Communications to the Editor

Study of Ion-Pair Return in 2-Norbornyl Brosylate by Means of ^{17}O NMR

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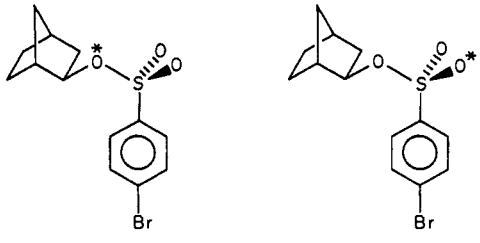
Ion pairs,[1] long known to inorganic chemists from spectroscopic studies of aqueous solutions, have also played an important role as transient intermediates in mechanistic organic chemistry.[2] Thanks to the illuminating studies of Goering and his group,[3] the fine details of the chemistry of ion-pair return have become known, for instance, in the case of allylic substrates, where return may be preceded by allylic rearrangement, racemization, and carbon- and oxygen-exchange reactions. The occurrence of ion pairs cannot always be made visible by means of processes altering the nature of the incipient cation (it may be achiral and/or incapable of rearrangement); however, rotational motion with oxyanions appears to be a universal process competing with return,[4] and hence oxygen isotope scrambling is perhaps the most reliable indicator of return. Application of this criterion has remained limited, however, by the notoriously difficult use of ^{18}O in such studies, requiring bond-specific degradation of substrates and products as well as tedious procedures for mass spectrometric assay. When in our studies concerned with carbene anion pairs and return[5] the oxygen-scrambling criterion came under consideration, we sensed that ^{17}O NMR promises to provide much more facile (i.e., in situ) access to this information. Bunnett's recent communication of a procedure to simplify ^{18}O assay by means of whole-molecule mass spectrometry[6] prompts us to report the viability of our approach by means of ^{17}O-labeled 2-norbornyl brosylates.

[^{17}O]-*exo*-2-Norbornyl brosylate (I) was prepared by heating



I II

2-norbornyl bromide with 1 equiv each of 40% ^{17}O-labeled water, mercuric bromide, and 2,6-di-*tert*-butylpyridine in glyme at 75 °C in a sealed tube for 48 h, followed by extraction with pentane, flash evaporation, sublimation, and conversion of the 2-norbornanol with *p*-bromobenzenesulfonyl chloride as described by Winstein.[7] The sulfonyl-^{17}O analogue (II) was prepared with labeled sulfonyl chloride obtained by hydrolyzing unlabeled material with 1 equiv of the enriched water in dioxane at 90 °C in a sealed tube for 48 h, and reconverting the sulfonic acid so obtained with thionyl chloride (30 min of reflux with a trace of dimethylformamide). The samples of I and II thus prepared were enriched to the extents of 30% and 10%, respectively.

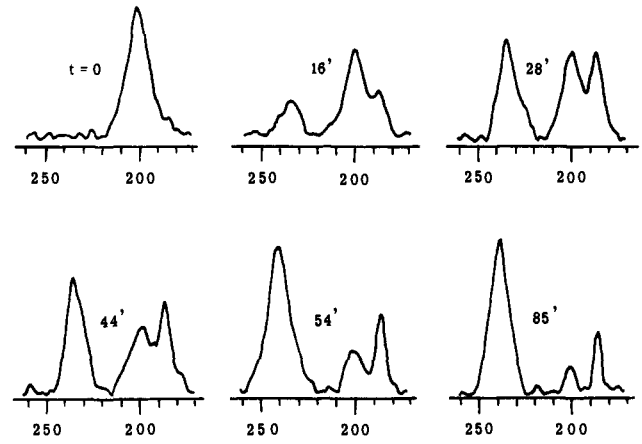


Figure 1. ^{17}O NMR spectra of sulfonyl-^{17}O-*exo*-2-norbornyl brosylate in ethanol at 25 °C at the times indicated. Chemical shifts are in parts per million relative to an external standard of water containing some shift reagent; the water and ethanol signals are not shown (pure water is at +28 ppm in these spectra). The growth of the sulfonic acid signal at 240 ppm and of the sulfonyl-^{17}O peak at 190 ppm can be clearly seen as the starting material declines at 200 ppm to a value half of the 190 ppm signal.

The ^{17}O NMR spectra were determined with a Nicolet 300-MHz spectrometer; good quality spectra were obtained in a few minutes with neat oxygen containing compounds of natural abundance or with 10^{-2} M solutions of enriched I and II. The sulfonyl oxygen appears at +160 ppm relative to external water[8] and the ether oxygen at +172 ppm; at 25 °C, the widths of half-height are about 0.2 and 0.4 Khz, respectively. Considerable sharpening occurs by raising the temperature even modestly.

Ethanolysis of 2.50 mL of 0.03 M II in a 10-mm NMR tube at 25 °C leads to a steady decrease in the sulfonyl peak and simultaneous appearance and growth of a signal at 172 ppm. As further study showed, the ether and acid signals coincide at this chemical shift, and hence return could not be observed; however, this problem is nicely solved by the addition of the small amounts of praseodymium(III) nitrate necessary (about 10 mole %) to shift the anionic oxygen down to ~+210 ppm (base-line separation); this does not affect the other resonances at all. The shift reagent makes it possible to see the solvolysis and scrambling separately, starting with either I or II;[9] the former reaction (with 0.006 M I) is more suitable for quantitative study since it goes to two-thirds conversion and since the sulfone peak is sharper than the ether signal. Figure 1 shows a series of spectra in the 150–250 ppm region. On the basis of these spectra we could calculate that k_S(25 °C) = 3.04×10^{-5} s^{-1} (r = 0.999; lit.[7] 2.66×10^{-5} s^{-1}; note that the shift reagent may cause small changes in rate because of ionic strength effects), with ΔH = 25.2 kcal/mol and ΔS = −5.8 cal/(mol K) and that k_{ex}(45 °C) = 3.83×10^{-4} s^{-1} (r = 0.996;

(1) For recent overviews, see the symposium proceedings in the following: (a) *J. Phys. Chem.*, **82**, (1978); (b) *Pure Appl. Chem.*, **51**, 49 (1979).
(2) (a) W. G. Young, S. Winstein, and H. L. Goering, *J. Am. Chem. Soc.*, **73**, 1958 (1951); (b) S. Winstein and K. C. Schreiber, *ibid.*, **74**, 2165 (1952); (c) M. Szwarc, "Ions and Ion-Pairs in Organic Reactions", Wiley, New York, 1972.
(3) H. L. Goering, *Rec. Chem. Prog.*, **21**, 109 (1960).
(4) H. L. Goering and J. F. Levy, *J. Am. Chem. Soc.*, **26**, 120 (1964); H. L. Goering and R. P. Anderson, *J. Am. Chem. Soc.*, **100**, 6469 (1978).
(5) W. J. le Noble, D. M. Chiou, and Y. Okaya, *J. Am. Chem. Soc.*, **101**, 3244 (1979).
(6) C. Paradisi and J. F. Bunnett, *J. Am. Chem. Soc.*, **103**, 946 (1981).
(7) S. Winstein and D. Trifan, *J. Am. Chem. Soc.*, **74**, 1147, 1154 (1952). These authors utilized 0.3 M solutions for their studies.
(8) Since ethanol was used as the solvent in these experiments and since the oxygen resonance in ethanol appears at +6 ppm, it was necessary for the purpose of chemical shift and integration standardization to add some europium chloride to the water. With the amount we used, the water was shifted upfield by 28 ppm; this gave base-line separation from the ethanol. The shifts reported in the text are relative to unshifted water.
(9) Ethanolic solutions of $Pr(NO_3)_3$ (10^{-2}–5 M) were metered in with a microliter syringe as required to keep the sulfonic acid resonance at 210 ppm. The minor dilutions (by less than 0.5 mL during the entire course of a solvolysis run) were taken into account before comparing spectra.

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see footnote 10). Since it is also known that racemization is several times faster in solvolyzing optically active 2-norbornyl brosylate than acid formation, it is clear that return occurs without the oxygens having fully equilibrated. This is in line with expectations derived from the work of Goering, for example, with the 1,2-dimethyl-2-norbornyl system.[11] It may also be noted that the final spectra show only the sulfonic acid and that no signal attributable to ethyl norbornyl ether can be seen, proving the absence of any *O*-acyl cleavage. Nor does any external return occur; enriched acid and natural abundance ester together in ethanol do not produce any hint of the presence of I or II.

In conclusion, we have detected and measured internal ion-pair return during solvolysis, in situ and without workup, and evaluated rate constants for both solvolysis of and oxygen scrambling in 2-norbornyl brosylate, the former in good agreement with known data. We believe that these experiments justify our claim that ^{17}O NMR is a rapid and convenient tool to detect return of pairs of ions and possibly of other species as well.[12]

Acknowledgment. We are pleased to acknowledge support by the donors of the Petroleum Research Fund, administered by the American Chemical Society, for this work. We also thank the NSF for its support to the Department in the form of Grant 8114412 to purchase the spectrometer.

Registry No. I, 85681-22-7; II, 85681-23-8; ^{17}O, 13968-48-4; $Pr(NO_3)_3$, 10361-80-5; O_2, 7782-44-7; 2-norbornyl brosylate, 4895-15-2; 2-norbornyl bromide, 29342-65-2; 2-norbornanol, 1632-68-4; europium chloride, 53801-49-3.

(10) The rate constant k_{ex} as recorded by most authors refers to the first-order approach to the equilibrium composition. It differs from k_I in the process

$$I \underset{k_{II}}{\overset{k_I}{\rightleftharpoons}} II$$

Here $k_I t = {}^2/_3 \ln (2 + 2r/(2 - r))$ (r = (II)/(I)).

(11) H. L. Goering and R. W. Thies, *J. Org. Chem.*, **40**, 925 (1975).

(12) it may be noted that in those cases where sulfonyl-^{17}O-labeled esters are adequate to the task at hand, the sulfonic acid liberated can be reused for the preparation of such esters with only the loss of one-third of its label.

Total Synthesis of (+)- and (−)-Tryptoquivaline G by Biomimetic Double Cyclization

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(+)-Tryptoquivaline G (**1**, Chart I) produced by *Aspergillus fumigatus*,[1] is one of several tryptoquivalines belonging to the tremorgic mycotoxin family. The novel structure was determined by chemical and physicochemical methods.[1] The first total synthesis was achieved by Buchi and co-workers,[2] who also established the absolute configuration. Subsequently, a formal synthesis of (±)-**1** was reported by Ban's group.[3]

We report here an abbreviated, facile biogenetic type total synthesis of (+)- and (−)-**1** by a different approach, utilizing the newly employed oxidative double cyclization of *N*-acyltryptophan precursor **10** (Chart II), which allowed an efficient formation of the unique ring system of **1** in one step.

Chart I

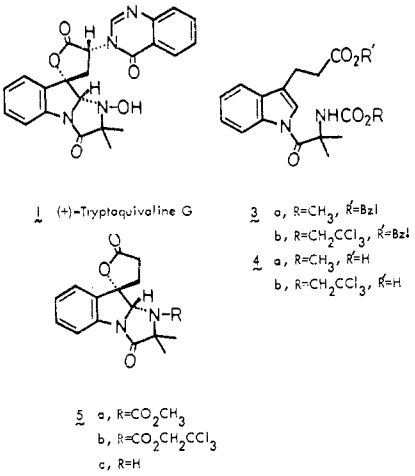
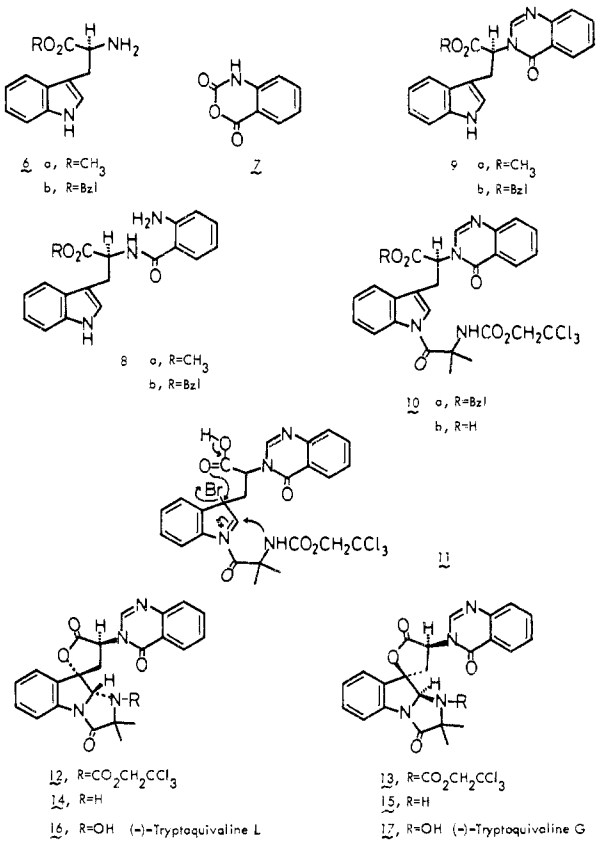


Chart II



From our studies on the bromination and oxidation of indoles[4] and also the results obtained by Witkop,[5] the formation of the imidazoindole spirolactone ring system could be envisaged as being derived from double cyclization of **10b** by bromination via **11**.

We first explored the acylation of indole nitrogen with amino acids as there is no established precedent for these reactions.[6]

Preliminary studies on the condensation of benzyl 3-indolepropionate with *N*-(methoxycarbonyl)- (**2a**) or *N*-[(trichloroethoxy)carbonyl]- (**2b**) methylalanine *p*-nitrophenyl esters in the presence of KF, 18-crown-6, and $EtN(i\text{-}Pr)_2$ in acetonitrile[7] led

(1) (a) Clardy, J.; Springer, J. P.; Buchi, G.; Mastuo, K.; Wrightman, R. J. *J. Am. Chem. Soc.* **1975**, *97*, 663-665. (b) Yamazaki, M.; Fujimoto, H.; Okuyama, E. *Tetrahedron Lett.* **1976**, 2861-2864. (c) Yamazaki, M.; Okuyama, E.; Maebayashi, Y. *Chem. Pharm. Bull.* **1979**, *27*, 1611-1617 and references therein.

(2) Buchi, G.; DeShong, P. R.; Katsumura, S.; Sugimura, Y. *J. Am. Chem. Soc.* **1979**, *101*, 5084-5086.

(3) Ohnuma, T.; Kimura, Y.; Ban, Y. *Tetrahedron Lett.* **1981**, *22*, 4969-4972.

(4) (a) Hino, T.; Nakagawa, M.; Wakatsuki, T.; Ogawa, K.; Yamada, S. *Tetrahedron* **1967**, *23*, 1441-1450. (b) Hino, T.; Nakamura, T.; Nakagawa, M. *Chem. Pharm. Bull.* **1975**, *23*, 2990-2997. (c) Hino, T.; Miura, H.; Murata, R.; Nakagawa, M. *Ibid.* **1978**, *26*, 3695-3703. (d) Nakagawa, M.; Kato, S.; Kataoka, S.; Hino, T. *J. Am. Chem. Soc.* **1979**, *101*, 3136-3137.

(5) Lawson, W. B.; Patchornik, A.; Witkop, B. *J. Am. Chem. Soc.* **1960**, *82*, 5918-5927.

(6) Preparation of 1-glycylindole and 1-glycylindoline were reported: Neklyudov, D. A.; Shchukina, L. A.; Suvorov, N. N. *Zh. Obshch. Khim.* **1967**, *37*, 797-800.

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