1F32 CA 05575-01) and V.M.K. by the J. N. Tata Endowment, India. We also wish to thank Professor H. S. Mosher for providing the optically active amino carbinol **1**.

References and Notes

(1) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions", Prentice-Hall, Englewood Cliffs, N.J., 1970; Reprint Edition, American Chemical Society Book Department, Washington, D.C., 1976. J. W. Scott and D. Valentine, *Science*, **184**, 943 (1974).

(2) For a review see S. Yamada and K. Koga in "Selective Crganic Transformations", Vol. 1, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N.Y., 1970, pp 1–33.

(3) Chiral lithium aluminum hydride reagents not included in ref 1 and 2: A. S. Angeloni, R. Andrisano, and S. Marzocchi, *Tetrahedron*, **29**, 913 (1973); A. I. Meyers and P. M. Kendall, *Tetrahedron. Lett.*, 1337 (1974); T. A. Whitney and A. W. Langer, *Adv. Chem. Ser.*, **No. 130**, 270 (1974); M. F. Grundon, D. G. McCleery, and J. W. Wilson, *Tetrahedron Lett.*, 295 (1976); D. Seebach and H. Daum, *Chem. Ber.*, **107**, 1748 (1974); J. P. Vigneron and I. Jacquet, *Tetrahedron Lett.*, 2065 (1974); J. P. Vigneron and I. Jacquet, *Tetrahedron*, **32**, 939 (1976); H. J. Schneider and R. Haller, *Chem. Ber.*, **106**, 1312 (1973); G. M. Giongo, F. Di Gregorio, N. Palladino, and W. Marconi, *Tetrahedron Lett.*, 3195 (1973).

(4) Chiral borohydrides: J. P. Masse and E. R. Parayre, *J. Chem. Soc., Chem. Commun.*, 438 (1976); S. Colonna and R. Fornasier, *Synthesis*, 531 (1975); and M. F. Grundon, J. A. Khan, D. R. Boyd, and W. R. Jackson, *J. Chem. Soc. C*, 2557 (1971).

(5) Chiral hydride reagents used in synthesis: M. J. Drabicky, P. C. Myhre, C. J. Reich, and E. R. Schmittou, *J. Org. Chem.*, **41**, 1472 (1976); D. Seebach and H. Meyer, *Angew, Chem., Int. Ed. Engl.*, **13**, 77 (1974); M. Lahav, F. Laub, E. Gati, L. Leiserowitz, and Z. Ludmer, *J. Am. Chem. Soc.*, **98**, 1620 (1976); and K. Kabuto and H. Ziffer, *J. Org. Chem.*, **40**, 3467 (1975).

(6) S. Yamaguchi, H. S. Mosher, and A. Pohland, *J. Am. Chem. Soc.*, **94**, 9254 (1972); and S. Yamaguchi and H. S. Mosher, *J. Org. Chem.*, **38**, 1870 (1973).

(7) When the reductions were performed at temperatures above −78 °C, significantly lower enantiomeric ratios were obtained. Moreover, when additions of the ketones were carried out in <5 min at −78 °C, low enantiomeric ratios also resulted.

(8) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969); and J. A. Dale and H. S. Mosher, *J. Am. Chem. Soc.*, **95**, 512 (1973).

(9) Cf. M. M. Midland, *J. Org. Chem.*, **40**, 2250 (1975).

(10) (a) K. Bowden, I. M. Heilborn, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946). (b) For the oxidation to ketone **4** see A. Nobuhara, *Agr. Biol. Chem.*, **33**, 1264 (1969); *Chem. Abstr.*, **72**, 89714† (1970).

(11) All new compounds demonstrate acceptable analysis and spectral data in accord with assigned structures.

(12) The synthesis of ketones **7–9** is described in detail in ref 16. For a description of the synthesis of the alcohol precursor to ketone **10**, see W. S. Johnson, S. Escher, and B. W. Metcalf, *J. Am. Chem. Soc.*, **98**, 1039 (1976). For alternate syntheses of the ketones used in runs 1 and 4, see E. S. Turbanova, Y. I. Porfir'eva, and A. A. Petrov, *Zh. Organ. Khim.*, **2**, 772 (1966), and L. S. Meriwether, E. C. Colthup, and G. W. Kennerly, *J. Org. Chem.*, **26**, 5163 (1961), respectively.

(13) We have learned in a private communication that N. Cohen and C. Neukom of Hoffmann-La Roche Inc., using the procedure described in the present paper, have effected asymmetric reductions of several acetylenic ketones and also have obtained generally high enantiomeric ratios.

(14) For example, see K. K. Chan, N. C. Cohen, J. P. DeNoble, A. C. Specian, Jr., and G. Saucy, *J. Org. Chem.*, **41**, 3497 (1976).

(15) For an example, see J. Fried, C. Lin, M. Mehra, W. Kao, and P. Dahren, *Ann. N.Y. Acad. Sci.*, **180**, 38 (1971); and R. Pappo, P. Collins, and C. Jung, *ibid.*, **180**, 64 (1971).

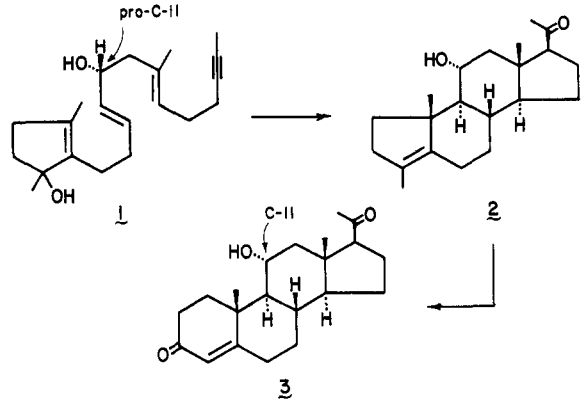
(16) W. S. Johnson, R. S. Brinkmeyer, V. M. Kapoor, and T. M. Yarnell, *J. Am. Chem. Soc.*, following paper in this issue.

Raymond S. Brinkmeyer,* Vijaya M. Kapoor
Department of Chemistry, Stanford University
Stanford, California 94305
Received August 10, 1977

Asymmetric Total Synthesis of 11α-Hydroxyprogesterone via a Biomimetic Polyene Cyclization[1]

Sir:

We have previously shown that the racemic form of substance **1** can be induced to undergo a stereoselective acid-catalyzed biomimetic cyclization so as to produce mainly a single tetracyclic product (**2** + enantio-**2**).[2] This latter material was readily converted, by ozonolysis followed by cyclodehydration of the resulting ring A seco diketone, into racemic 11α-hydroxyprogesterone (**3** + enantio-**3**). The failure to detect any racemic 11β isomer at this stage showed that the cyclization step was proceeding asymmetrically owing to the influence of the chiral center at pro-C-11 (see formula **1**). It, therefore, became of prime importance to ascertain whether cyclization of the optically active form of the substrate **1** (with the *R* configuration at pro-C-11) would occur faster than racemization to produce an optically active product **2.** The outcome of this finding has been the realization of an asymmetric total synthesis of 11α-hydroxyprogesterone (**3**) which is the key intermediate in the commercial production of hydrocortisone acetate.[3]

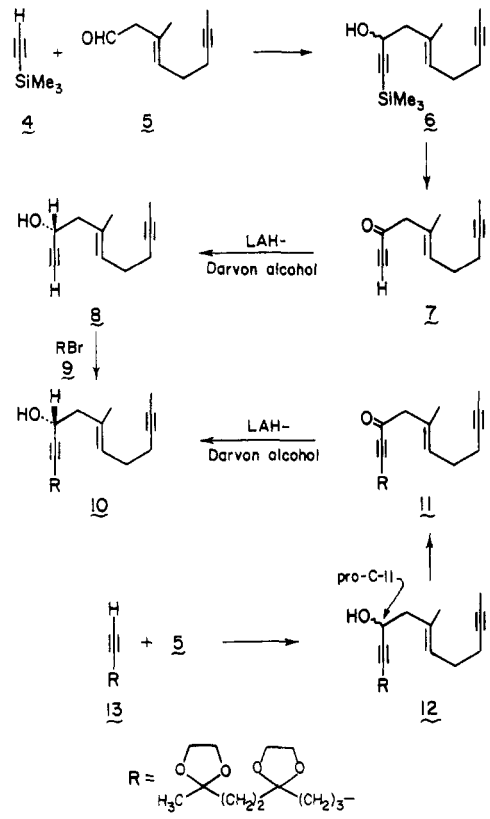


The reported synthesis[2] of the racemic form of the cyclization substrate **1** involved, as the convergent step, addition of the lithium acetylide of the diketal **13** to the aldehyde **5** to give the propargylic alcohol **12,** which was then submitted to the following steps: hydride reduction to the trans allylic alcohol; ketal hydrolysis; cyclodehydration of the resulting δ diketone giving the cyclopentenone system; and then, finally, reaction with methyllithium. Thus the pro-C-11 chiral center first appeared at the stage of the propargylic alcohol **12.** Preliminary attempts to resolve this substance were unpromising; therefore attention was turned to an alternative synthesis in which the chiral center was established at an earlier stage in a smaller molecule which promised to be more susceptible to resolution.

The new scheme was first examined in the racemic series. Thus the aldehyde **5** was treated with the lithium salt of trimethylsilylacetylene (**4**)[4] to give the trimethylsilylacetylenic alcohol **6**[5] (Scheme I) in 92% yield after distillation.[6] Treatment of **6** with aqueous methanolic potassium hydroxide effected desilylation and the product (**8** + enantio-**8**),[5] obtained in 100% yield after distillation,[6] was converted to the known diketal propargylic alcohol **12** as follows. Treatment of **8** + enantio-**8** with *tert*-butyldimethylsilyl chloride and imidazole in DMF gave a 92% yield of the *O*-silyl ether,[5] which was converted into the lithium salt with *n*-butyllithium in glyme containing 20% HMPA. Alkylation of this salt with the diketal bromide **9** (15 h at 25 °C), afforded the *tert*-butyldimethylsilyl ether[5] of **12** which was isolated in 71% yield after chromatography on silica gel. Desilylation of this ether with tetra-*n*-butylammonium fluoride in THF gave a quantitative yield of **12,** identical with authentic material by IR, NMR, and VPC comparison.

The racemic propargylic alcohol (**8** + enantio-**8**) could be partially resolved as the brucine salt of the half-acid phthalate. Hydrolysis of the fraction which crystallized from benzene/ether yielded the product **8**, $[\alpha]^{EtOH}_{D}$ + 14.8° (*c* 1.87)[7] corresponding to an enantiomeric ratio of ~90:10, as estimated by GC analysis of the methoxytrifluoromethylphenylacetic (MTPA) ester[8] on a 12-ft OV-3 column (baseline separation). The absolute configuration of the dextrorotatory product[9] was confirmed as **8** by relating it to 11α-hydroxyprogesterone (see

Scheme I



below). The mother liquor material from the aforementioned crystallization yielded, on hydrolysis, material enriched in enantio-**8**, $[\alpha]^{EtOH}_D$ −10.4° (*c* 1.83).[7]

An asymmetric synthesis of **8** leading to a product of slightly higher optical purity than that described above was developed by Brinkmeyer and Kapoor[9] involving the asymmetric reduction of the acetylenic ketone **7** with the complex from lithium aluminum hydride and Darvon alcohol.[10] Thus the product **8** was produced in 70% yield after chromatography on Florisil, $[\alpha]^{EtOH}_D$ +15.1° (*c* 2.01),[7] $[\alpha]^{CHCl_3}_D$ +63.5° (*c* 2.08).[7] The enantiomeric ratio of this specimen was estimated to be ~91:9 by GC of the MTPA ester. The ketone **7**[5] required for the asymmetric reduction was prepared in 78% yield by desilylation (see above) followed by Jones oxidation[11] and chromatography on silica gel.

The +15.1° sample of **8** was converted, by the procedures described above, into **10**, $[\alpha]^{EtOH}_D$ +5.2° (*c* 4.1).[7] The enantiomeric ratio of this specimen was regarded as being also ~91:9 because the reaction conditions involved in the conversion of **8** to **10** were not considered likely to cause any racemization.

A product of somewhat higher optical purity was obtained by reduction of the ketone **11** with lithium aluminum hydride–Darvon alcohol complex.[9,10] Thus a 93% yield of **10**, $[\alpha]^{EtOH}_D$ +5.4° (*c* 4.1),[7] was obtained after chromatography on Florisil. An enantiomeric ratio of 92:8 was calculated from the rotation data. This became the method of choice for the preparation of **10** because the ketone **11**[5] was easily produced in 92% yield by oxidation of the racemic alcohol **12** with Jones reagent[11] at 0 °C, followed by chromatography on neutral alumina.

The specimen of **10** (estimated enantiomeric ratio 92:8) was converted into **1** (see above) which was cyclized by an improved procedure involving slow addition over 2–3 h of a solution of 0.9 mmol of the substrate in 5–6 mL of methylene chloride to a mixture composed of 90 mL of trifluoroacetic acid and 242 mL of trifluoroethanol at −15 °C. After 16 h at 25 °C, the solvent was removed by distillation at reduced pressure, and the residue was treated with potassium carbonate in aqueous methanol and then acetylated with acetic anhydride and pyridine. Chromatography on silica gel gave, after an early fraction (~10% yield) containing what we presume to be mainly 13α isomers,[12] a 40% yield of the acetate of **2** as a mixture of 17β and 17α epimers, predominantly the former. Ozonolysis followed by cyclodehydration[2] afforded, in 80% overall yield from the acetate of **2**, a mixture of **3** (the major product) and its 17α epimer along with some of their enantiomeric forms. A major portion of the 17β epimer was isolated by crystallization, and the remainder was separated completely from the 17α fraction by liquid chromatography of the mother liquors at 1000–1200 psi on a Li Chrosorb Si 60 column (1:1 pentane–ethyl acetate containing 1% acetonitrile). The total combined 17β fractions (70% by weight) exhibited $[\alpha]^{CHCl_3}_D$ +147° (*c* 1.0),[7] $[\alpha]^{EtOH}_D$ +139° (*c* 1.0),[7] as compared with the values of +176 and +165, respectively, found by us for authentic 11α-hydroxyprogesterone (purified by liquid chromatography), mp 166–168 °C. From these data the ratio of **3** to enantio-**3** in the synthetic material is calculated to be 92:8. The major fraction (30% by weight) from the aforementioned crystallization melted at 164–166 °C, $[\alpha]^{CHCl_3}_D$ +180° (*c* 0.8).[7] A mixture of this specimen with the authentic 11α-hydroxyprogesterone melted at 166–168 °C.

The 17α fraction (see above) exhibited $[\alpha]^{CHCl_3}_D$ −12.5° (*c* 0.8),[7] reported for the 17α epimer of 11α-hydroxyprogesterone, $[\alpha]^{CHCl_3}_D$ −12° (*c* 0.995).[13]

The foregoing results demonstrate that *the cyclization* ***1*** → ***2****, as well as the subsequent steps of the synthesis, proceeds without any perceptible racemization, thus providing an asymmetric total synthesis of 11α-hydroxyprogesterone.*

Acknowledgment. This work was supported by the National Institutes of Health and the National Science Foundation. R.S.B. was also assisted by an NIH Postdoctoral Fellowship (National Cancer Institute Grant No. 1F32 CA 05575-01), and V.M.K. by the J. N. Tata Endowment, India.

References and Notes

(1) For a recent paper in this series see F. E. Brot, w. S. Johnson, B. E. Ratcliffe, and G. D. Stelling, *Bioorgan. Chem.*, **6**, 257 (1977).
(2) W. S. Johnson, S. Escher, and B. W. Metcalf, *J. Am. Chem. Soc.*, **98**, 1039 (1976).
(3) In a personal communication, Dr. Philip F. Beal, III, of the Upjohn Co. has indicated that the commercial conversion of **3** into hydrocortisone acetate is accomplished in ~50% yield according to a simplified and refined version of the published method: J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze, and R. W. Jackson, *J. Am. Chem. Soc.*, **77**, 4436 (1955).
(4) W. Findeiss, W. Davidsohn, and M. C. Henry, *J. Organomet. Chem.*, **9**, 435 (1967).
(5) (a) The NMR and IR spectra were entirely consistent with the assigned structure. (b) Satisfactory C, H analysis were obtained.
(6) Evaporative bulb-to-bulb distillation using a Buchi Kugelrohrofen.
(7) Rotations were determined at 20 °C using a 1-dm tube in a Perkin-Elmer 141 polarimeter.
(8) J. A. Dale, D. L. Dull and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969).
(9) R. S. Brinkmeyer and V. M. Kapoor, *J. Am. Chem. Soc.*, preceding paper in this issue.
(10) S. Yamaguchi and H. S. Mosher, *J. Org. Chem..*, **38**, 1870 (1973).
(11) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(12) Evidence has been gradually accumulating in our laboratory suggesting that the cyclization of substrates like **1** having an acetylenic terminator often, but not always, leads to products contaminated by some 13α (C/D cis) isomers. For some time these contaminants were not recognized because they generally were produced in small amounts (sometimes <3%) and were inadvertnely eliminated by chromatography in an early eluent. More recently we found an example of a cyclization involving the phenylacetylenic terminator in which as much as one-fifth of the product was a single crystalline 13α isomer (see W. S. Johnson, *Bioorgan. Chem.*, **5**, 90 (1976)). Since the constitution of this substance was established unequivocally by x-ray analysis, we have been alerted to the possibility of the presence of this type of contaminant, and have found evidence for it in some systems involving the acetylenic but not the olefinic bond. In due course we plan to report in detail on this problem which involves some abnormal behavior of the type first observed by P. T. Lansbury and G. E. DuBois,

Chem. Commun., 1107 (1971). See also P. T. Lansbury, T. R. Demmin, G. E. DuBois and V. R. Haddon, *J. Am. Chem. Soc.*, **97**, 394 (1975).
(13) H. C. Murray and D. H. Peterson, U.S. Patent 2 602 769; *Chem. Abstr.*, **46**, P8334*b* (1952).

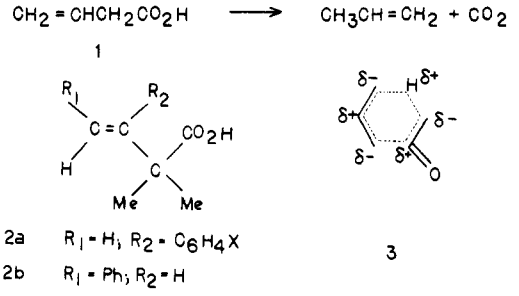
William S. Johnson,* Raymond S. Brinkmeyer
Vijaya M. Kapoor, Thomas M. Yarnell
Department of Chemistry, Stanford University
Stanford, California 94305
Received August 10, 1977

Thermal Decarboxylation of But-3-enoic Acid. MINDO/3 Calculations of Activation Parameters and Primary Kinetic Isotope Effects

Sir:

While typical pericyclic reactions have traditionally been considered[1,2] to take place in a synchronous manner,[3] recent MINDO/3[4] molecular orbital calculations suggest that this is rarely so. Thus the Diels–Alder reactions of ethylene with butadiene, and of acetylene or ethylene with cyclobutadiene, are predicted to involve highly unsymmetrical transition states in which one of the new bonds is essentially formed while the other is barely formed at all.[5,6] A similar situation was found for the "allowed" conversion of benzvalene to benzene[7] and in several chelotropic reactions.[8] The "allowed" thermal ring opening of bicyclobutane to butadiene[9] and the degenerate Cope rearrangement of bicyclo[2.2.0]hexane[10] were predicted by MINDO/3 to be not only nonsynchronous[3] but two-step[3] reactions involving stable biradical intermediates. It was therefore with interest that we discovered that according to our MINDO/3 calculations the retro-ene decarboxylation of but-3-enoic acid (**1**) proceeded via a six-center transition state in a synchronous manner.

The kinetics of decomposition of **1** have been reported sev-



eral times.[11-13] Most of the mechanistic studies, however, owing largely to Bigley and coworkers,[12,14-18] have been concerned with the analogous 2,2-dimethylbut-3-enoic acid derivatives **2** since these are free of complications arising from isomerization to the α,β-unsaturated acids and show a lower tendency to lactone formation.[19] These studies [20]pointed to a synchronous reaction via a six-membered transition state for the gas phase thermal decomposition of **1** and related acids. Thus the reaction is homogeneous and first order,[13,17] has a

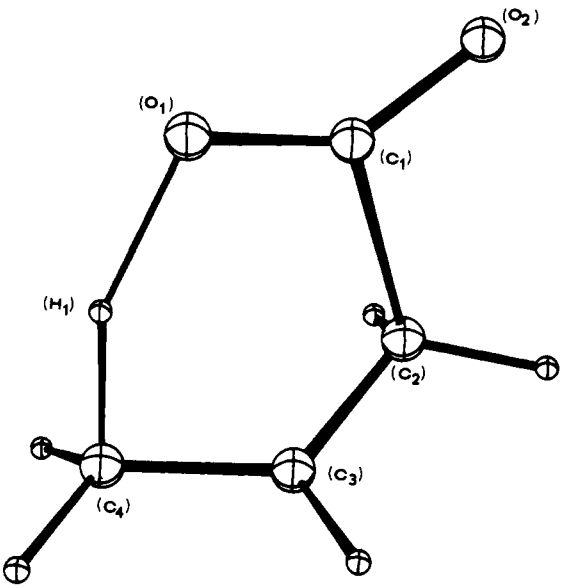


Figure 1. ORTEP plot of the calculated transition state for thermal decomposition of but-3-enoic acid.

negative entropy of activation,[12,16,17] proceeds at the same rate in the gas as in the liquid phase,[17] and shows significant deuterium[11,15] and ^{14}C[16] kinetic isotope effects (see below). Substituent effects in a series of substituted 2,2-dimethyl-3-phenylbut-3-enoic acids **2a** have been reported,[14] and, on the basis of a Hammett σ^+ correlation, suggest approximately a 20% positive charge development at C_3 in the transition state.

The transition state predicted by our MINDO/3 calculations is shown in Figure 1 and Table I and is completely consistent with these experimental data and the pictorial representation **3** of this transition state assumed by workers in this field.[20] Several features may be noted with respect to the "synchronicity" of this reaction. Thus the C_2C_3 and C_3C_4 bonds are of equal length (cf. 1.34 and 1.49 Å in **1**) in the transition state. The breaking bonds C_1C_2 and H_1O_1 are *both* substantially extended. The hydrogen atom H_1 is approximately midway between C_4 and O_1 and the OCO angle is intermediate between that in **1** (121.9) and the incipient CO_2 molecule. The geometry of Figure 1 corresponds approximately to a rather flattened boat. Consequently we assumed at first that there must be an alternative reaction path via an analogous chair conformer, but despite our most diligent efforts we were unable to locate such a transition state. In agreement with the studies[14] of substituent effects, the calculations imply development of a sizable positive charge at C_3 (column 4, Table I). The calculations also bear out the "intuitive" transition state model **3** in predicting development of negative charge at C_2 and C_4. The only available data concerning substituent effects at these positions are for various methylated and phenylated[12,16] derivatives in which it is not possible to distinguish the electronic and steric influences.

In view of our recent success in calculating molecular vibrational frequencies,[21] isotopic shifts,[22] and absolute en-

Table I. Structural Parameters and Formal Charge Distribution for But-3-enoic Acid Retro-ene Transition State (Figure 1)

Bond lengths, Å	Bond angles, degrees	Formal charges	δ^a
C_1C_2, 1.680	$C_1C_2C_3$, 106.58	C_1, 0.8926	0.0737
C_2C_3, 1.420	$C_2C_3C_4$, 125.24	C_2, 0.1640	−0.1051
C_3C_4, 1.420	$C_3C_4H_1$, 90.25	C_3, 0.2469	0.2255
O_1C_1, 1.248	$C_4H_1O_1$, 150.21	C_4, −0.1210	−0.0877
O_2C_1, 1.218	$H_1O_1C_1$, 114.01	O_1, −0.6143	−0.1018
H_1O_1, 1.419	$O_1C_1C_2$, 111.39	O_2, −0.5716	−0.0400
H_1C_4, 1.218	$O_1C_1O_2$, 139.80	H_1, 0.1987	−0.0591

[a] Charge development; i.e., $\delta = q$ (transition state) $- q$ (reactant).