ring size. That the increase is not entirely due to the former factor is readily seen in Table I. Dividing k' by the number of oxygen atoms in the macrocycle yields the catalytic efficiency of **1** and **2** on a per mole of oxygen scale. Since this value increases as macrocyclic size increases, it is apparent that ring size is a contributing factor to catalysis. From the trend, an even greater catalytic effect may be expected from larger macrocycles.

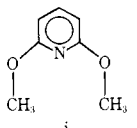
Precise answers to the question of how and why these macrocycles are such effective catalysts remain to be resolved by further studies. The increasing catalytic ability of the macrocycle with increasing ring size, indicates that the polyether chains might be attracting the entire transition-state structure not just the cationic part. A CPK model of **2** ($n = m = 5$) indicates an ellipsoidal cavity (having a major axis of ~12 Å and a minor axis of ~8 Å) which can easily accommodate most of a CPK model of $T^{\pm}$ (it is likely that the transition-state structure resembles $T^{\pm}$). It may not be necessary that the transition-state structure be inside the cavity, a host-guest[12] relationship. An alternative idea is that the flexible polyether chains are folding around the transition-state structure. Both ideas are similar in that they describe a local "solvation" effect on the polar transition-state structure, viz., stabilization of the charged species in the apolar solvent by interaction with the oxygens of the polyether chains.

In summary, catalysis of ester aminolysis in an aprotic solvent by macrocyclic polyether compounds shows a striking dependence on ring size. It may be that the optimum ring size for maximal catalysis has not yet been achieved in the compounds studied. These macrocycles may serve as models of a polar solvent shell. It is suggested that catalysis may arise from electrostatic stabilization of a polar transition-state structure. Work is in progress in this laboratory to uncover the nature of this catalysis.

Acknowledgment. This research was supported by the Research Corporation and in part by National Institutes of Health Biomedical Research Support Grant S05-RR07039-04, awarded to Louisiana State University and allocated by the LSU Council on Research to one of us (R.D.G.) for the purchase of a Cary 118C spectrophotometer. We also thank Dr. Frank Fronczek for a sample of dibenzo-18-crown-6 and John C. Hogan for helpful discussions.

References and Notes

(1) A preliminary account of this work was presented at the 29th SERACS Meeting, Tampa, Fla., 1977, Abstract 157.
(2) F. M. Menger and J. H. Smith, *J. Am. Chem. Soc.*, **94**, 3824 (1972).
(3) A. C. Satterthwait and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 7018 (1974); M. J. Gresser and W. P. Jencks, *ibid.*, **99**, 6970 (1977).
(4) C.-W. Su and J. W. Watson, *J. Am. Chem. Soc.*, **96**, 1854 (1974).
(5) G. R. Newkome, A. Nayak, G. L. McClure, F. Danesh-Khosboo, and J. Broussard-Simpson, *J. Org. Chem.*, **42**, 1500 (1977).
(6) A typical kinetic experiment would employ a concentration of 0.1 M of butylamine and a concentration range of 0.007–0.03 M of macrocycle. For *1* ($n = 1$), the value of k' was found to be independent of butylamine concentration.
(7) W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, **90**, 2622 (1968).
(8) The failure of 2,6-dimethoxypyridine to catalyze this reaction may stem from two factors: (a) basicity of nitrogen and (b) inaccessibility to the nitrogen. In aqueous solution, 2,6-dimethylpyridine is 5 pK units stronger in basicity than 2,6-dimethoxypyridine,[9] but this may not be representative of their basicities in chlorobenzene. In fact the methoxy group increases the proton affinity of pyridine in the gas phase,[10] and MINDO/3 calculations[11] suggest that 2,6-dimethoxypyridine has a greater proton affinity than pyridine. MINDO/3 calculations[11] also suggest that conformation i



i

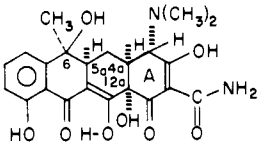
is the most stable conformation of 2,6-dimethoxypyridine. If this is correct when the molecule is in chlorobenzene, then the steric factor would appear to be the better explanation for the lack of catalysis by 2,6-dimethoxypyridine.
(9) A. R. Katritzky, F. D. Popp, and J. D. Rowe, *J. Chem. Soc. B*, 562 (1966).
(10) R. W. Taft in "Proton Transfer Reactions", V. Gold and E. F. Caldin, Ed., Chapman-Hall, London, 1975.
(11) B. K. Kruelskie and R. D. Gandour, unpublished results.
(12) E. P. Kyba, R. C. Helgeson, K. Madan, G. W. Gokel, T. L. Tarnowski, S. S. Moore, and D. J. Cram, *J. Am. Chem. Soc.*, **99**, 2564 (1977).

Richard D. Gandour,* David A. Walker
Ashutosh Nayak, George R. Newkome
Department of Chemistry, Louisiana State University
Baton Rouge, Louisiana 70803
Received December 27, 1977

3-Benzyloxyisoxazole System in Construction of Tetracyclines

Sir:

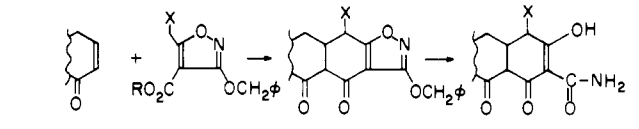
The complex and sensitive functionality present in the important antibiotics related to tetracycline (**1**) has generated synthetic approaches of considerable sophistication.[1] A number



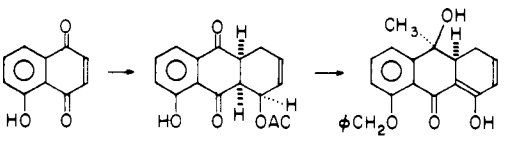
1

of these use a Claisen cyclization to form the C_1–C_{12a} bond.[2,3,4] This attractive approach is complicated, however, by the density of functional groups in ring A. We show in this communication that derivatives of 3-hydroxyisoxazoles admirably serve the purpose of storing the β-keto amide system of the A ring of tetracyclines and illustrate the principles involved with the synthesis of dedimethylamino-12a-deoxyanhydrotetracycline (**14**) and of 12a-deoxyanhydrotetracycline (**16**).

The fundamental process of this scheme (A → B → C → D) seemed especially promising because the tricyclic dienolone **3** which we shall call "Shemyakin ketone" is available in six steps,[5] beginning with the Diels–Alder reaction of 5-hydroxy-1,4-naphthoquinone (juglone) and 1-acetoxybutadiene.[6]



A B C D

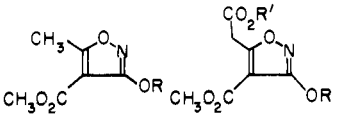


2 3

The attractiveness of this route to **3** was greatly enhanced by the finding that the difficultly separable mixtures of regioisomers (3:1 in favor of **2**) obtained under the reported conditions could be avoided under carefully defined Lewis acid catalysis (0.04 mol equiv of boron trifluoride etherate, benzene, or chloroform, 55 ± 5 °C). The desired regio isomer **2** was then obtained (94%) to the exclusion (<0.5%) of the unwanted one.[7] The rest of the synthesis of **3** followed the Shemyakin procedure.

We eventually settled on a 3-benzyloxyisoxazole so that the C → D transformation could be effected in a single hydrogenolytic step. The feasibility of the scheme was tested with the ethoxyethyl ester **7b**. The required isoxazole was prepared

0002-7863/78/1500-3609$01.00/0



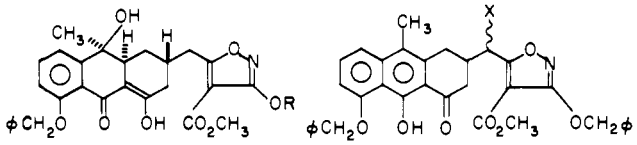
4 5: R′ = H. 6: R′ = CH_3
7: R′ = $CH_3C(H)OC_2H_5$

a: R = H; b: R = $CH_2\phi$

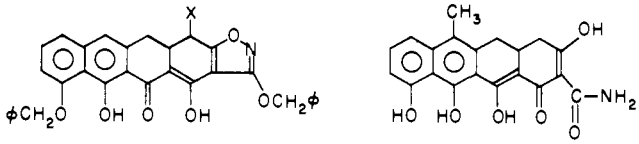
by direct carboxylation (2.2 equiv of LDA, THF, −75 °C, dry ice) of methyl 3-hydroxy-5-methylisoxazole-4-carboxylate (**4**), mp 104–106 °C[8] (prepared like the ethyl ester[9]), and the resulting acid **5a** (mp 135–137 °C) was esterified with methanol and 2,2-dimethoxypropane, under HCl catalysis,[10] to the dimethyl ester **6a** (mp 85–87 °C) which, with phenyldiazomethane in chloroform, gave the *O*-benzyl ether **6b** (mp 53.6–54.8 °C), accompanied by its *N*-benzyl isomer in a 2:1 ratio. After separation on silica gel, **6b** was selectively saponified (1.01 equiv of NaOH, aqueous CH_3OH, ~0 °C) to afford the acid **5b** (mp 123.7–124.9 °C) in ~30% overall yield from **4**.

Michael addition to **3** was then attempted using the rather unstable ethoxyethyl ester **7b** (from ethyl vinyl ether and a trace of mineral acid).

It had been a tacit assumption of the approach involving Michael addition of an isoxazole such as **7b** to **3** that strongly basic conditions which are known to destroy ring C in the tetracyclines (internal retro-Claisen to the γ-lactone system of the "isotetracyclines") would be unnecessary because of the strong electron withdrawing provided by the substituted isoxazole ring. This proved to be the case. Addition of a 50% excess of **7b** in portions (to minimize deesterification and decarboxylation prior to reaction) to a warm (35–45 °C) solution of **3** in DMF containing ~7 equiv of triethylamine (Et_3N) led to smooth Michael addition. When **3** had been completely consumed, the temperature was raised to 50–60 °C to complete the deesterification–decarboxylation, giving **8**, mp 108–111 °C, in 86% yield, after chromatography and crystallization.



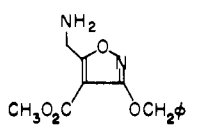
8 9: X = H
10: X = NH_2. 11: X = $N(CH_3)_2$



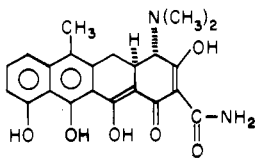
12: X = H
13: X = $N(CH_3)_2$ 14

Dehydration (*p*-toluenesulfonic acid in hot chloroform) removed the problem of the relative stereochemistry at **4a–5a**[11] (tetracycline numbering) and gave **9** which was cyclized (excess NaH, toluene, reflux, 2–3 hr) to **12** (mp 204–205 °C dec) in 85% yield. Hydrogenolysis (1 atm H_2, Pd/C, THF–methanol) gave,[12] in >90% yield, the desired (±)-dedimethylamino-12a-deoxyanhydrotetracycline (**14**), after filtration through cellulose with benzene. A sample further purified by crystallization from DMF–methanol exhibited mp 224–226 °C dec and chromatographic (TLC on silica gel and polyamide; paper) and spectral properties (including high resolution mass spectra, fragmentation pattern, and time and solvent-dependent electronic spectra) identical with those of material prepared by degradation of tetracycline.[13]

With these model studies complete, we turned to the possibility of extending the isoxazole route[14] to compounds such as 12-deoxyanhydrotetracycline (**16**), having the usual amino function in ring A. The required isoxazole was made by a



15



16

Curtius sequence starting with the acid **5b** (oxalyl chloride; NaN_3, aqueous acetone; 90% acetic acid, 50–90 °C) to the amine **15** (mp 59.5–61 °C, crude). Michael addition (Et_3N, DMF, 50–60 °C) to **3** of the Schiff base obtained from **15** and benzaldehyde again[15] proceeded smoothly to give a mixture of epimers which, without purification, was dehydrated (with hydrolysis of the Schiff base) to **10** (epimeric mixture; one isomer of mp 173.5–175.5 °C) by warming with dilute HCl. The crude product from the dehydration was reductively methylated[16] (formalin, sodium cyanoborohydride, aqueous CH_3CN; pH maintained at 6–7 with acetic acid), giving **11** (mixture of epimers; major isomer of mp 192–194 °C) in ~40% yield. Cyclization of **11** (large excess sodium hydride in refluxing toluene) then gave the tetracyclic **13** in 74% yield. The more abundant isomer of 13, mp 200.5–202.5 °C dec, exhibited $J_{4,4a}$ = 10.5 Hz in 5% $CF_3CO_2H/CDCl_3$, suggesting that it had the correct 4,4a-trans stereochemistry of the natural tetracyclines. Hydrogenolysis of the mixture proceeded smoothly, provided that a trace of Et_3N was added after the benzyl groups had been cleaved. Polyamide chromatography separated **16** from its epimer, and the product (HBr salt of mp ~240 °C dec) exhibited spectral and chromatographic properties identical with those of the substance derived from tetracycline.[17]

It may be noted that there is a formal possibility of converting **16** into tetracycline (**1**) itself: numerous methods exist for the introduction of the angular hydroxyl into 12a-deoxytetracyclines,[18] and the C ring of anhydrotetracyclines may be "hydrated" stereospecifically, using the photooxygenation–reduction procedure of Scott.[19] This last reduction, however, proceeds poorly[20] (or not at all)[21] in the absence of a 7-chloro substituent. Although one could obviously use this route to tetracyclines, assuming that the 7-chloro analogue of **3** could be made from 8-chlorojuglone, we are continuing our studies on the isoxazole approach to the tetracyclines, with the goal of synthesizing the antibiotics themselves without passing through the anhydrodeoxy compounds.

Acknowledgments. The work at Columbia was supported by the National Institutes of Health, including a postdoctoral fellowship to A.A.H. during part of it; the completion of the research, at Rutgers, was supported by the Rutgers Research Council. J. Gedan, M. L. Hagedorn, and W. Wang provided invaluable technical assistance. We also thank Drs. J. H. Boothe and V. J. Nair, Lederle Laboratories Division, American Cyanamid, for a sample of 12a-deoxydedimethylaminoanhydrotetracycline.

References and Notes

(1) W. Dürckhelmer, *Angew. Chem., Int. Ed. Engl.*, **14**, 721 (1975), and references therein. For a recent paper in this field, cf. D. H. R. Barton, S. V. Ley, P. D. Magnus, and M. Rosenfeld, *J. Chem. Soc., Perkin Trans. 1*, 567 (1977).
(2) J. J. Korst, J. D. Johnston, K. Butler, E. J. Bianco, L. H. Conover, and R. B. Woodward, *J. Am. Chem. Soc.*, **90**, 439 (1968), and earlier communica-

tions.
(3) T. L. Fields, A. S. Kende, and J. H. Boothe, *J. Am. Chem. Soc.*, **83**, 4612 (1961), and earlier papers.
(4) A. I. Gurevich, M. G. Karapetyan, M. N. Kolosov, V. G. Korobko, V. V. Onoprienko, S. A. Popravko, and M. M. Shemyakin, *Tetrahedron Lett.*, 131 (1967).
(5) M. N. Kolosov, S. A. Popravko, and M. M. Shemyakin, *Justus Liebigs Ann. Chem.*, **668**, 86 (1963).
(6) H. H. Inhoffen, H. Muxfeldt, H. Schaefer, and H. Kramer, *Croat. Chem. Acta*, **29**, 329 (1957).
(7) A similar observation has been reported very recently: B. M. Trost, J. Ippen, and W. C. Vladuchick, *J. Am. Chem. Soc.*, **99**, 8116 (1977). Remarkably, with more catalyst, *or at lower temperatures*, the specificity drops rapidly. Details of this curious observation will be published separately by A.A.H..
(8) All new compounds gave satisfactory ^{1}H NMR (including integrations), IR, and, for polycyclic compounds, UV–vis, and mass spectra; in addition, all compounds were homogeneous by TLC. Melting points were determined in open, untreated soft glass capillaries and are uncorrected. The direction and extent of enolization of polycyclic compounds are drawn arbitrarily.
(9) K. Bowden, G. Crank, and W. J. Ross, *J. Chem. Soc. C*, 172 (1968).
(10) N. S. Radin, A. K. Hajra, and Y. Akahori, *J. Lipid. Res.*, 1, 250 (1960).
(11) The Michael addition to **3** produces the unnatural configuration at 4a (tetracycline numbering) as shown in **8**. The elucidation of this stereochemical point is discussed in a separate communication: A. A. Hagedorn III, and M. L. Hagedorn, submitted for publication).
(12) Cf. A. J. Boulton, A. R. Katritzky, A. M. Hamid, and S. Oksne, *Tetrahedron*, **20**, 2835 (1964), for the formation of β-ketoamides from 3-hydroxyisoxazoles.
(13) A. Green, R. G. Wilkinson, and J. H. Boothe, *J. Am. Chem. Soc.*, **82**, 3946 (1960).
(14) A method involving a different construction and cleavage of an isoxazole precursor to ring A of tetracyclines is outlined in U.S. Patent 3 409 616 (L. H. Conover to Chas. Pfizer and Co., Inc., Nov 5, 1968).
(15) For recent use of the benzylidene derivative of α-amino esters in Michael additions cf. G. Stork, A. Leong, and A.-M. Touzin, *J. Am. Chem. Soc.*, **41**, 3491 (1976). The first report of activation of an α-aminocarbonyl system as its benzylidene derivative appears to be by E. H. W. Bohme, H. E. Applegate, B. T. Toeplitz, J. E. Dolfini, and J. Z. Gougoutas, *J. Am. Chem. Soc.*, **93**, 4324 (1971).
(16) R. F. Borch and A. I. Hassid, *J. Org. Chem.*, **37**, 1673 (1972).
(17) A. Green and J. H. Boothe, *J. Am. Chem. Soc.*, **82**, 3950 (1960).
(18) C. E. Holmlund, W. W. Anders, and A. J. Shay, *J. Am. Chem. Soc.*, **81**, 4748, 4750 (1959); H. Muxfeldt, Gr. Hardtmann, F. Kathawala, E. Vedejs, and J. B. Mooberry, *ibid.*, **90**, 6534 (1968); H. Muxfeldt, G. Buhr, and R. Bangert, *Angew. Chem., Int. Ed. Engl.*, 1, 157 (1962).
(19) A. I. Scott and C. Y. Bedford, *J. Am. Chem. Soc.*, **84**, 2271 (1962).
(20) M. Schach von Wittenau, *J. Org. Chem.*, **29**, 2746 (1964).
(21) H. Muxfeldt, personal communication to W. Dürckheimer, quoted in ref 1.

Gilbert Stork,* Alfred A. Hagedorn III
Department of Chemistry, Columbia University
New York, New York 10027, and
Department of Chemistry, Rutgers University
New Brunswick, New Jersey 08903
Received December 12, 1977

Olefin Homologation with Titanium Methylene Compounds

Sir:

A family of methylene-bridged compounds, $Cp_2TiCH_2AlXR_2$ ($Cp = \eta^5$-C_5H_5) has been prepared. These compounds are versatile methylene transfer reagents for homologation of olefins and for conversion of ketones to terminal olefins. Under certain conditions the compounds react with olefins to generate cyclopropanes in low yield.

Although $Cp_2TiCH_2AlClMe_2$ (**1**) is the first well-characterized compound of this type, α-elimination from CH_3TiCl_3 to give a transient methylene species was proposed[1] as early as 1961. More recently Sinn and coworkers conducted detailed studies of methane formation from mixtures of $AlMe_3$ and Cp_2TiCl_2.[2] Several $TiCH_2Al$ species were postulated as coproducts, and in one case an isolated solid was assigned the formula $Cp_2TiCH_2AlCl_2Me$.[2] Stimulated by reports of tantalum alkylidene compounds[3] and of the role of tungsten methylene compounds in olefin metathesis,[4] we investigated the titanium–aluminum–methyl system to determine the nature of isolated products.

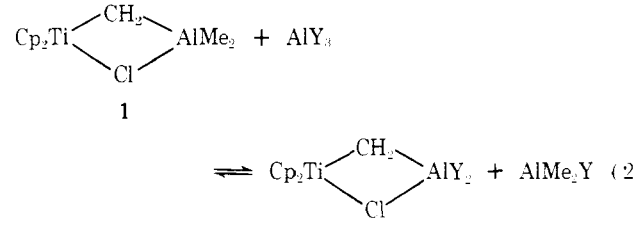
The reaction of 2 equiv of $AlMe_3$ with Cp_2TiCl_2 produces **1** and methane according to the equation

$$Cp_2TiCl_2 + 2AlMe_3 \rightarrow CH_4 + \underset{\mathbf{1}}{Cp_2TiCH_2AlClMe_2} + AlMe_2Cl \quad (1)$$

In a preparative experiment, a solution of 62 g of Cp_2TiCl_2 and 48 mL of Me_3Al in 250 mL of toluene was allowed to stand 60 h at room temperature. The nonvolatile products were recrystallized from toluene to produce 35 g of crude **1** (80–90% pure). Recrystallization from a solution of Me_3Al in toluene and from pentane gave analytically pure[5] reddish orange crystals of **1**. The same product is formed by reaction of $Cp_2Ti(CH_3)_2$ with $AlMe_2Cl$. Similarly, Cp_2TiMe_2 reacts slowly with $AlMe_3$ to produce $Cp_2TiCH_2AlMe_3$ (**2**) and methane. Although **2** is always contaminated with Cp_2TiMe_2, its ^{1}H NMR spectrum[6] confirms a structural analogy with **1**. The persistence of Cp_2TiMe_2 is significant because it decomposes autocatalytically with loss of Cp hydrogens[8] in the absence of alkylaluminum compounds. It seems likely that a weak complex such as Cp_2TiMe_2·$AlMe_3$ stabilizes the system and is an intermediate in the formation of the methylene compound.

Dimethylzinc and Cp_2TiMe_2 or Cp_2TiCl_2 react to yield methane and products which we believe contain the $TiCH_2Zn$ group, based on the appearance of low-field ^{1}H NMR resonances[6] in the region characteristic of $TiCH_2Al$ and their reactivity with ketones (see below). The Cp_2TiMe_2 reaction is slow and we have not obtained isolable amounts of product. The Cp_2TiCl_2 reaction proceeds at a convenient rate and yields products whose solubility characteristics change with time. In a typical reaction, 0.515 g (2.07 mmol) of Cp_2TiCl_2 with 0.28 mL (4.1 mmol) of Me_2Zn in 5 mL of C_6D_6 yielded 2.7 mmol of CH_4 after 4 h at room temperature.

The methyl groups in **1** exchange with certain aluminum alkyls and halides, but the methylene group is unreactive (eq 2). The NMR of **1** after reaction with $Al(CD_3)_3$ is consistent



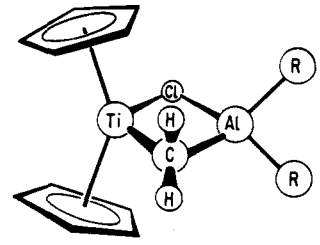
1

$$\rightleftharpoons Cp_2Ti\begin{matrix}CH_2\\Cl\end{matrix}AlY_2 + AlMe_2Y \quad (2)$$

$Y = Cl,\ CD_3,\ CH_2CMe_3$

with statistical scrambling of methyl groups between free and titanium-bound aluminum alkyl, with no deuterium incorporation in the Cp or CH_2 positions.[9] Partial exchange of the methyl groups of **1** with $Al(CH_2CMe_3)_3$ or $AlCl_3$ produces the unsymmetrical species $Cp_2TiCH_2AlClMeY$ ($Y = CH_2CMe_3$ or Cl[2]) which exhibits nonequivalent methylene and Cp protons in its ^{1}H NMR spectrum.[6] Pure $Cp_2TiCH_2AlCl(CH_2CMe_3)_2$ has been obtained by repeated exchange with $Al(CH_2CMe_3)_3$. A small amount of **2** is produced by the exchange of **1** with $AlMe_3$.

The geometry of the chloride containing derivatives, from ^{1}H NMR spectra,[6] is that of a heterocycle which contains Ti,



0002-7863/78/1500-3611$01.00/0