 96/4 ratio: ¹H NMR (major diastereomer) (300 MHz, CDCl₃) δ 7.3–7.1 (5 H, m), 4.43 (1 H, m), 2.92 (1 H, m), 2.72 (3 H, m), 1.24 and 1.23 (6 H, two overlapping doublets), 0.99 (3 H, d, J = 7.4 Hz); IR (thin film) 3026, 2973, 2932, 2874, 1558, 1456, 1379, 884 cm⁻¹; MS *m/e* 217, 202, 173, 126, 105, 91, 81, 73, 65. Anal. Calcd for C₁₄H₁₉NO: C, 77.38; H, 8.81. Found: C, 77.11; H, 8.78.

[3*R**,4α,5β]-5-Butyl-4,5-dihydro-4-methyl-3-(1-methylpropyl)isoxazole (Table I, Entry 5). Starting material was prepared by endo alkylation of 5-butyl-3-ethyl-4,5-dihydroisoxazole according to the method of Jäger. See ref 6a-c. Purification was performed by MPLC (10% Et-OAc/hexane), to give a partially separable mixture of diastereomers (72%, 86/14 ratio): ¹H NMR (major diastereomer) (300 MHz, CDCl₃) δ 4.02 (1 H, m), 2.83 (1 H, m), 2.46 (1 H, m), 1.8–1.3 (8 H, m), 1.19 (6 H, two overlapping d), 0.91 (6 H, two overlapping t); IR (thin film) 2963, 2932, 2874, 1456, 1381, 889 cm⁻¹; MS, *m/e* 179, 182, 169, 155, 140. Anal. Calcd for C₁₂H₂₁NO: C, 73.04; H, 11.85. Found: C, 73.25; H, 11.86.

[3*R**,4α,5β]-5-Butyl-4,5-dihydro-4-methyl-3-(1-methyl-2-phenylethyl)isoxazole (Table I, Entry 6). Purification was performed by flash chromatography (9% EtOAc/hexane), to give an inseparable mixture of diastereomers (62%, 91/9 ratio): ¹H NMR (major diastereomer) (300 MHz, CDCl₃) δ 7.32–7.18 (5 H, m), 4.90 (1 H, m), 2.94 (1 H, dd), 2.8–2.5 (3 H, m), 1.45–1.2 (6 H, m), 1.21 (3 H, d, *J* = 6.3 Hz), 1.14 (3 H, d, *J* = 7.2 Hz), 0.90 (3 H, t); IR (thin film) 3027, 2961, 2932, 2872, 1603, 1497, 1455, 1379, 1290, 1084, 1030, 887, 748 cm⁻¹; MS, *m/e* calcd for C₁₇H₂₃NO (M⁺) 259.1936, found 259.1934.

 $[3R^*,4\alpha,5\beta]$ -5-Butyl-4,5-dihydro-4-methoxy-3-(1-methyl-2-phenylethyl)isoxazole (Table I, Entry 7). Starting material was prepared by oxygenation of 5-butyl-3-ethyl-4,5-dihydroisoxazole according to the procedure of Jäger¹⁶ followed by O-methylation. Purification was performed by MPLC (10% EtOAc/hexane), to give a partially separable mixture of diastereomers (52%, 85/15 ratio): ¹H NMR (major diastereomer) (300 MHz, CDCl₃) & 7.3-7.1 (5 H, m), 4.27 (1 H, m), 3.93 (1 H, d), 3.20 (3 H, s), 2.91 (2 H, m), 2.79 (1 H, m), 1.28 (3 H, d), 1.5-1.0

⁽¹⁵⁾ General: Unless otherwise noted all reactions were run under a nitrogen atmosphere. Temperatures of reaction refer to cold bath temperatures obtained by using a Flexi-Cool (flexible cooling probe) available from FTS Systems, Inc. Tetrahydrofuran (THF) was distilled under nitrogen from sodium-benzophenone. Nuclear magnetic resonance (NMR) spectra were obtained on a FT-Brüker WH-300 (300 MHz for ¹H; 75 MHz for ¹³C) spectrometer. Infrared (IR) spectra were obtained on an IBM IR/32 FTIR spectrometer in chloroform (CDCl₃) using 0.2-mm path sodium chloride microcavity cells or as a neat thin film on an NaCl salt plate. X-ray structures were obtained on a Nicolet P3 diffractometer. Low-resolution mass spectra (Ms) were obtained on a LKB-9000 instrument, and high-resolution spectra were obtained on a Varian MATCH-50F instrument. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Medium-pressure liquid chromatography (MPLC) was performed with Kieselgel 60 (230-400 mesh) silica gel or on prepacked EM Lobar LiChroprep Si/60 columns. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 precoated plastic plates. Analytical gas chromatography was performed on a HP-5890 instrument equipped with a fused silica capillary (SPB-1,30 M, 0.25 μ M) 0.32-mm-i.d. column and a flame-ionization detector (FID) using helium as a carrier gas. The following temperature program was used to determine the diastereomeric ratio: the initial temperature, 100 °C; temperature ramp, 5 °C/min (or 25 °C/min); final temperature, 200 or 250 °C; injection temperature, 250 °C; detector temperature, 250 °C; carrier gas flow rate: 2 mL/min.

⁽¹⁶⁾ Schwab, W.; Jäger, V. Angew. Chem., Int. Ed. Engl. 1981, 20, 603.

(6 H, m), 0.90 (3 H, t); IR (thin film) 3065, 3024, 2959, 2934, 2874, 1495, 1455, 1996 cm⁻¹; MS, m/e calcd for $C_{17}H_{23}NO_2$ (M⁺) 275.1879, found 275.1885

 $[3R^*, 4\alpha, 5\beta]$ -4,5-Dihydro-4-methyl-3-(1-methyl-2-phenylethyl)-5phenylisoxazole (Table I, Entry 8). Purification was performed by MPLC (10% EtOAc/hexane) to give a partially separable mixture of diastereomers (53%, 91/9 ratio). Recrystallization from 2% EtOAc/ hexanes at -4 °C gave crystals of the pure major diastereomer suitable for X-ray diffraction: mp 52-53 °C; ¹H NMR (300 MHz, CDCl₃) δ 7.38–7.12 (10 H, m), 4.97 (1 H, d, J = 8.3 Hz), 2.93 (2 H, m), 2.71 (2 H, m), 1.27 (6 H, two overlapping d); IR (thin film); 3029, 2970, 2932, 1653, 1559, 1495, 1456, 750 cm⁻¹; MS, *m/e* calcd for C₁₉H₂₁NO (M⁺) 279.1257, found 279.1575.

Acknowledgment. We thank the National Institutes of Health (GM 31678) for support of this work. We are especially grateful to Stuart Pharmaceuticals, Merck, and American Cyanamid for unrestricted support.

A Single Transition State in the Transfer of the Methoxycarbonyl Group between Isoquinoline and Substituted Pyridines in Aqueous Solution

Edwin Chrystiuk and Andrew Williams*

Contribution from University Chemical Laboratories, Canterbury, England CT2 7NH. Received August 15, 1986. Revised Manuscript Received November 22, 1986

Abstract: N-Methoxycarbonylisoquinolinium ion reacts with nucleophiles in aqueous solution according to the equation



The rate constants, k_2 , for attack of substituted pyridines on the isoquinolinium species exhibit a linear Brønsted relationship $(\beta_{nuc} = 0.58)$ over a range of nucleophile pK_a greater than and less than the pK_a of isoquinoline. The Brønsted data indicate a smaller change in effective charge on nucleophilic nitrogen for formation of a putative tetrahedral intermediate than for its decomposition to product. This is opposite to what is expected for the stepwise process where the largest bonding change to attacking nitrogen is in the addition step. The results are consistent with a single transition state in the transfer of the methoxycarbonyl group between pyridines in aqueous solution; they contrast with those for reaction of pyridines and tertiary amines with neutral acyl derivatives where relatively stable zwitterionic tetrahedral intermediates have been demonstrated. The transition state for transfer between pyridines is symmetrical, and the effective charge on its pyridine nitrogen is consistent with about 40% of a single bond between nitrogen and acyl carbon. An imbalance of effective charge indicates that the MeO-CO component of the transition state has considerable acylium ion character pointing to an almost square-planar structure.

Myron Bender demonstrated in a classical paper that carbonyl oxygen in esters exchanges with solvent oxygen under conditions of alkaline hydrolysis in aqueous solution.¹ The results indicated that hydrolyses of nonactivated esters involve a tetrahedral intermediate.² There have now been many fine reports of tetrahedral adducts between acyl functions and nucleophiles,^{3,4} and there is no doubt that a stepwise addition-elimination (AE)^{5a}

Scheme I

AF

$$N_{U}^{T}$$
 + RCOL \rightarrow Nu - C - L - RCONu + L

concerted borderline

$$Nu^{-} + RCOL \longrightarrow \begin{vmatrix} R \\ Nu^{b-1} \\ Nu^{b-1} \\ \vdots \\ \vdots \\ a^{b} - \end{vmatrix} \longrightarrow RCONu + L^{-}$$

EA

mechanism is involved in transfer of an acyl group between strong nucleophiles in polar solvents, especially water.

In recent years, evidence has accumulated for a mechanism of acyl group transfer in water with an elimination-addition (EA)^{5a} timing of bond fission and formation and an acylium ion or stabilized acylium ion intermediate. Structural alterations cause the mechanism to swing from one to the other of the mechanistic extremes,^{5a} and it is logical to suppose that borderline conditions of structure and solvent could exist where leaving group and

0002-7863/87/1509-3040\$01.50/0 © 1987 American Chemical Society

Bender, M. L. J. Am. Chem. Soc. 1951, 73, 1626.
Bender, M. L. Chem. Rev. 1960, 60, 53.
McClelland, R. A.; Santry, L. J. Acc. Chem. Res. 1983, 16, 394. (4) Capon, B.; Ghosh, A. K.; Grieve, D. M. A. Acc. Chem. Res. 1981, 14, 306

^{(5) (}a) Williams, A.; Douglas, K. T. Chem. Rev. 1975, 75, 627. (b) We employ Dewar's definition of concertedness^{5c} where a reaction occurs in a single step and possesses a single transition state. In other words, the reaction coordinate in the multidimensional potential energy surface does not transverse a minimum energy value except at reactant and product states. Concertedness in this definition does not imply a particular relationship between bond order in forming and breaking bonds in the transition state. The definition is the same as that of Jencks⁵⁴ which states that a concerted mechanism ensues when the intermediate in a two-step mechanism has a lifetime less than a bond vibration period. A synchronous mechanism has both bonds changing in unison and can only have a pathway along the "north-east" diagonal in Figure 1. A concerted mechanism could have a reaction coordinate anywhe.e on the potential energy surface and could traverse paths normally associated with the discrete EA or AE processes. (c) Dewar, M. J. J. Am. Chem. Soc. 1984, 106, 209. (d) Jencks, W. P. Acc. Chem. Res. 1980, 13, 161.