evaported. Column chromatography of the residue yielded **34** (0.18 g, 61%) as an oil: IR (neat) 3300, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.02-2.17 (m, 1 H), 2.39-2.42 (m, 1 H), 3.64-3.67 (m, 1 H), 3.94-3.95 (m, 1 H), 4.10, 4.92 (AB q, J = 15.2 Hz, each 1 H), 4.27-4.32 (m, 1 H), 4.42-4.51 (m, 1 H), 5.01 (s, 2 H), 6.02-6.04 (br s, 1 H), 7.32 (s, 10 H); HRMS calcd for $C_{22}H_{21}F_3N_2O_5$ 450.1403, found 450.1411.

***trans*-*N*-Benzyl-2-(acetoxymethyl)-4-(acetylamino)-pyrrolidine (33).** A suspension of **33** (0.18 g, 0.40 mmol) and $Pd(OH)_2$ (15 mg) in methanol (4 mL) was stirred under hydrogen at atmosphere for 3 h. The mixture was filtered through Celite and washed with methanol. The combined solvents were evaported and dried in vacuo to give crude *trans*-*N*-benzyl-5-[(trifluoroacetoxy)methyl]-3-aminopyrrolidin-2-one (**35**) (0.14 g). Without further purification, to a solution of **35** (0.14 g) in THF (5 mL) was added $LiAlH_4$ (31 mg, 0.8 mmol) with ice cooling. The reaction mixutre was refluxed for 7 h. To the mixture was successively added water (0.02 mL), 10% NaOH solution (0.02 mL), water (0.04 mL), and THF (10 mL), and then the mixture was dried with potassium carbonate. The mixture was filtered through Celite, and the filtrate was evaporated to afford the crude *trans*-*N*-benzyl-5-(hydroxymethyl)-3-aminopyrrolidine (**36**) (0.1 g). To a solution of **36** (0.06 g) in pyridine (0.39 ml) was added triethylamine (0.11 mL, 0.8 mmol) and acetic anhydride (0.19 mL, 2 mmol) with ice cooling. The reaction mixture was stirred at room temperature for 15 h, diluted with ethyl acetate, and washed with water and brine. The combined aqueous washings were extracted with methylene chloride. The combined organic solvents were dried and evaporated. Column chromatography of the residue yielded **33** (0.06 g) in 52% yield from **34**: mp 69-70 °C (lit.[16] 72-73 °C); IR (Nujol) 3300, 1720, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.77-1.78 (m, 1 H), 1.91 (s, 3 H), 2.07 (s, 3 H), 2.13-2.14 (m, 2 H), 3.00-3.05 (m, 1 H), 3.25 (dd, J = 6.3, 6.8 Hz, 1 H), 3.47 (d, J = 13.2 Hz, 1 H), 4.05-4.10 (m, 3 H), 4.32-4.40 (m, 1 H), 5.41 (br s, 1 H), 7.28-7.29 (m, 5 H).

X-ray Analysis of 28a. Crystals were obtained from the ethyl acetate solution which was kept in the desiccator filled with *n*-hexane vapor. The diffraction experiments were carried out using a crystal, the size of which was 0.3 × 0.2 × 0.1 mm. The diffractometer AFC/5(RIGAC) was used with a gfaphite-monochromated Cu Kα (r = 1.5418 Å) radiation. The unit cell dimensions were refined using the precisely measured 2θ values in the range of 30-60°. The crystal data are as follows: a = 14.166 (3) Å, b = 9.550 (2) Å, c = 15.226 (3) Å, β = 105.23 (9)°, U = 1987.4 $Å^3$, space group $P2_1/c$, Z = 4, D_x = 1.552 kg/m^3, μ(Cu Kα) = 130.95 cm^{-1}, 3376 unique reflections (2θ ≤ 130°) were measured, of which 2803 with $|F_{obs}| \geq 2.667\sigma(F)$ were used in the analysis. The structure was solved by the direct method using the program SIR85[17] and the difference Fourier method. The refinement of atomic parameters was carried out using the block-diagonal matrix least-squares method. After all the non-hydrogen atoms were refined with isotropic temperature factors, the empirical absorption corrections were applied following the DIFABS method.[18] The corrected structure factors were used throughout the successive refinement cycles. The anisotropic temperature factors were used for all the non-hydrogen atoms and the isotropic ones for the hydrogen atoms. The final R and R_w values were 0.076 and 0.081, where the minimized function was $\sum w = (|F_o| - |F_c|)^2$ and $\sqrt{w} = 1/\sigma(F)$. The maximum residual electron density is 0.4 $e/Å^3$. The atomic scattering factors were taken from the *International Tables for X-ray Crystallography*.[19]

Acknowledgment. We acknowledge partial financial support from the Ministry of Education, Sciences and Culture, the Japanese Government [Scientific Research (No. 63570986)].

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Synthesis and Crystal and Molecular Structure of the Conformationally Restricted Methionine Analogue (±)-2-*exo*-Amino-6-*endo*-(methylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylic Acid and Neighboring Group Participation in Its Anodic Oxidation

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(±)-2-*exo*-Amino-6-*endo*-(methylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (**1c**) was synthesized by amination of the lithium enolate of methyl 6-*endo*-(methylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylate with *O*-(mesitylenesulfonyl)hydroxylamine followed by hydrolysis. Its crystal and molecular structure was determined by single-crystal X-ray analysis. It crystallizes in the monoclinic space group $P2_{1/c}$ with a = 9.681 (6) Å, b = 10.276 (5) Å, c = 9.773 (4) Å, β = 91.23 (4)°, and Z = 4. The structure was solved by direct methods. Full-matrix least-squares refinement led to a conventional R factor of 0.048 after several cycles of anisotropic refinement. The structure is compared both with 6-*exo*-(methylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (**3**) and the HBr salt of 2-*exo*-aminobicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (**2**). Electrochemical oxidation of **1c** in acetonitrile, using the technique of cyclic voltammetry, revealed two oxidation waves with peak potentials of 0.90 and 1.35 V. Controlled potential electrolysis of **1c** provided the corresponding sulfoxides as a mixture of diastereomers (in 60 and 25-30% yield, respectively), which were also prepared by chemical oxidation, derivatized, separated, and characterized. The remarkable cathodic shift of 450 mV for **1c** is ascribed to neighboring carboxylate participation in oxidation of the thioether moiety.

Electrochemical oxidation of the salt obtained from *endo*-acid **1a** and 2,6-di-*tert*-butylpyridine occurs with bromide catalysis of oxidation of the thioether moiety with neighboring carboxylate participation.[1] The bromide ion is oxidized to bromine at a peak potential of 0.65 V vs Ag/0.1 M $AgNO_3$ in acetonitrile reference electrode. The bromine then reacts with the thioether, and bromide ion is rapidly displaced by the neighboring carboxylate group

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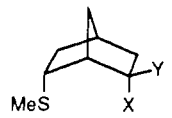


1a: X = CO_2H; Y = H **d**: X = CO_2Me; Y = H
b: X = H; Y = CO_2H **e**: X = CO_2Me; Y = NH_2
c: X = CO_2^-; Y = NH_3^+ **f**: X = CO_2Me; Y = NHCOPh

to form an acyloxysulfonium salt. Then the regenerated bromide is again oxidized to bromine, continuing the cycle. At a substrate to catalyst ratio of 2, the salt of **1a** shows a catalytic enhancement of 38, leading to a diffusion-controlled oxidation of the substrate.[2] If no bromide ion is present, then the oxidation of the salt of **1a** occurs with a peak potential of 1.20 V, which is close to that of the salt of **1b** (1.28 V) in which neighboring carboxylate participation is geometrically precluded. Thus, there is no substantial cathodic shift of the potential of direct electrochemical oxidation of the thioether moiety in the salt of **1a**, where neighboring group participation is possible. This paper reports the synthesis and structural characterization by X-ray methods of the constrained methionine analogue **1c**, which only differs from **1a** by having a 2-*exo*-amino group, and the electrochemical oxidation of this compound which shows a substantial facilitation of direct oxidation of the thioether group that, unlike the facilitated oxidation of the salt of **1a**, does not require bromide catalysis. The results presented in this paper may be important in understanding the oxidation of the thioether side chain of methionine-containing proteins, an area of considerable current interest.

Results and Discussion

Synthesis. Conversion of endo ester **1d**[3] into its enolate by treatment with lithium *N,N*-diisopropylamide in tetrahydrofuran containing hexamethylphosphoric acid triamide followed by the addition of *O*-(mesitylenesulfonyl)hydroxylamine[4] gave a mixture of products from which amino ester **1e** was isolated in 38% yield as a crystalline solid.[5]

Hydrolysis of amino ester **1e** with potassium hydroxide in aqueous methanol provided amino acid **1c** after neutralization and workup. Recrystallization of this compound from ethanol gave crystals suitable for X-ray crystallographic structure analysis.

X-ray Structure Study. The compound crystallized in the monoclinic space group $P2_1/c$, and crystal data are given in Table I. A stereoscopic view of the molecule is shown in Figure 1. The bond length, bond angles, and torsion angles are within the expected ranges.

Table I. Crystal Data[a] for Amino Acid 1c

molecular formula	$C_9H_{15}NO_2S$
molecular weight	201.29
space group	$P2_1/c$ (no. 14)[b]
cell dimensions	
a, Å	9.681 (6)
b, Å	10.276 (5)
c, Å	9.773 (4)
β, deg	91.23 (4)
V, Å^3	972.1
Z	4
d_{obsd}, g cm^{-3} [c]	1.40
d_{calcd}, g cm^{-3}	1.38
no. of unique data	1725
no. of data used in the calculations	1649
absorption coefficient ($\mu\lambda$), cm^{-1}	2.9

[a] The standard deviation of the least significant figure is given in parentheses in this table. [b] Based upon the systematic absences; $h0l$, $l = 2n$; $0k0$, $k = 2n$; and subsequent least-squares refinement. [c] Density was determined by the flotation method using a solution of dichloromethane and carbon tetrachloride.

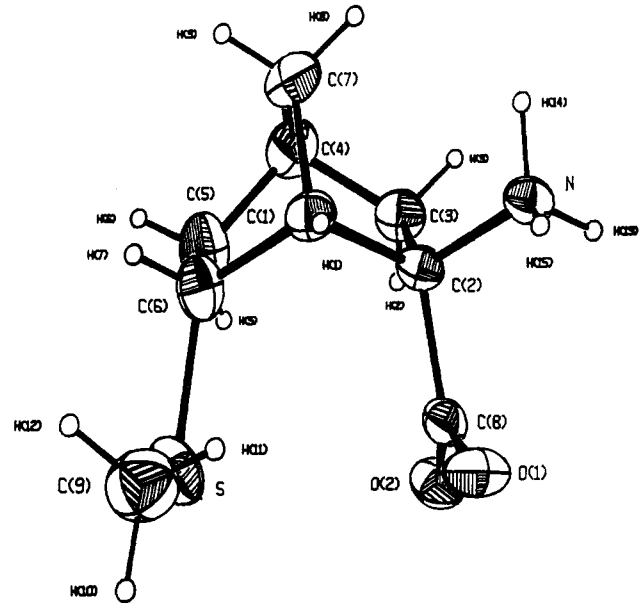
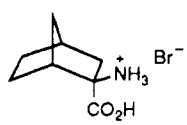
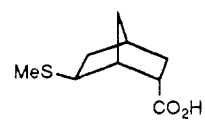


Figure 1. ORTEP[27] drawing of amino acid **1c**. The hydrogen atoms have been assigned arbitrary thermal parameters. Thermal ellipsoids are drawn to enclose 50% of the probability distribution.

The molecular structures of *endo*-acid **1a**[3] and amino acid salt **2**[6] have been reported, and it is instructive to compare their molecular structures with that of amino acid **1c**. The norbornyl rings of all three compounds show



2



3

distortion from the C_{2v} symmetry of the parent hydrocarbon. Amino acid salt **2** and amino acid **1c** show a synchro twist,[7] whereas *endo*-**1a** exhibits a contra twist. The twisting in amino acid **1c** can be seen from the C(1)–C(2)–C(3)–C(4) and C(4)–C(5)–C(6)–C(1) dihedral angles of −1.6 and −10.5, respectively. The conformation about the C(6)–S bond in amino acid **1c** and *endo*-acid **1a**

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are comparable. That is, the C(9) methyl group is approximately anti to C(5) and gauche to C(1) as indicated by the C(9)–S–C(6)–C(5) and C(9)–S–C(6)–C(1) torsion angles of 168.8 and 68.5°, respectively, in amino acid **1c** and 167.9 and 73.0°, respectively, in *endo*-acid **1a**. The plane of the carboxylate group in amino acid **1c** and the plane of the carboxylic acid moiety in *endo*-acid **1a** are almost coplanar with the C(8)–C(2)–C(3) plane in the respective molecules. This is in contrast to the orientation of the carboxylic acid plane with respect to the C(8)–C(2)–C(3) plane in amino acid salt **2**. The O–C(8)–C(2)–N angle is 16° in amino acid salt **2**, but 51° in amino acid **1c**. However, both values are within the 0–70° range reported[8] for the absolute value of the dihedral angle O–C–Cα–N in amino acids and peptides. It should also be noted that amino acid **1c** is an analogue of methionine, but owing to geometric constraints imposed by the norbornyl ring, the side chain is not in the zigzag trans planar fully extended conformation characteristic of the β-form of methionine and many of its derivatives.[9] This conformation of amino acid **1c** results in unfavorable short contacts between S and the carboxylate group. The S···C(8) distance is 3.158 (1) Å. Furthermore, the geometry of the carboxylate with respect to the C(9)–S–C(6) plane is unusual. The carboxylate sulfur contact is type I;[10] that is, the S···CO_2^- direction is less than 40° from the perpendicular to the Y–S–Z plane. Such contacts are ordinarily between sulfides and electrophiles, but not nucleophiles. However, a similar orientation of the carboxylic acid moiety with respect to the C(9)–S–C(6) plane is also obtained for *endo*-acid **1a**. A mitigating factor in the S-carboxylate/carboxylic acid contact in amino acid **1c** and *endo*-acid **1a** is that the sulfur atom is closer to the carbon atom (the positive end of the C–O dipole) of the carboxylate and carboxylic acid moieties, respectively, than the oxygen atoms (the negative end of the dipole). The steric interactions between the bulky 2-endo and 6-endo substituents in *endo*-acid **1a** are relieved by opening the C(2)–C(1)–C(6), C(1)–C(2)–C(8), and S–C(6)–C(1) bond angles to 111.9 (3), 120.0 (3), and 117.8 (3) Å, respectively. The 2-*exo*-ammonium group in amino acid **1c** disfavors comparable opening of the C(1)–C(2)–C(8) bond angle, and the observed value of 115.2 (1)° is comparable to that of 114.5° for this bond angle in amino acid salt **2** and 115.4 (2)° in 6-*exo*-(methylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylic acid **3**.[3] However, this effect is compensated for in amino acid **1c** by even greater opening of the C(2)–C(1)–C(6) and S–C(6)–C(1) bond angles to 113.0 (1) and 120.4 (1)°, respectively. This results in a significantly greater S···C(8) separation in amino acid **1c** than *endo*-acid **1a**: 3.158 (1) versus 3.118 (4) Å, consistent with the expected increased repulsion between a negatively charged carboxylate ion than a neutral carboxylic acid group and sulfur HOMO.

The carboxylate moiety in amino acid **1c** has equal C–O bond distances as expected for a CO_2^- group. In contrast, the C–O bond distances in *endo*-acid **1a** and amino acid salt **2** are unequal as expected for a carboxylic acid moeity. Each of the oxygen atoms of the carboxylate moiety in amino acid **1c** appears to be intermolecularly hydrogen bonded, as suggested[8] by intermolecular N–O(1) and N–O(2) distances of 2.762 (2) and 2.791 (2) Å, respectively.

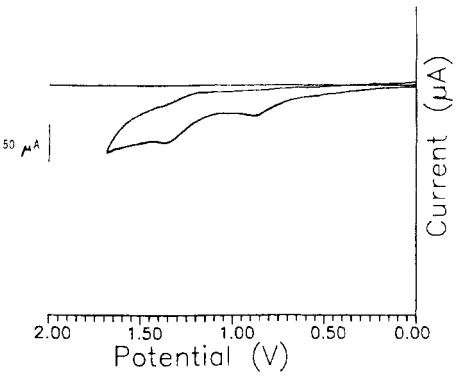

Figure 2. Cyclic voltammogram of 0.9 mM amino acid **1c** in 0.1 M $LiClO_4$ acetonitrile solution using a Pt working electrode (0.4 cm^2), Pt counter electrode, Ag/0.1 M $AgNO_3$ in acetonitrile reference electrode, and a 100 mV/s scan rate.

Electrochemistry. Cyclic voltammetry of amino acid **1c** in 0.1 M $LiClO_4$ in acetonitrile shows two oxidation waves as shown in Figure 2. The first wave at about 0.9 V versus Ag/0.1 M $AgNO_3$ reference electrode is broad with no distinct peak. A second step is observed at 1.35 V, which is more normal in shape. The two oxidation steps are confirmed as irreversible and essentially diffusion-controlled based on the absence of corresponding cathodic peaks and on the scan rate dependence of the peak currents, respectively. The first step shows a shift in peak potential of about 70 mV/decade change in scan rate, which is consistent with a totally irreversible process with a rate-determining step involving one electron. The second wave shifts anodically and becomes broader with increasing scan rate. A peak shift of 80 mV/decade is observed.

More detailed examination of the first step shows that the potential of the first wave shifts anodically with increasing concentration. Rotating disk electrode (RDE) studies on the first step (E_{appl} = 1.2 versus Ag/0.1 M $AgNO_3$ reference electrode) lead to a slightly concave nonlinear Levich plot (i_L versus $\omega^{1/2}$).[11] This suggests possible kinetic control of the oxidation. This point will be discussed subsequently. An apparent "n" value of 1.1 is obtained from this plot. The second step is found to be diffusion-controlled according to the Levich plot, and an "n" value of 2.2 is obtained for this process. Addition of water to the acetonitrile solution has no effect on the current–voltage curves. The current ratio of the first to second step remains constant and slightly less than 0.5 as the concentration is varied. In the presence of a 2-fold excess of the nonnucleophilic 2,6-di-*tert*-butylpyridine,[1] a single broad anodic wave is observed at about 1.07 V. The peak current for this wave is equal to the sum of the currents for the two original waves. If excess trifluoroacetic acid is added to the acetonitrile solution, a well-defined wave at 1.35 V is observed whose current is again equal to the sum of the original two waves. Addition of less than equimolar amounts of lithium bromide to an acetonitrile solution of amino acid **1c** does not yield a catalytic current enhancement in contrast to the dramatic enhancement obtained with the salt of *endo*-acid **1a**.[1]

Controlled potential electrolysis of a millimolar solution of **1c** in acetonitrile at an applied potential of 1.1 V was carried out in the presence of excess base and water. Measurement of the total charge passed to obtain exhaustive electrolysis gave an "n" value of 1.9 ± 0.2. This corresponds to an overall two electron oxidation. ^{1}H NMR

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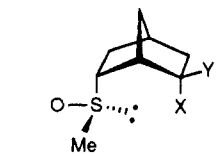
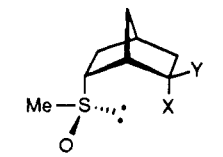
spectroscopic analysis of the reaction medium showed a mixture of two diastereomeric sulfoxides **4a** and **5a** formed in 60 and 25% yields, respectively. Controlled potential electrolysis of amino acid **1c** in 0.1 M aqueous sodium acetate with acetic acid added to adjust the initial pH to 8.3 similarly gave a mixture of the same two diastereomeric sulfoxides **4a** and **5a** formed in 70 and 10% yields, respectively. The mixture of diastereomeric sulfoxides **4a** and **5a** obtained by controlled potential electrolysis could not be separated by HPLC; however, their benzamido methyl ester derivatives **4b** and **5b** could be so separated. Furthermore, authentic samples of both diastereomeric benzamido ester sulfoxides **4b** and **5b** could be obtained pure, and their structures including stereochemistry assigned. Oxidation of benzamido ester **1f** with sodium metaperiodate in aqueous methanol produced predominantly sulfoxide **4b** as a mixture with sulfoxide **5b**. Sulfoxide **4b** was obtained pure by preparative HPLC followed by vapor-diffusion recrystallization. The parent amino acid sulfoxide of this diastereomer, that is, **4a**, could also be obtained pure in the following way. Treatment of amino acid **1c** in acetic acid with hydrogen peroxide gave sulfoxide **4a** in 75% yield after recrystallization.[12] An authentic sample of sulfoxide **5b** was secured by oxidation of benzamido ester **1f** with the bromine complex of 1,4-diazabicyclo[2.2.2]octane[13,14] (DABCO·2Br$_2$) in aqueous acetic acid which afforded sulfoxides **4b** and **5b** in a combined yield of 80% and in a ratio of 45:55, respectively. Sulfoxide **5b** was obtained pure by repeated HPLC of the DABCO·2Br$_2$ oxidation product. The stereochemistry of the sulfoxides could be assigned on the basis of ^{1}H NMR spectroscopic analysis. Both diastereomeric sulfoxide esters **4c** and **5c** have been prepared and their relative



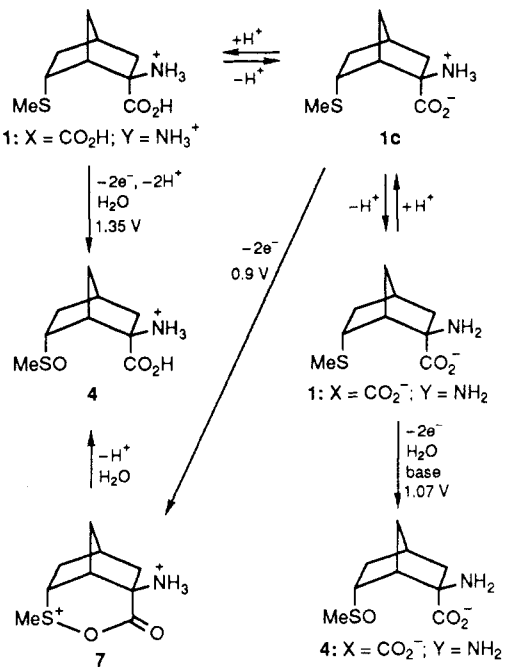
4a: X = CO_2^-; Y = NH_3^+
b: X = CO_2Me; Y = NHCOPh
c: X = CO_2Me; Y = H



5a: X = CO_2^-; Y = NH_3^+
b: X = CO_2Me; Y = NHCOPh
c: X = CO_2Me; Y = H

stereochemistries unequivocally established by conversion of the sulfoxide acid, whose structure was determined by X-ray crystallographic analysis, into sulfoxide ester **4c**.[13] Analysis of the ^{1}H NMR spectra of **4c** and **5c** reveals that H(1) resonates at 2.84 and 3.21 ppm, respectively. This is in accord with the principal rotamer about the C(6)–S bond being as shown and the anisotropic sulfoxide group deshielding H(1) in diastereomer **5c**.[15] This provides a basis for assigning the stereochemistry in the diastereomeric benzamido ester sulfoxides **4b** and **5b**. Thus, sulfoxide **4b** is assigned the stereochemistry shown because H(1) resonates at 2.79 ppm in this compound and the stereochemistry of sulfoxide **5b** is assigned as shown because its H(1) resonates at 3.76 ppm. In addition, the resonance of the hydrogen atoms of the MeS(O) group in each diastereomeric series follow the same pattern of

Scheme I



relative chemical shifts (2.62 and 2.45 ppm for **4c** and **5c**, respectively, and 2.55 and 2.41 ppm for **4b** and **5b**, respectively). This assignment is also consistent with the mechanistic arguments presented previously for the oxidation of ester **1d**.[13] Namely, attack by periodate on benzamido ester **1f** should occur from the less hindered side, resulting in delivery of oxygen as in diastereomer **4b**. Attack by bromine on benzamido ester **1f** should occur from the same direction, and subsequent displacement of bromide by water from the intermediary bromosulfonium salt results in inversion at sulfur, producing diastereomer **5b**. The key result is that electrochemical oxidation of amino acid **1c** provided the corresponding sulfoxides **4a** and **5a** in high yield. There was no detectable decarboxylation. Therefore, neither Kolbe[16] oxidation (2-aminocyclohexanecarboxylic acid showed no electrochemistry below an applied potential of 1.6 V), nor pseudo-Kolbe[16,17] oxidation occurred.

In order to properly interpret the electrochemistry, it is necessary to establish the relevant acid–base equilibria in acetonitrile. The infrared spectrum of **1c** in the electrochemical medium (0.1 M $LiClO_4$ in acetonitrile) showed one band in the carbonyl/carboxylate region at 1650 cm^{-1}. Methionine shows a similar band at 1657 cm^{-1}.[18] Addition of trifluoroacetic acid to the acetonitrile solution results in a loss of the band in the 1650 cm^{-1} region and a build up of two sharper bands at 1760 and 1740 cm^{-1} for **1c** and one broad band at 1756 cm^{-1} for methionine. If 2,6-di-*tert*-butylpyridine is added to a solution of **1c**, a spectrum very similar to that of a solution of **1c** alone is obtained but with a slight shoulder at 1635 cm^{-1}. The spectrum of

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(16) Eberson, L.; Utley, J. H. P. In *Organic Electrochemistry*, 2nd ed.; Baizer, M. M., Lund, H., Eds.; Dekker: New York, 1983; pp 435–518.
(17) Coleman, J. P.; Eberson, L. *J. Chem. Soc., Chem. Commun.* **1971**, 1300.
(18) The assignments of the IR stretching frequencies are based on the IR spectroscopic studies of α-amino acids in aqueous solution in which the asymmetric carboxylate stretching frequency of RCH(NH_3^+)CO_2^- is reported in the range of 1540–1625 cm^{-1}, that for RCH(NH_2)CO_2^- occurs near 1570 cm^{-1}, and the carbonyl stretching frequency in RCH(NH_3^+)-CO_2H is in the range of 1720–1740 cm^{-1}: Pearson, J. F.; Slifkin, M. A. *Spectrochemica Acta* **1972**, *28a*, 2403. Greenstein, J. P.; Winitz, M. *The Chemistry of the Amino Acids*; Wiley: New York, 1961; pp 1695–1722. Gore, R. C.; Barnes, R. B.; Peterson, E. *Anal. Chem.* **1949**, *21*, 382.

the sodium salt of **1c** shows one broad peak at 1635 cm^{-1}. The conclusion from these results is that **1c** exists in acetonitrile in the zwitterionic form. Addition of acid protonates the carboxylate while the addition of 2,6-di-*tert*-butylpyridine converts a small amount (10%) of the protonated amine into the free-base form. Thus, in acetonitrile, the predominant form is the zwitterion even in the presence of added 2,6-di-*tert*-butylpyridine. In the light of the above observations, the electrochemistry may be interpreted on the basis of Scheme I. The oxidation of **1c**, the predominant form, is favored because of the possibility of neighboring group participation resulting in the formation of the intermediate acyloxysulfonium salt **7**.[1] The direct oxidation of **1**, X = CO_2H, Y = NH_3^+, leads to the same product sulfoxide and may also involve the intermediacy of acyloxysulfonium salt **7**, but requires a much higher potential. The resulting decomposition of the acyloxysulfonium salt by trace water in the unbuffered solvent produces protons which convert **1c** into **1**, X = CO_2H, Y = NH_3^+. If this reaction were strictly stoichiometric, an "*n*" value of 1.0 would be expected at the potential corresponding to the first step. This is consistent with the RDE studies. Differential pulse polarography gives a ratio for the currents of the first and second peaks, respectively, of 0.26, which should be compared with the theoretical 0.5. The lower peak ratio is probably due to the fact that the first step is partially kinetically controlled which would result in a lower than expected peak current. The addition of acid converts all of the substrate into **1**, X = CO_2H, Y = NH_3^+, which is then oxidized exclusively at the higher potential to **4**, X = CO_2H, Y = NH_3^+. Addition of base is somewhat more complicated and appears mainly to promote adsorption on the electrode surface. As shown in Scheme I, oxidation of **1**, X = CO_2^-, Y = NH_2, leads to sulfoxide **4**, X = NH_2, Y = CO_2^-. Acyloxysulfonium salt **7** could also be an intermediate in this reaction.

The oxidation of **1c** leading to sulfoxide formation is significantly facilitated as evidenced by the more than 400-mV cathodic shift in the peak potential from 1.35 to 0.9 V. It has been pointed out previously[1] that the oxidation of the salt of **1a** occurs at 1.20 V, a potential characteristic of unassisted oxidation. Only when bromide is added can the effect of neighboring group participation be observed. The bromide-catalyzed reaction occurs at a potential characteristic of bromide and not of the thioether. The striking result of the present study is that **1c** exhibits facilitated oxidation even in the absence of a catalyst whose addition moreover has essentially no effect.

The basis for neighboring carboxylate group participation resulting in facilitated oxidation in amino acid **1c**, but not the salt of **1a** on *direct* electrochemical oxidation may be due to two factors. Amino acid **1c** is sterically more congested than the salt of **1a**, and this congestion is relieved on oxidation of the thioether moiety and bond formation with the carboxylate group. A second factor derives from pulse radiolysis studies. Such studies reveal that the one-electron transient oxidation products involving S/O interaction have absorption maxima at 390[19] and 355 nm,[20] respectively, for the oxidation of *endo*-acid **1a** and amino acid **1c**. A correlation between bond strength and absorption maxima for 2c,3e bonded species has been suggested.[21] The shorter the wavelength of the absorption, the stronger the bond. On this basis, the blue shift of 35 nm demonstrates that the S/O bond in the one-electron oxidation product of amino acid **1c** is stronger than that in the one-electron oxidation product of *endo*-acid **1a**. This result is also consistent with the expectation that the electron-withdrawing ammonium group in the one-electron oxidation product of amino acid **1c** strengthens a two-center, three-electron bond between S and O by withdrawing electron density from the antibonding σ^* orbital. Thus electrochemical oxidation of amino acid **1c** is facilitated relative to the salt of **1a** because removal of an electron from the former results in the formation of a stronger bond than in the latter. The comparison of these two systems illustrates two different ways in which neighboring group participation can facilitate oxidation. If the three-electron bond is relatively stable, as is the case for one-electron oxidation of amino acid **1c** or for 1,5-dithiocane,[22] then oxidation is facilitated by the formation of the three-electron bonded cyclic intermediate followed by removal of a second electron. In the case where this bond is weak, the important intermediate is the two-electron oxidized species leading to an S–O bond which is much more stable. Bromine facilitates this reaction by atom transfer coupled with formal two-electron oxidation. Bromine and the thioether moiety equilibrate with the corresponding adduct. The neighboring group in this case serves to rapidly displace the bromine, determining the overall rate of oxidation of the thioether group by bringing all of the material through this equilibrium to form the two-electron oxidation product with an S–O bond.

Experimental Section

All melting points are uncorrected and were taken in open-ended glass capillary tubes using a Thomas-Hoover melting point apparatus. IR spectra were obtained on a Perkin-Elmer Model 983 spectrometer. FTIR spectra were measured using a Perkin-Elmer Model 1800 spectrometer. ^1H NMR spectra were measured at 250 MHz using a Bruker WM-250 spectrometer on samples containing an internal standard: tetramethylsilane in deuteriochloroform and 3-(trimethylsilyl)-1-propanesulfonic acid sodium salt in deuterium oxide. ^{13}C NMR spectra were measured at 62.89 MHz using a Bruker WM-250 spectrometer. HPLC was performed with an Altex/Beckman 110b pump equipped with a preparative pump head. An Altex Ultrasil-ODS 10 mm × 250 mm reverse-phase and Phenomenex Maxisil 10 mm × 250 mm normal phase 10 μm particle size columns were used. An ISCO V^4 absorbance detector along with a Linear Model 0555 strip chart recorder were used to monitor the HPLC. Elemental analyses were done at Atlantic Microlab, Inc., Atlanta, GA.

Reagent grade 2,6-di-*tert*-butylpyridine, trifluoroacetic acid, lithium bromide, and *n*-butyllithium solution (2.7 M in hexane) were used as received from Aldrich Chemical Co. Reagent-grade acetonitrile was heated at reflux for at least 12 h over phosphorus pentoxide and then distilled from phosphorus pentoxide under a nitrogen atmosphere. Reagent grade methanol and ethyl acetate were used as received. *N,N*-Diisopropylamine was purified and dried by distillation from calcium hydride. Tetrahydrofuran (THF) was purified and dried by distillation from sodium and benzophenone. Hexamethylphosphoric acid triamide was purified and dried by distillation from sodium under reduced pressure. Lithium perchlorate was dried in a vacuum oven overnight at 110 °C.

Methyl 2-*exo*-Amino-6-*endo*-(methylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylate (1e). Freshly distilled *N,N*-diisopropylamine (0.60 g, 6 mmol) and dry THF (20 mL) were placed in a three-necked flask under argon, and the solution was cooled

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to −78 °C. *n*-Butyllithium (2.7 M, 4.55 mL, 12 mmol) was then added over a period of 15–20 min, and the resulting yellow solution was stirred at −78 °C for 1 h. A solution of endo ester **1d**[3] (1.0 g, 5 mmol) in dry THF (10 mL) and hexamethylphosphoric acid triamide (1.1 g, 6 mmol) was added by syringe over a period of 20 min. The resulting solution was stirred for 3 h at −78 °C, and then a solution of *O*-(mesitylenesulfonyl)hydroxylamine[4] (1.0 g, 6 mmol) in dry THF (6 mL) was added at once. The resulting mixture was stirred at −78 °C for 2 h and then it was slowly warmed to room temperature and stirred overnight at this temperature. The reaction mixture was then poured onto ice–water (ca. 200 mL), and the aqueous layer was repeatedly extracted with diethyl ether (4 × 50 mL). The combined ether extracts were concentrated to about 100 mL on a rotary evaporator and then washed with 5% aqueous hydrochloric acid (6 × 25 mL). The ether layer was dried over anhydrous $MgSO_4$ and concentrated to an oil (352 mg) under reduced pressure. Analysis of this oil showed that its major component was unreacted starting material (180 mg) and the rest a complex mixture of unidentified compounds. The combined acid extracts were made basic with the addition of 20% aqueous sodium hydroxide solution. This basic solution was extracted with diethyl ether (5 × 30 mL), and the combined ether extracts were dried over anhydrous $CaSO_4$. Concentration under reduced pressure gave a light-yellow oil (375 mg) which solidified upon cooling. Recrystallization from diethyl ether–petroleum ether afforded white crystalline amino ester **1e** (320 mg, 38% yield based on consumed endo ester **1d**): mp 63–64 °C; IR (KBr) 3371, 3290 (NH_2), 1726 (C=O)cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (1 H, ddd, J = 12.6, 6.6, 2.6 Hz), 1.27–1.38 (2 H, m), 1.54 (2 H, s, NH_2), 2.01 (3 H, s, SMe), 2.03–2.14 (2 H, m), 2.19–2.31 (2 H, m), 2.31–2.43 (1 H, m), 3.02 (1 H, ddd, J = 11.8, 6.6, 3.6 Hz), 3.68 (3 H, s, CO_2Me); ^{13}C NMR ($CDCl_3$) 16.5 (SMe), 35.7, 36.4, 38.2, 41.5, 45.5, 51.1, 62.8, 176.9 (C=O); MS m/z 216 (M + 1, 1.3), 215 (M^+, 11.5). Anal. Calcd for $C_{10}H_{17}NO_2S$: C, 55.81; H, 7.91; N, 6.51; S, 14.88. Found: C, 55.85; H, 7.99; N, 6.44; S, 14.87.

2-*exo*-Amino-6-*endo*-(methylthio)bicyclo[2.2.1]heptane-2-*endo*-carboxylic Acid (1c). To a stirred solution of amino ester **1e** (110 mg, 0.51 mmol) dissolved in a solution of methanol (10 mL) and water (3 mL) was added potassium hydroxide (40 mg, 0.70 mmol). This solution was stirred and heated at reflux under an argon atmosphere for 24 h. The solution was then allowed to cool to room temperature, and the solvent was removed under reduced pressure. A white solid residue was obtained which was washed with diethyl ether (2 × 15 mL) and then dissolved in the minimum amount of water. The aqueous solution was placed on a column of Dowex 50W-4X ion exchange resin eluted with a 10% aqueous solution of ammonium hydroxide (200 mL). The eluted solution was lyophilized to a white solid, which was recrystallized from ethanol to give amino acid **1c** as white needles: mp 285 °C dec; IR (KBr) 3595, 3363–3190 (NH_3^+), 1611, 1553 (CO_2^-) cm^{-1}; ^{1}H NMR (D_2O) δ 0.68 (1 H, ddd, J = 12.3, 6.5, 2.5 Hz), 1.08–1.21 (2 H, m), 1.68–1.74 (1 H, m), 1.83 (3 H, s, SMe), 1.83–1.96 (2 H, m), 2.08 (1 H, br s), 2.20 (1 H, br s), 2.86 (1 H, ddd, J = 11.5, 6.5, 3.6 Hz, H2); ^{13}C NMR (D_2O) 15.4 (SMe), 35.2, 35.8, 37.5, 41.1, 44.9, 50.3, 64.2, 183.0 (CO); MS m/z calcd for $C_9H_{15}NO_2S$ 201.0824, found 201.0835.

X-ray Single-Crystal Structure Study of Amino Acid 1c. A colorless plate crystal 0.50 × 0.40 × 0.12 mm of amino acid **1c** grown by allowing a solution of the compound in 95% ethanol to slowly evaporate at room temperature was mounted on a Syntex $P2_1$ auto diffractometer equipped with a scintillation counter and Mo Kα radiation with a graphite monochromator. Cell constants, which are given in Table I, and an orientation matrix for data collection were obtained from least-squares refinement, using the setting angles of 25 reflections in the range $20 < 2\theta < 35$. Data were collected using the $2\theta/\theta$ scan technique. The scan rate varied from 2 to 12.5°/min with a fast scan rate for intense reflections and a slow scan rate for weak reflections. Data were collected to a maximum 2θ of 50.0°. The scan width was −1.0 to +1.0°. The data were reduced to F_o^2 and $\sigma(F_o^2)$. Lorenz and polarization factors were applied to all reflections. No decay correction was applied because the check reflections remained constant within experimental error throughout the data collection.

The structure was solved by the direct methods program MULTAN.[23] A total of twelve atoms were located from the first solution. The remaining atoms were located in succeeding Fourier syntheses. Hydrogen atoms were included in the refinement, but restrained to ride on the atom to which they are bonded. The structure was refined by full-matrix least-squares techniques[24] using neutral atom scattering factors[25] and including anomalous dispersion effects.[26] The final cycles of refinement included 118 variable parameters converged with unweighted and weighted agreement factors (R values) of 0.048 and 0.059, respectively. The 1393 reflections with $I < 3\sigma(I)$ gave unweighted and weighted agreement factors of 0.04 and 0.057, respectively, and GOF = 2.082.

Cyclic Voltammetry. Voltammograms were measured on solutions approximately 10^{-3} M in substrate and 0.1 M in lithium perchlorate, which serves as supporting electrolyte, in acetonitrile with a Ag/0.1 M $AgNO_3$ in acetonitrile reference electrode. A 0.3-cm^2 platinum flag, which was rinsed with nitric acid and heated to incandescence in a flame prior to each run, served as the working electrode. The electrochemical apparatus was purged with inert gas, and the experiment was run under an inert gas atmosphere. The electrochemical instrumentation, data acquisition, and data processing systems used were either those previously described[28] or a Cyprus Systems electrochemical data acquisition system model CYSY-1.

Rotating Disk Electrode (RDE) Voltammetry. A platinum disk electrode, surface area 0.79 cm^2, was used as the working electrode and was placed in the center of a three-chambered electrochemical cell with fritted-glass disk separators. A platinum counter electrode, surface area ≈1 cm^2, was placed in one side compartment and a Ag/0.1 M $AgNO_3$ reference electrode was placed in the other side compartment. A Pine Instrument Model PIR analytical rotator was used to rotate the working electrode at rotation rates between 400 and 3600 rpm. A PARC Model 362 potentiostat was used to sweep the potential at 20 mV/s, and the current/voltage response was measured on a Houston Model 200 x-y recorder. Solutions of approximately 10^{-3} M in amino acid **1c** were used.

Differential Pulse Polarography. Differential pulse polarography was performed using the same electrodes, cell, and concentration of substrate as for the cyclic voltammetry. The step height was 30 mV, the pulse amplitude was 25 mV, and the pulse width 2 ms.

Oxidation of Amino Acid 1c with Hydrogen Peroxide in Acetic Acid. To a suspension of amino acid **1c** (50 mg, 0.25 mmol) in chilled (10 °C) acetic acid (3 mL) was added 30% aqueous hydrogen peroxide (300 μL, 0.265 mmol) dropwise. The solid was dissolved, and the solution was stirred for 3 h and then allowed to warm to room temperature. The solution was concentrated to a solid by rotary evaporation. The solid was dissolved in water (2 mL) and precipitated with acetone. The precipitate was recrystallized from hot ethanol to yield pure sulfoxide **4a** (39 mg, 75% yield): mp 258–260 °C dec; ^{1}H NMR (D_2O, 250 MHz) δ 1.41 (ddd, 1, J = 15, 10, 4 Hz), 1.54 (m, 2), 1.75 (dd, 1, J = 15, 4 Hz), 1.92 (ddd, 1, J = 20, 5, 5 Hz), 2.20 (dd, 1, J = 20, 10 Hz), 2.43 (br s, 1, bridgehead H), 2.52 (s, 3, SMe), 2.71 (br s, 1, bridgehead H), 3.01 (ddd, 1, J = 15, 10, 5 Hz); IR (KBr) 3100–2300 (NH_3^+), 1597 (CO_2^-), 1537 (NH_3^+) 981 cm^{-1} (SO); MS m/z 217 (M^+, 0.2), 172 (M − CO_2H, 1.8), 154 (M − CO_2H, H_2O, 33).

Controlled Potential Electrolysis of Amino Acid 1c in Acetonitrile. A sample of amino acid **1c** (21 mg, 0.1 mmol) dissolved in degassed acetonitrile (15 mL) 0.1 M in lithium perchlorate and containing 2,6-di-*tert*-butylpyridine (45 μL, 0.2 mmol) and water (10 μL, 0.50 mmol) was exhaustively electrolyzed at a constant potential of 1.1 V versus a Ag/0.1 M $AgNO_3$ in acetonitrile reference electrode using a carbon cloth (obtained

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(24) All calculations were performed on a PDP-11 computer using SDP-PLUS: Frenz, B. A. In *Computing in Crystallography*; Schenk, H., Olthof-Hazelkamp, R., van Konigsveld, R., Bassi, G. C., Eds.; Delft University Press: Delft, Holland, 1978; pp 64–71.
(25) Cromer, D. T.; Waber, J. T. *International Tables for X-ray Crystallography*; Kynoch Press: Birmingham, England, 1974; Vol. IV, Table 2.2B.
(26) Ibers, J. A.; Hamilton, W. C. *Acta Crystallogr.* **1964**, *17*, 781.
(27) ORTEP, Johnson, C. K. Oak Ridge National Laboratory, Oak Ridge, TN.
(28) Langhus, D. L.; Wilson, G. S. *Anal. Chem.* **1979**, *51*, 1139.

from Union Carbide)[29] working electrode whose area was 0.5 cm^2. When the current decayed to zero 19.2 C had passed corresponding to a "*n*" value of 1.91. Distilled water (2 mL) was added to the solution, and the acetonitrile was removed by rotary evaporation. The aqueous solution was then purified on an Altex Ultrasil-ODS 10 mm × 250 mm reverse-phase HPLC column eluting with 30% aqueous acetonitrile. The flow rate was set at 5 mL/min, and the UV detector was operated at 230 nm. The fraction (22 mg) containing sulfoxide **4a** was analyzed by ^1H NMR spectroscopy. Addition of a known amount of authentic sulfoxide **4a** prepared chemically to this fraction resulted in an increase in the area due to the *S*-methyl peak. By measuring this increase, it was then calculated that sulfoxide **4a** formed with a yield of 62%. The *S*-methyl singlet at 2.38 is due to the other diastereomeric sulfoxide **4a**, and its yield is 25–30%. An IR spectrum of this fraction showed the broad ammonium peak, the carboxylate peaks, and a peak at 991 cm^{-1} for the sulfoxide, but there was also a large peak at 1100 cm^{-1} attributable to some residual perchlorate from the supporting electrolyte. There was no indication of starting material.

The controlled potential electrolysis of amino acid **1c** (30 mg, 0.15 mmol) was repeated as above. The mixture of diastereomeric sulfoxides **4a** obtained after HPLC purification as above (ca. 32 mg, 0.12 mmol) was dissolved in a minimal amount of 3 M aqueous sodium hydroxide solution. The solution was cooled to −5 °C, and benzoyl chloride (32 μL, 0.27 mmol) was added slowly with vigorous agitation over 40 min. The pH of the solution was monitored periodically, and additional portions of 3 M aqueous sodium hydroxide solution were added if needed to maintain the pH between 9 and 11. After completion of the addition, the solution was stirred for 1 h and allowed to warm to room temperature with stirring overnight. The reaction mixture was then filtered, acidified with 4 M aqueous hydrochloric acid solution, and extracted with ethyl acetate (4 × 10 mL). The organic extracts were concentrated by rotary evaporation to a white solid. This solid was dissolved in chloroform (10 mL), cooled in a dry ice–acetone bath, and treated dropwise with an ethereal solution of diazomethane until the yellow color persisted for more than 1 min. Evaporation of the solvents gave a mixture of diastereomeric benzamido ester sulfoxides **4b** as a white solid (13 mg, 24% yield). ^1H NMR spectroscopic analysis of this mixture showed that the ratio of diastereomers **4b**:**5b** was 70:30, and all of the peaks in the pure diastereomers were present in the same ratio, in this mixture. Furthermore, HPLC analysis revealed the same retention times for this mixture as for the authentic diastereomeric compounds.

Controlled Potential Electrolysis of Amino Acid 1c in Aqueous Sodium Acetate Buffer. A sample of **1c** (22 mg, 0.11 mmol) was dissolved in pH 8.3 sodium acetate solution in the center compartment of a three-chambered electrochemical cell. A carbon cloth working electrode was placed in the center compartment. A Pt counter and an SCE reference electrode were placed in the two side compartments. A cyclic voltammogram run on the solution before starting the electrolysis showed one peak with a peak potential of 1.14 V. After zeroing the coulometer, the potential was set at 1.18 V and the cell connected. Since the cyclic voltammogram showed considerable background current at this potential, the current was allowed to flow until 2.5 equiv of current had passed to allow for complete oxidation. When the electrolysis was complete, the pH was 7.5. A cyclic voltammogram run after the electrolysis showed only background current. The reaction mixture was put into a 25-mL round-bottom flask, and the carbon cloth electrode was ground up and triturated with distilled water, which was added to the reaction mixture. The water was removed by lyophilization to yield a white solid. A ^1H NMR spectrum of the crude mixture revealed a 72% yield of the major diastereomeric sulfoxide. Addition of authentic sulfoxide **4a** prepared chemically indicated a yield of 74%. The other diastereomer was present in only 10–12%.

Synthesis of Benzamido Ester 1f. Amino ester **1e** (75 mg, 0.34 mmol) was dissolved in acetonitrile (0.5 mL) and cooled to −5 °C in an ice–salt bath. Saturated aqueous sodium bicarbonate solution (1 mL) was added to keep the solution basic. Benzoyl chloride (80 μL, 0.66 mmol) was added slowly with rapid stirring over 30 min. The solution was allowed to stir overnight at room temperature. Water (5 mL) was then added, and the acetonitrile was removed by rotary evaporation. The aqueous solution was then extracted with ethyl acetate (3 × 20 mL) with the final extraction done on a sodium chloride saturated solution. Evaporation of the solvent gave a white solid which upon purification by preparative TLC on silica gel (50% EtOAc in hexanes, R_f 0.6) gave pure amino ester **1e** (85 mg, 75% yield): mp 120–122 °C; ^1H NMR (250 MHz) δ 1.24 (ddd, 1, *J* = 10.6, 5.4, 3.1 Hz), 1.93 (ddd, 1, *J* = 11.3, 9.4, 1.2 Hz), 2.04 (s, 3, SMe), 2.02 (m, 1), 2.15 (m, 2), 2.44 (br s, 1, bridgehead), 2.66 (br s, 1, bridgehead), 2.80 (dd, 1, *J* = 13.6, 2.9 Hz), 3.06 (ddd, 1, R_2CHS, *J* = 15.1, 11.1, 17.4 Hz), 3.73 (s, 3, MeO), 7.4 (m, 3, *m*-, *p*-ArH), 7.7 (dd, 2, *o*-ArH, *J* = 5.8, 1.2 Hz); IR (KBr) 3378 (NH), 1725 (CO_2Me), 1649, 1520 cm^{-1}; MS *m*/*z* 319 (M^+, 10.4).

Oxidation of Benzamido Ester 1f with Sodium Metaperiodate. A sample of benzamido ester **1f** (30 mg, 0.09 mmol) was dissolved in methanol (0.5 mL) and cooled in an ice–salt bath to −5 °C. Sodium metaperiodate (72 mg, 0.34 mmol) was dissolved in a minimum amount of water, and methanol (0.5 mL) was added. The sodium metaperiodate was then added to the benzamido ester solution over about 10 min. The solution was allowed to warm to room temperature and left stirring overnight. A white precipitate formed and was filtered off. After the solution was saturated with sodium chloride, the solution was extracted with ethyl acetate (3 × 20 mL). Preparative HPLC (20% methanol in ethyl acetate, C18 column) gave three fractions. Fraction one contained a small amount of starting material. Fraction two contained mostly one diastereomer of the sulfoxide, and fraction three contained a mixture of sulfoxides, still predominated by the sulfoxide in fraction two. Vapor diffusion recrystallization of the residue from fraction two dissolved in methanol with ethyl ether gave thin, clear needles of major sulfoxide diastereomer **4b**: mp 218–219 °C; ^1H NMR ($CDCl_3$, 250 MHz) δ 1.70 (dd, 1, *J* = 11.9 Hz), 1.81 (ddd, 1, *J* = 13.4, 6.9, 2.0 Hz), 1.98 (ddd, 1, *J* = 14.0, 4.2, 4.2 Hz), 2.23 (m, 1), 2.14 (dd, 1, *J* = 10.4, 1.3 Hz), 2.62 (br s, 4, bridgehead and S(O)Me), 3.06 (ddd, 1, $R_2CHS(O)$, *J* = 15.0, 6.8, 3.4 Hz), 3.75 (s, 3, OMe), 6.4 (s, 1, NH), 7.4 (m, 3, *m*-, *p*-ArH), 7.69 (d, 2, *o*-ArH, *J* = 7.9, 2.6 Hz); IR (KBr) 3378 (NH), 3000 (CH stretch), 1721 (CO_2Me), 1649 (amide I band) 1523, 1488, 1037 (SO), 692 cm^{-1}; MS *m*/*z* 335 (M^+, 0.05). Anal. Calcd for $C_{17}H_{21}O_4SN$: C, 60.88; H, 6.31; N, 4.18. Found: C, 60.81; H, 6.32; N, 4.14.

Oxidation of Benzamido Ester 1f with the 1,4-Diazabicyclo[2.2.2]octane–Bromine Complex. A sample of benzamido ester **1f** (20 mg, 0.06 mmol) was dissolved in 80% aqueous acetic acid (1.5 mL). To the stirred solution was added DABCO·$2Br_2$ (35 mg, 0.08 mmol) all at once. The complex slowly dissolved, and a clear solution was obtained. After being stirred for 30 min the solution was concentrated by rotary evaporation to a white solid. The solid was triturated with dichloromethane, and the solution obtained was filtered through a fine glass frit. The solution was concentrated by rotary evaporation to a white semisolid whose ^1H NMR spectrum in deuteriochloroform indicated the presence of the two diastereomeric sulfoxides **4b** and **5b** in a ratio of about 45/55 with a combined yield of 80%. The sample was applied to a silica gel HPLC column and was eluted with 20% methanol in ethyl acetate. The flow rate was set at 5.0 mL/min, and the UV detector was operated at 230 nm. The fractions enriched in **5b** were recycled twice to obtain pure **5b** as determined by ^1H NMR spectroscopy: ^1H NMR ($CDCl_3$, 250 MHz) δ 1.25 (m, 2), 1.65 (br d, 1, *J* = 14.3 Hz), 1.91 (m, 2, ring protons), 2.12 (d, 1, *J* = 10.9 Hz, ring proton), 2.44 (s, 3, SMe), 2.59 (br s, 1, bridgehead), 2.91 (dd, 1, *J* = 15.1, 6.1 Hz), 3.01 (ddd, 1, R_2CHS, *J* = 14.0, 6.5, 3.6 Hz), 3.79 (s, 3, OMe), 6.75 (s, 1, NH), 7.45 (m, 3, *m*-, *p*-ArH), 7.75 (d, 2, *J* = 8.7 Hz, *o*-ArH); IR (KBr) 3380 (NH), 3000 (CH), 1725 (CO_2Me), 1640 (amide I band), 1045 (SO), 685 cm^{-1}; MS *m*/*z* 335 (M^+, 0.04).

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FTIR spectra were measured by Dr. S. Muralidharan in the Strategic Metals Recovery Research Facility of the University of Arizona.

Supplementary Material Available: Stereoscopic view of the packing of the molecule in the unit cell, tables of final atomic positional and thermal parameters, bond length, bond angle, and selected torsion angle data (8 pages); listings of structure factor amplitudes for amino acid **1c** (10 pages). Ordering information is given on any current masthead page.

Ab Initio C_s Transition State for the Diels–Alder Reaction of Acetylene and Butadiene

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Ab initio calculations are reported for the Diels–Alder reaction between acetylene and butadiene. An activation energy of 60.9 kJ mol^{-1} and an enthalpy of −287.8 kJ mol^{-1} have been calculated at the MP4SDQ/6-31G*//HF/6-31G* level of theory. A full set of vibrational frequencies, calculated at the 4-31G level, exhibited a single imaginary frequency for the transition structure with C_s symmetry. The geometry of this transition structure was almost identical with the critical point determined at the HF/6-31G* level of theory. An analysis of the distortion energy of the reactants in the forward reaction at infinite separation showed that the magnitudes of the repulsive and attractive electronic contributions to the transition barrier are approximately equal. The increase in energy of the filled π-orbital of acetylene not involved in bonding changes is a major contributor to the activation energy for the Diels–Alder reaction of butadiene with acetylene being greater than that of butadiene and ethylene.

The Diels–Alder [$_\pi$4 + $_\pi$2] cycloaddition continues to challenge experiment and theory. A concerted synchronous mechanism is now favored by the highest levels of theory[1] and supported by experiment,[2] however, controversy still exists. Ortega et al.[3] have argued that the inclusion of correlation energy contributions increases the tendency toward asynchronicity, but the validity of this result is limited by the restriction imposed in the calculation such that the sum of the lengths of the two σ-bonds being formed is 4.4 Å. Dewar,[4] from studies at the HF level of theory, considers open-shell singlet "diradical" configurations to be important in the transition state. This is supported by the AM1 study of Chai and Lee[5] on substituent rate trends. However, recent ab initio studies by Houk et al.[1e] using a 3-21G basis set and RHF procedures also reproduced substituent effects for the reaction of butadiene with substituted alkenes, and the transition states showed little or no asynchronicity despite the nature of the unsymmetrical dienophiles.

A study of the butadiene–ethylene hypersurface, which included calculations with both minimal and nonminimal basis sets and the inclusion of correlation energy by the multiconfiguration SCF (MCSCF) method, has been reported by Bernardi et al.[1a] With a minimal STO-3G basis set, a "asynchronous diradicaloid" mechanism involving two intermediates and three "transition states" of differing conformation was found to be thermodynamically favored to a concerted process. However, with use of an extended 4-31G basis set, the surface around the "diradicaloid" pathway is flattened and the synchronous process is favored. These calculations did not include zero-point vibrational energy (ZPVE) corrections.[6]

An ab initio study at the RHF/6-31G* level of theory has similarly given[1d] a symmetrical transition state for the reaction of ethylene and butadiene. This is the largest basis set used to date in a study of the Diels–Alder reaction. The inclusion of correlation energy and polarization functions gave a calculated activation energy (106.3 kJ mol^{-1}, MP4SDTQ/6-31G*//HF/6-31G*) close to the experimental value (115.1 kJ mol^{-1}).

The analogous reaction between *cisoid*-1,3-butadiene and acetylene has to date not been the subject of theoretical investigation despite the fact that numerous synthetic examples exist for which this reaction is the prototype and an industrial process for the parent reaction is patented.[7] We now report the first ab initio calculation and transition-state structure for the reaction of *cisoid*-1,3-butadiene and acetylene.

Results and Discussion

Most theoretical studies of the [$_\pi$4 + $_\pi$2] reaction have used small basis sets and not included polarization functions. The inadequacy of such calculations in comparing alternative reaction pathways is well-known. The use of

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(6) A preliminary study of the ethylene–butadiene reaction has revealed that the less constrained asynchronous transition state has a lower ZPVE. Inclusion of zero-point vibrational energy brings the synchronous and asynchronous transition states to almost equal energy. The region around the synchronous transition state is very flat, and differences in vibrational energies should not be ignored.

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