Table I. Experimentally Determined Solvent Isotope Effects[7]

solvent	substrate	sensitizer	$k_{obsd}^{d}/k_{obsd}^{h}$ [a]
acetone	rubrene	rose bengal	19.9 ± 1.3
	DPBF	rose bengal	17.0 ± 3.8
	DPBF	methylene blue	17.8 ± 2.0
acetonitrile	rubrene	rose bengal	8.7 ± 1.0
	DPBF	rose bengal	7.2 ± 1.6
benzene[b]	rubrene	methylene blue	15.9 ± 2.1
	DPBF	methylene blue	16.8 ± 1.0
chloroform	rubrene	methylene blue[d]	15.6 ± 1.6
	DPBF	methylene blue	5.8 ± 2.6
	rubrene/TBP[c]	methylene blue	10.4 ± 1.2
	DPBF/TBP[c]	methylene blue	9.8 ± 0.9

[a] Equivalent to $k_{decay}^{h}/k_{decay}^{d}$. See text. [b] Contained 0.8% MeOH in order to dissolve methylene blue. [c] $2.0\text{-}4.0 \times 10^{-5}$ M TBP. [d] During the period of photolysis methylene blue bleached significantly (~20%) in $CDCl_3$ but showed negligible changes in concentration in $CHCl_3$. Consequently, $CDCl_3$ solutions were prepared with a slightly greater amount of methylene blue than $CHCl_3$ solutions. The average concentration of methylene blue in $CDCl_3$ during photolysis was then equivalent to that in $CHCl_3$. The addition of TBP had no effect on the bleaching of methylene blue.

For a test of the assumption that K is invariant, β values (k_d/k_a) for 2,3-dimethyl-2-butene were determined[9] in both acetonitrile-d_3 and -h_3. The ratio of these values yielded a solvent isotope effect (8.0 ± 1.0) within the error limits of the k_{obsd} values for rubrene and DPBF (8.7 and 7.2, respectively). Similarily, the ratio of β values determined[10] for 1-methylcyclohexene in both acetone-d_6 and acetone-h_6 yielded a solvent isotope effect (11.8 ± 4.3) only slightly lower than those determined from the k_{obsd} values for the other substrates (approximately 18).[12]

Upon the addition of a quencher to the photooxygenation of a substrate (A) by singlet oxygen, two limiting cases are obtained.[11] In the first, the added quencher affects the lifetime of ^{3}Sens and/or ^{1}Sens but does not deactivate singlet oxygen. In this case, plots of $[AO_2]^{-1}$ vs. $[A]^{-1}$ have intercepts (K^{-1}) which are dependent on the quencher concentration. If, however, the quencher does not affect the lifetime of either ^{3}Sens or ^{1}Sens but deactivates only singlet oxygen, the plots yield a common intercept, independent of the quencher concentrations used. Since the data in Table I suggest that singlet oxygen is longer lived in deuterated solvents, the corresponding protiated solvent may be considered as a quencher. Plots of $[AO_2]^{-1}$ vs. $[A]^{-1}$ for the photooxygenation of 1-methylcyclohexene are given in Figure 1. The constant intercept is excellent corroborating evidence that the lifetime of ^{3}Sens is independent of solvent deuteration. There is ample precedent in the literature for the conclusion that τ^1_{Sens} does not change upon solvent deuteration.[5,14,15]

Our observations suggest that the approach taken by Kearns[1a] does not provide an adequate description for the quenching of singlet oxygen by solvent interactions. In particular, a direct correlation was not found between solvent isotope effects on the lifetime of singlet oxygen and the optical densities of the solvent in regions that correspond to the transitions [$^1\Delta_g(v = 0) \rightarrow 3\sum_g^-$] where oxygen is left in its ground electronic state with varying amounts of vibrational quanta.[16] Further work needs to be done, therefore, in the development of a satisfactory theory for the quenching of singlet oxygen by solvent interactions. Such work is presently being undertaken. The results of experiments in which the lifetime of singlet oxygen is determined directly from the decay of singlet oxygen luminescence should provide significant insight into the problem.[17] In fact, it has long been recognized that for solvents in which the rate constant for singlet oxygen decay (k_d) is small, the currently accepted indirect methods for determining singlet oxygen lifetimes cannot be used with any reasonable degree of accuracy.[3b] Byteva[17d] has noted that values for the lifetime of singlet oxygen in solution determined by the indirect method[1-3] are significantly smaller than values determined from the direct luminescence of singlet oxygen. This conclusion supports the results reported in this communication.

Acknowledgment. This work was supported by National Science Foundation Grant CHE77-21560.

(9) Determined by using Young's technique.[3a] The experimental apparatus is identical with that outlined in ref 7. DPBF decay curves were analyzed by a DEC PDP-11/45 computer using a program originally written by Dr. J. V. V. Kasper and Dr. R. W. Wake and revised by Dr. L. Levine and P. R. Ogilby.

(10) Calculated from the data shown in Figure 1.[12] 1-Methylcyclohexene was distilled prior to use. Samples were photooxygenated by a tungsten lamp in a merry-go-round apparatus. After having been reduced with triphenylphosphine, the samples were chromatographed on a Hewlett-Packard 5880A flame ionization gas chromatograph using a 6.0-ft × 0.085-in. column of 10% UCW 98 on a support of WHP. 1,4-Dimethoxybenzene was used as internal standard.

(11) C. S. Foote, ref 1e, p 139.

(12) It is important to recognize that in both types of β-value determinations (Young's method and the reciprocal plots of Figure 1), the formation constant for singlet oxygen (K) is canceled internally.[3,11,13] In taking the ratio of β values, therefore, the only assumption is that k_a is invariant to solvent deuteration. The large error in the isotope effect determined by using methylcyclohexene reflects the error in the intercepts in the plots of $[AO_2]^{-1}$ vs. $[A]^{-1}$.

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Chiral Discrimination in the Energetics of Ion Aggregation†

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Received November 17, 1980

Tables I and II present the first data known to us which compare directly the energetics of aggregation of chiral ions in solution to make diastereomeric ion pairs. It has been obvious since the principles of stereochemistry were first established over a century ago that diastereomers should differ in all of their physical properties, including heats of formation. However, until recently[1] the methods of purification and measurements were not sufficiently sensitive to detect the differences between diastereomeric solvates or ion pairs in solution[2] with certainty.

Tables I and II give unequivocal evidence that diastereomeric ion pairs formed by aggregation of even rather simple chiral ions can differ by 200–350 cal/mol in their heats of formation from the free ions—a factor sufficient to account for the difference between a 50:50 yield in a reaction and a 60:40 yield, for example. Highly purified solutions of the bases shown were titrated with solutions of mandelic acid. The compounds were chosen because the configurations of both enantiomers were well established[3] and (in addition to their pharmacological relevance) because both were readily available in high purity. This permitted us to apply the absolute method of cross-chiral checks between enantiomeric ion pairs [e.g., *R,R* vs. *S,S* or *R,S* vs. *S,R*].

Thermometric titration of (*R*)- or (*S*)-α-phenethylamine with (*R*)- or (*S*)-mandelic acid in water yielded a single value regardless of the configuration of the acid or base. Since only free ions should be formed in this solvent over the concentration range of the

† Work done at the University of Pittsburgh.

(1) Horeau, A.; Guette, J. P. *Tetrahedron* **1974**, *30*, 1923–1931. This reference discusses many early attempts to measure such small energetic differences and has shown that most reported values may be rejected for one reason or another.

(2) It is widely realized that the structures and lattice energies of diastereomeric compounds and salts differ considerably in the crystalline state.

(3) Wilen, S. H. *Top. Stereochem.* **1971**, *6*, 107–176.

0002-7863/81/1503-1221$01.25/0

Table I. Heats of Neutralization at 25 °C for α-Phenethylamine and Mandelic Acid

base	acid	$-\Delta H$, kcal/mol in dimethyl sulfoxide	dioxane	water
R	R	7.630 ± 0.013	8.757 ± 0.026	12.67 ± 0.01
S	S	7.612 ± 0.035	8.759 ± 0.023	12.61 ± 0.02
R	S	7.431 ± 0.014	8.416 ± 0.028	12.63 ± 0.02
S	R	7.374 ± 0.024	8.409 ± 0.024	12.63 ± 0.02

Table II. Heats of Neutralization at 25 °C in Me_2SO for Ephedrine and Pseudoephedrine [$C_6H_5CH(OH)CH(CH_3)NHCH_3$] and Mandelic Acid

compd	base	acid	$-\Delta H$, kcal/mol
ephedrine	1R,2S	R	7.294 ± 0.017
	1S,2R	S	7.325 ± 0.030
	1R,2S	S	7.550 ± 0.029
	1S,2R	R	7.607 ± 0.028
pseudoephedrine	1R,2R	R	6.672 ± 0.025
	1S,2S	S	6.657 ± 0.018
	1R,2R	S	6.401 ± 0.019
	1S,2S	R	6.380 ± 0.017

titration (0–9.5 × 10^{-3} M), this experiment is simply a check on the purity of the compounds and the consistency of the technique.

In dimethyl sulfoxide all three bases, α-phenethylamine (Table I), ephedrine, and pseudoephedrine (Table II), show clear differences, well outside experimental error, between diastereomeric combinations. For each case, enantiomeric combinations agree within experimental error. The average difference between diastereomeric combinations of α-phenethylamine with the mandelic acid antipodes is 225 cal/mol compared to 265 cal/mol for ephedrine and 274 cal/mol for pseudoephedrine, suggesting that the larger number of hydrogen-bonding sites in the latter two bases provides a slightly greater opportunity for chiral discrimination in ion aggregation. Conductance could be detected for all three mandelate salts in dimethyl sulfoxide by using a standard Jones-type cell with a 1% bridge.[4] This indicates the presence of free ammonium and carboxylate ions in dimethyl sulfoxide solutions which are probably in equilibrium with the hydrogen-bonded ion pair.

In dioxane the diastereomeric salts of α-phenethylammonium mandelate do not dissociate enough to give measurable conductance. The chiral discrimination factor for these salts in this solvent is now 345 cal/mol compared to 225 cal/mol in Me_2SO where it is less associated.

The question of structures of the ion aggregates is presently being examined by high field (300 and 600 MHz) ^1H NMR spectroscopy. The concentration dependence of the chemical shifts of different protons in diastereomeric solutions in Me_2SO is clearly different and behaves in a manner consistent with the notion that the diastereomeric ion pairs vary both in structure and in their ion-pairing association constants. We would expect the entropies of association to be nearly identical for diastereomeric ion pairs. If this were so, the observed differences in heats of neutralization in Me_2SO are determined both by the inherent enthalpy of ion pairing for each combination and by their different degrees of association. Since association in dioxane is virtually complete, the measured enthalpy difference should be uncomplicated by association differences.

Heats of neutralization were determined by thermometric titration of solutions of the base (or acid) in the solvent introduced into a solution of the acid (or base). Both the usual single buret method[5] and the double buret method[6] were used with comparable results.

(4) Precise conductance studies are currently under way using a high quality Jones bridge.

(5) Christensen, J. J; Ruckman, J.; Eatough, D. J.; Izatt, R. M. *Thermochim. Acta* **1972**, *3*, 203–218. Eatough, D. J.; Christensen, J. J.; Izatt, R. M. *Ibid.* **1972**, *3*, 219–246.

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Acknowledgment. This work was supported by NIH Grant GM-23086 and NSF Grant CHE-7622369 for which we are most grateful. We appreciate the help of Robin Avery and Ismene Petrakis in checking the thermometric titrations.

Synthesis of 16-Membered-Ring Macrolide Antibiotics. 3.[1] Carbomycin B and Leucomycin A_3: Retrosynthetic Studies

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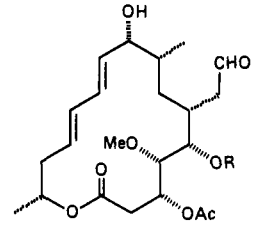
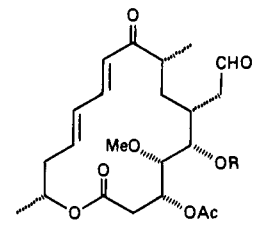
Received August 28, 1980

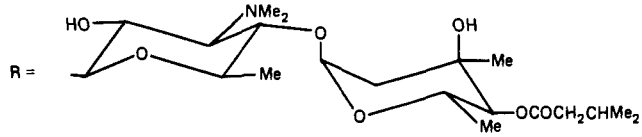
The 16-membered-ring macrolide antibiotics constitute an important, clinically useful series of naturally occurring compounds within the macrolide class of antibiotics.[2] Their rather complex molecular structures with the characteristic diene and polyoxygenated systems may be regarded as "structural turning points" from the lower ring size macrolide antibiotics (e.g., erythromycins)[2] to the higher size polyene macrolides (e.g., amphotericin).[2] Due to the complexity of these molecules, serious synthetic efforts in this area have only recently been reported.[1,3,4] In this series of papers we report the synthesis of carbomycin B (**1**)[5,7] (magnamycin B) and leucomycin A_3 (**2**)[6,7] (josamycin) in their optically active



(1)



(2)



forms from α-D-glucose by a strategy first outlined by us in 1979.[1,8]

† Fellow of the A. P. Sloan Foundation, 1979–1983; Recipient of a Camille and Henry Dreyfus Teacher-Scholar Award, 1980–1985.

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