Steric Acceleration of a Ring Closure to an Oxazepinone by Steric Hindrance (1)

Jonathan Turk, William M. Haney, Georgia Heid, Richard E. Barlow, and Leallyn B. Clapp

Department of Chemistry, Brown University, Providence, Rhode Island 02912

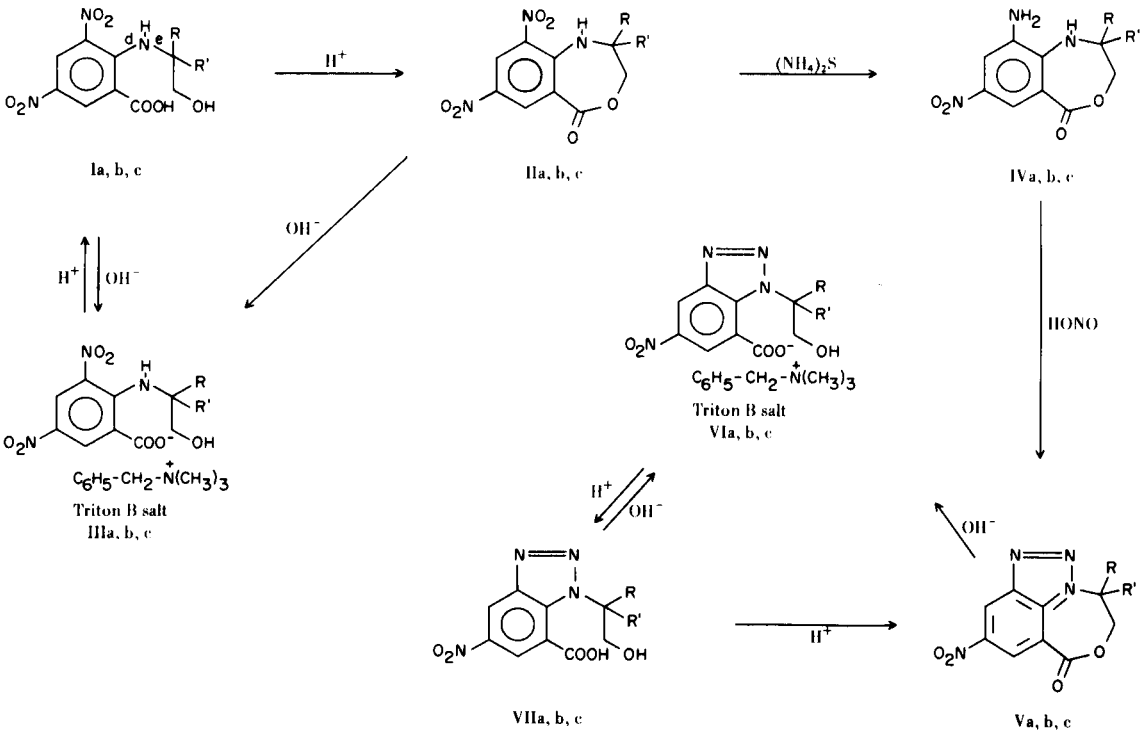
Received October 9, 1970

The *gem*-dialkyl effect, first mentioned in 1922, (2) has been reviewed by Bruice (3). Bruice and coworkers treated the formation and hydrolysis of alkyl substituted glutaric anhydrides quantitatively. They found that in similar homologs involving quite different kinds of reactions, the quantitative effects of an alkyl group, particularly methyl, was additive with respect to rate. We now report a heterocyclic cyclization in which the increased rate of reaction of one and two alkyl substitutions is of the same order of magnitude as that reported by Bruice. However, in a second case, a second alkyl substitution accelerates the rate by 140,000 times while the first substitution has only a slight accelerating effect.

When two methyl groups are substituted on the carbon α to the nitrogen in a substituted dinitroanthranilic acid (I), the ring closure to the corresponding benzoxazepinone (II) is accelerated by 24 times (Table I). However, when the movement about the nitrogen is restricted by making it a part of a triazolo ring (VII), then the same substitutions accelerate the corresponding ring closure to V by 140,000 times (Table I).

In compound Ia the tail on the amino nitrogen can flail about either C-N bond (d or e in Chart I) and hence the alcoholic OH group and the protonated carboxyl group come into contact with favorable conformations relatively few times. In Ic, the methyl groups, R and R′ and the

CHART I



a. R = R′ = H
b. R = C_2H_5, R′ = H
c. R = R′ = CH_3

TABLE I

Relative Rates of Ring Closure of Substituted Anthranilic Acids I and Substituted Triazolobenzoic Acids VII at 45°.

Ia	1.0
Ib	3.7
Ic	24.
VIIa	0.52
VIIb	0.63
VIIc	73000.

large nitro and carboxyl groups restrict some of the flailing of the tail and ring closure is 24 times faster. In VIIa the hydrogens (R and R′) again are ineffective in promoting ring closure even though the tail is now anchored at the nitrogen atom because of the triazolo and the aromatic ring. But in VIIc, a remarkable "steric acceleration through regulation of rotational conformations" (4) occurs. The compounds Ib and VIIb with one alkyl (R) group cyclize only slightly faster than those with no substitution.

In order to study the relative rates of ring closure in these series, Triton B salts III and VI were prepared since they were more easily purified than the potassium salts. Furthermore, compound IIc rearranges to a benzomorpholine (5) with prolonged reflux in alcoholic potassium hydroxide.

The compounds in Chart I other than the Triton B salts were previously reported (5) or were prepared by analogous methods (See Experimental).

EXPERIMENTAL

Relative Rates.

The rates of ring closure represented by the transformations I → II and VII → V were followed by titration of unused carboxylic acid I and VII except in the case of VIIc where the ring closure was too rapid to follow by this technique (see below). Methanol was chosen as solvent to keep organic substrates, potassium hydroxide, and hydrochloric acid in solution but it was found empirically that the indicator, bromcresol purple, gave a sharper color change in the acid-base titration (yellow to dark green) when some benzene was present. Reactions were therefore run in 70:30 (V/V) methanol: benzene, approximately 0.017 *M* in Triton B salt with various concentrations of hydrochloric acid.

In preliminary experiments if was found that the oxazepinone ring in compounds II and V did not open rapidly enough in the solvent used to interfere with the titration method. The rates were found to be linear with concentration of acid on Ia for 0.02-0.10 *M* solutions. At low concentration there was no deviation to 100% completion of the reaction and at the highest concentration, the rate was linear to at least 80% completion. The rate for compound Ia follows the law:

$$\text{rate} = k[\text{Ia}][H^+]$$

which suggests that the cyclization is similar to an ordinary esterification, known to be acid catalyzed. Relative rates for other ring closures were determined at acid concentrations near 0.02 *M* at 45.0 ± 0.3°. All values are the result of three or more runs on the same compound. The absolute rates of reaction at 45° were of the order of 10^{-5} l/mole/sec. for the slowest compound. The average deviation in rate was 3-7% for the various trials. Relative rates have an estimated accuracy of ± 2 in the second significant figure.

The rate of ring closure of VIIc to Vc was followed by uv absorption at 310 mμ in the appearance of Vc. The Triton B salt had a maximum absorption at 292 mμ which did not interfere. In the methanol-benzene solvent, Beer's law was followed by Vc for concentrations below $5 \times 10^{-3} M$. A concentration of $2 \times 10^{-5} M$ of Vc was found convenient for the rate study with a large excess of acid ($8 \times 10^{-4} M$) at 45°. Relative rates are given in Table I.

N-(1-Ethyl-2-hydroxyethyl)-3,5-dinitroanthranilic Acid (Ib).

Compound Ib was prepared from 2-chloro-3,5-dinitrobenzoic acid and 2-amino-1-butanol by the method previously described (5) in 90% yield, m.p. 143-145°. Dissolution in 5% sodium hydrogen carbonate, precipitation with cold dilute hydrochloric acid, and drying at 75° gave the analytical sample, m.p. 145.2-145.8°; IR spectrum, ν cm^{-1}; NH and OH, broad, 3500; NO_2, 1590 and 1340; CO, 1700.

Anal. Calcd. for $C_{11}H_{13}N_3O_7$: C, 44.13; H, 4.35; N, 14.05. Found: C, 43.82; H, 4.02; N, 13.95.

7,9-Dinitro-2-ethyl-1,2,3,5-tetrahydro-4,1-benzoxazepin-5-one (IIb).

The benzoxazepinone (IIb) was also prepared by a reported method (5) in 86% yield, m.p. 134-136°. Recrystallization from ethanol-carbon tetrachloride gave the analytical sample, m.p. 139.5-141.5°; IR spectrum, ν cm^{-1}; NH, broad, 3300; NO_2, 1580 and 1340; CO, 1690.

Anal. Calcd. for $C_{11}H_{11}N_3O_6$: C, 46.98; H, 3.94; N, 14.94. Found: C, 46.94; H, 4.07; N, 14.76.

Triton B Salts of Dinitroanthranilic Acids, I (IIIa,b,c).

Eleven g. (0.037 mole) of IIc (Ic could not be isolated since it cyclized rapidly.) was dissolved in 125 ml. of methanol and 16.4 g. (0.044 mole) of 40% benzyltrimethylammonium hydroxide (Triton B) in methanol was added. The solution was refluxed for two hours and the solvent removed leaving a syrup. The syrup was taken up in ethyl acetate and crystals precipitated on standing, yield 77%, m.p. 149.5-151.5°. The Triton B salt (IIIc) was recrystallized from ethyl acetate to give the analytical sample, m.p. 153.5-154.5°.

Anal. Calcd. for $C_{21}H_{28}N_4O_7$: C, 56.30; H, 6.24; N, 12.48. Found: C, 56.40; H, 6.36; N, 12.75.

The Triton B salts IIIa and IIIb were prepared in similar fashion. Both salts were hygroscopic.

IIIa, yield 36%, m.p. 100-102°; NMR spectrum (deuterium oxide, 10%, δ): 3.2 (s, 9) $N(CH_3)_3$; 3.3 (t, 2) CH_2OH; 3.4 (t, 2) NCH_2; 4.5 (s, 2) $NCH_2C_6H_5$; 7.5 (s, 5) C_6H_5; 8.9 (two d, 2) arom. The NH and OH protons were coupled with H_2O at δ 4.7.

Anal. Calcd. for $C_{19}H_{24}N_4O_7 \cdot \frac{1}{2}H_2O$: C, 53.02; H, 5.81; N, 13.01. Found: C, 52.75; H, 5.81; N, 13.04.

IIIb, yield 40%, m.p. 147-149°; NMR spectrum (deuterium oxide, 10%, δ): 0.9 (t, 3) CH_3CH_2; 1.7 (q, 2) CH_3-CH_2; 3.2 (m, 1) $CHCH_2OH$; 3.25 (s, 9) $N(CH_3)_3$; 3.7 (d, 2) CH_2OH; 4.5 (s, 2) $NCH_2C_6H_5$; 7.6 (s, 5) $CH_2C_6H_5$; 8.7 (two d, 2) arom. Again the NH and OH coupled with water at δ 4.7.

Anal. Calcd. for $C_{21}H_{28}N_4O_7 \cdot \frac{1}{2}H_2O$: C, 55.14; H, 6.35; N, 12.25. Found: C, 55.38; H, 6.28; N, 12.33.

2-Ethyl-7-nitro-9-amino-1,2,3,5-tetrahydro-4,1-benzoxazepin-5-one (IVb).

The amino group in compound IIb was reduced with 20% aque-

ous ammonium sulfide by a published method (5) in 74% yield, m.p. 192.5-195°, bright orange-red crystals. Recrystallization from methanol gave the analytical sample, m.p. 195-196.5°; IR spectrum, ν cm^{-1}; NH, 3380; NO_2, 1590 and 1330; CO, 1670.

Anal. Calcd. for $C_{11}H_{13}N_3O_4$: C, 52.59; H, 5.21; N, 16.73. Found: C, 52.69; H, 5.48; N, 16.92.

4-Ethyl-9-nitro-3,4,5,7-tetrahydrotriazolo-[1.5.4-j,k]-4,1-benzoxazepin-7-one (Vb).

Diazotization of IVb by the method used to prepare Va and Vc (5) gave Vb in 22% yield after recrystallization from ethanol, m.p. 162-164°. NMR spectrum (deuterioacetone, 10%, δ): 1.1 (t, 3) CH_3CH_2; 2.2 (q, 2) CH_3CH_2; 5.0 (d, 2) CH_2O; 5.4 (q, 1) NC*H*; 9.0 (two d, 2) arom.

Anal. Calcd. for $C_{11}H_{10}N_4O_4$: C, 50.38; H, 3.82; N, 21.37. Found: C, 50.47; H, 3.93; N, 21.37.

Triton B Salts of VII (VIa,b,c).

The Triton B salts of the carboxylic acids VII were prepared from the triazolobenzoxazepinones V by the method described for compounds III above. The syrups crystallized in ethyl acetate and were recrystallized from ethyl acetate.

VIa, m.p. 170-173°, 62%; NMR spectrum (deuterium oxide, 10%, δ): 3.3 (s, 9) $N(CH_3)_3$; 4.0 (t, 2) NCH_2CH_2; 4.5 (s, 2) $NCH_2C_6H_5$; 4.7 (br, 1) OH; 5.3 (t, 2) CH_2OH; 7.5 (s, 5) C_6H_5; 8.7 (two d, 2) arom.

Anal. Calcd. for $C_{19}H_{23}N_5O_5$: C, 56.85; H, 5.77; N, 17.45. Found: C, 56.81; H, 5.71; N, 17.37.

VIb, m.p. 136-140°, 73%; NMR spectrum (deuterium oxide, 10%, δ) 0.9 (t, 3) CH_3CH_2; 2.0 (q, 2) CH_3CH_2; 3.2 (s, 9) $N(CH_3)_3$; 4.2 (d, 2) CH_2OH; 4.5 (s, 2) $NCH_2C_6H_5$; 4.7 (br, 1) OH; 5.5 (q, 1) C*H*; 7.5 (s, 5) C_6H_5; 8.7 (two d, 2) arom.

Anal. Calcd. for $C_{21}H_{27}N_5O_5$: C, 58.73; H, 6.33; N, 16.31. Found: C, 58.84; H, 6.23; N, 15.75.

VIc, m.p. 191-193°, 35%; NMR spectrum (deuterium oxide, 10%, δ): 2.0 (s, 6) $C(CH_3)_2$; 3.3 (s, 9) $N(CH_3)_3$; 4.3 (s, 2) CH_2OH; 4.5 (s, 2) $NCH_2C_6H_5$; 7.6 (s, 5) C_6H_5; 8.6 (two d, 2) arom. The OH coupled with H_2O at δ 4.7.

Anal. Calcd. for $C_{21}H_{27}N_5O_5 \cdot 3/2\ H_2O$: C, 55.28; H, 6.58; N, 15.33. Found: C, 55.35; H, 6.43; N, 15.13.

REFERENCES

(1) Taken from the Senior Theses of Jonathan Turk, 1967, and Richard E. Barlow, 1970, and the MAT Theses of William M. Haney, 1969, and Georgia Heid, 1966.

(2) C. K. Ingold, *J. Chem. Soc.*, 2676 (1922).

(3) T. C. Bruice and U. K. Pandit, *J. Am. Chem. Soc.*, **82**, 5858 (1960); T. C. Bruice and W. C. Bradbury, *ibid.*, **87**, 4838, 4846, 4851 (1965).

(4) Title of a paper on the Smiles rearrangement, J. F. Bunnett and T. Okamoto, *ibid.*, 78, 5363 (1956).

(5) C. G. Wood, A. Geertsema, L. Freeburg, E. J. Reardon, H. R. Jurgens, and L. B. Clapp, *J. Heterocyclic Chem.*, **2**, 414 (1965).