Yates[23] and Figueras and co-workers[10] observed the effects of different supports (Al_2O_3, SiO_2, TiO_2, MgO, and zeolite) for CO adsorption on supported Ni.

In our comparative studies of SMAD vs. conventional Ni/support catalysts we have found that electronic support effects are minimal for the SMAD catalysts but are significant for the conventional systems. Thus, the Ni–support interactions are definitely different in the two systems.

For an explanation of this difference, recall that during low-temperature clustering of nickel atoms in organic media a competition exists between Ni–Ni bond formation (cluster growth) and reaction of the forming clusters with the organic medium. This process leads to extensive C–C and C–H cleavage of alkanes at temperatures even as low as −130 °C,[2] and a great deal of carbonaceous material is incorporated into the final clusters. Scott and co-workers[20] and we[2] have demonstrated that the final Ni clusters are surrounded by a protective carbonaceous layer.

Arenes react similarly to alkanes with the bare Ni clusters. However, at low temperatures (<−50 °C) formation of a stable π-arene–Ni complex prevents much cluster formation, and so C–C and C–H bond cleavage probably does not occur until the π-arene complex starts to decompose (>−50 °C). At this time the catalyst support is present in the melted Ni–arene solution. Thus, as decomposition of the π-arene–Ni complex occurs, Ni clusters begin to form and can react with the excess arene and thereby incorporate carbonaceous residues. These residues or arene fragments could serve as a mode of attachment of the Ni clusters to the surface of the support (see Scheme II). It is possible that this would lead to a robust Ni–support attachment but would also serve to insulate the Ni clusters from electronic effects of the support. That such a sequence of reactions takes place seems likely on the basis of our previous work and the current data.

In support of the above explanation, we have determined that after treatment of a 8.9 wt % of Ni/MgO SMAD catalyst wth H_2 at 400 °C some of the incorporated carbon remains. The final value was 0.33 wt % of carbon (Ni/C molar ratio of 5.5), and this would likely be the carbon buried under the metal cluster and in close proximity to the support surface. It is not likely that this remaining carbon is dispersed over the support surface since the Ni/Al_2O_3 catalyst still exhibited acidic character (IPA dehydration activity), and the Ni/MgO catalyst still exhibited basic character (bifunctional CO methanation activity). Therefore, the active support sites not containing Ni do still exist after the SMAD treatment.

The available data lead us to conclude that the SMAD catalysts consist of very small Ni clusters probably attached to the support through carbonaceous residues. This mode of attachment precludes electronic support effects but still allows bifunctional catalysis to occur, as is the case with methanation over the Ni/MgO SMAD catalyst. In the future we hope to obtain further information through surface spectroscopic studies as well as high-resolution transmission electron microscopy.

Acknowledgment. The support of the National Science Foundation and the Department of Energy is greatly appreciated.

Registry No. Nickel, 7440-02-0; methylcyclopentane, 96-37-7; toluene, 108-88-3; isopropyl alcohol, 67-63-0; carbon monoxide, 630-08-0.

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Synthesis and Thermal Isomerization of Tricyclo[4.2.2.0^{1,6}]dec-7-ene ([4.2.2]Propell-7-ene) to 3,8-Dimethylenecyclooctene

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Tricyclo[4.2.2.0^{1,6}]dec-7-ene ([4.2.2]propell-7-ene ([4.2.2]propell-7-ene; **1**) has been prepared from *cis*-4-cyclohexene-1,2-dicarboxylic anhydride through a conventional 12-step reaction sequence by way of bicyclo[4.2.0]oct-1(6)-ene and tricyclo[4.2.1.0^{1,6}]nonane-9-carboxaldehyde tosylhydrazone. It is isomerized thermally to 3,8-dimethylenecyclooctene (**2**) with activation parameters $E_a = 35.8 \pm 1.3$ kcal mol^{-1} and $\log A = 12.6 \pm 0.6$. Two possible explanations for the isomerization are considered: reaction by way of a short-lived bicyclo[4.2.2]deca-1(8),6-diene intermediate or direct cleavage of C(1)–C(6) and C(9)–C(10) simultaneously.

Bicyclo[2.2.0]hex-2-ene[1] isomerizes thermally to give 1,3-cyclohexadiene.[2-4] This electrocyclic reaction must be disrotatory and thus orbital symmetry forbidden; nevertheless, it is favored kinetically over alternative modes of rearrangement such as cyclobutane cleavage, degenerate [1,3] sigmatropic carbon shift, and retro-ene reaction.

5-Methylenebicyclo[2.2.0]hex-2-ene[5] and 5,6-dimethylenebicyclo[2.2.0]hex-2-ene[6] react similarly, giving 1-methylene-2,4-cyclohexadiene and 1,2-dimethylene-3,5-cyclohexadiene (*o*-xylylene), respectively.

cis-1,3,5-Hexatriene is not an important intermediate in the bicyclo[2.2.0]hex-2-ene isomerization to 1,3-cyclohexadiene; were it formed, it would be detected, for its rate of isomerization to cyclohexadiene is comparatively slow.[7,8]

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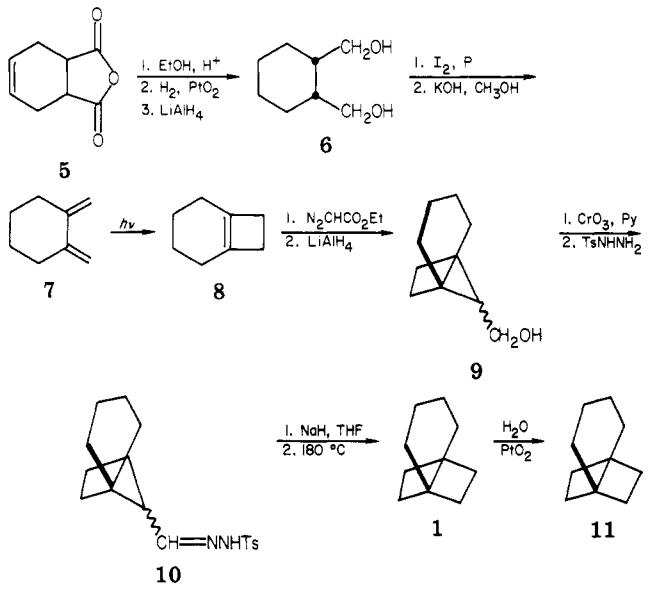
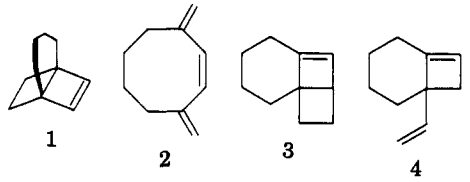
Scheme I



5 6 7 8 9 10 1 11

A study[9] which followed the thermal isomerization of bicyclo[2.2.0]hex-2-ene[1] in C_6D_6 by NMR spectroscopy found no proton resonance adsorptions appropriate to *cis*-1,3,5-hexatriene as 1,3-cyclohexadiene was formed at 135 °C. According to the mechanistic sequence bicyclo[2.2.0]hex-2-ene → *cis*-1,3,5-hexatriene → 1,3-cyclohexadiene, the hexatriene concentration should have reached a maximum of about 54 mol % at this temperature.[10]

A 1,4-bridged bicyclo[2.2.0]hex-2-ene such as tricyclo[4.2.2.0^{1,6}]dec-7-ene (**1**; [4.2.2]propell-7-ene[11-13]) ought to preclude or at least impede the cyclobutene → butadiene type of electrocyclic reaction and, by default, permit one or several otherwise unobservable reactions to occur.



1 2 3 4

The [1,3] carbon shift isomer **3** and the retro-ene product **4**, if formed, might well react further to give 1(6),2- and 1,5-bicyclo[4.4.0]decadiene, respectively. Still other modes of reaction might obtain.[14]

We have synthesized tricyclo[4.2.2.0^{1,6}]dec-7-ene (**1**) in order to examine its thermal chemistry:[15] with the normal bicyclo[2.2.0]hex-2-ene electrocyclic isomerization thwarted by the tetramethylene bridge across the bridgehead bond, this bicyclohexene undergoes a facile cycloreversion to give 3,8-dimethylenecyclooctene (**2**).

Results

Synthesis. The synthesis, outlined in Scheme I, proceeded by way of bicyclo[4.2.0]oct-1(6)-ene (**8**), which was prepared following literature procedures.[16-23] In basic methanol the diiodide from **6** gives 1,2-dimethylenecyclohexane (**7**);[18,19] photoisomerization of the diene provides a nearly quantitative yield of bicyclo[4.2.0]oct-1(6)-ene (**8**).[20-23]

The copper-catalyzed reaction between ethyl diazoacetate and bicyclo[4.2.0]oct-1(6)-ene[24] gave a mixture of epimeric 9-(carboethoxy)tricyclo[4.2.1.0^{1,6}]nonanes, which were converted in turn to the corresponding primary alcohols **9** (3:1 mixture by NMR analysis). Oxidation of the alcohols with chromium trioxide in pyridine–methylene chloride[25] gave the aldehydes, which were converted without purification to tosylhydrazone **10**. The sodium salt of the tosylhydrazone at 180 °C gave [4.2.2]propell-7-ene (**1**) by way of a cyclopropylcarbene → cyclobutene isomerization.[26] After purification of this hydrocarbon by preparative GLC on an SE-30 column, a 19% yield (from the tosylhydrazone) was realized.

The identity of the product was confirmed by its spectral characteristics and by catalytic hydrogenation to tricyclo[4.2.2.0^{1,6}]decane ([4.2.2]propellane; **11**).[27]

Thermal Isomerization. When degassed solutions of tricyclo[4.2.2.0^{1,6}]dec-7-ene (**1**) in benzene were heated to temperatures from 180 to 240 °C, first-order conversion of the substrate to 3,8-dimethylenecyclooctene (**2**) was observed. The monocyclic isomeric product had NMR absorptions at δ 6.15 (s, 2 H), 4.95 (s, 4 H), 2.4 (br m, 4 H), and 1.4 (m, 4 H).[28]

Kinetic work in sealed ampules at three temperatures (181.1–240.3 °C) led to estimates of the activation parameters for this first-order isomerization: $E_a = 35.8 \pm 1.3$ kcal mol^{-1} and log $A = 12.6 \pm 0.6$.

Discussion

The isomerization of [4.2.2]propell-7-ene (**1**) to 3,5-dimethylenecyclooctene (**2**) provides a novel example of a bicyclo[2.2.0]hex-2-ene to *cis*-1,3,5-hexatriene rearrangement; alternatively, it may be viewed as a cyclobutane fragmentation or cyclodissociation of a bicyclo[2.2.0]hexane derivative comparable to the isomerization of a bicyclo[2.2.0]hexane to a 1,5-hexadiene.[29-31]

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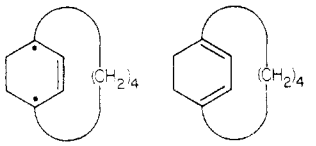
[n.2.2]Propellanes isomerize through cyclobutane fragmentations at relatively low temperatures if considerable strain energy may be released in the process; [4.2.2]propellane and [3.2.2]propellane are thermally stable at temperatures up to at least 160 °C,[27] while a substituted [2.2.2]propellane prepared by Eaton and Temme[32] rearranged to 1,4-dimethylenecyclohexanes with a half-life of about 28 min at 25 °C. The olefinic moiety in 1 does not appear to be a particular help or hindrance to the cycloreversion observed, for bicyclo[2.2.0]hexane isomerizes to 1,5-hexadiene at 180 °C only a factor of 4 or 5 faster[29] than 1 isomerizes to 2. (The bicyclo[2.2.0]hex-2-ene rearrangement to 1,3-cyclohexadiene is nearly 10^3 faster[2-4].)

While formation of 3,8-dimethylenecyclooctene (2) from 1 was not a surprise, the rate of this reaction was not anticipated: we did not expect it to be so comparable to the rate of the bicyclo[2.2.0]hexane → 1,5-hexadiene reaction. That process is thought to proceed by cleavage of the C(1)–C(4) bond to generate a 1,4-cyclohexadiyl diradical or 1,4-π-bonded intermediate,[30,31,33] an intermediate which can serve to rationalize the stereochemistry of hexadiene products and the skeletal inversion shown by some bicyclo[2.2.0]hexanes. The 1,4-tetramethylene bridge spanning C(1)–C(4) of the bicyclo[2.2.0]hexene unit in 1 would be as discouraging to the formation of a comparable diradical (12) as to bicyclo[4.2.2]deca-1(8),6-diene (13). Indeed, differences between these structures could be subtle and hard to detect.



12 13

Two explanations for the similarities in rates seem most plausible to us now. Perhaps bias against intervention of 13 as an intermediate based on a conservative prejudice against Bredt's rule violations is not valid; the reaction sequence could then be 1 → 13 → 2, with the second step being very much faster than the first and the similarity in overall rates for 1 → 2 and bicyclo[2.2.0]hexane → 1,5-hexadiene being a mere coincidence. Or perhaps the cyclobutane cleavage in this case (1 → 2) takes place with simultaneous elongation of both cyclobutane bonds that are broken; this view would hold that 1,4-cyclohexadiyl diradicals may be preferred but are not required intermediates, and that a range of geometrical and timing options may be available to any particular bicyclo[2.2.0]hexane or related system.[34]

Experimental Section

All ^1H NMR spectra were determined as $CDCl_3$ solutions on Varian XL-100 or HA-100 spectrometers. Mass spectra were taken on a CEC 110-21B instrument by Dr. Richard Wielesek. Analytic GLC analyses were done with a Hewlett Packard 700 gas chromatograph equipped with a 5771A control module, an F & M Scientific 220 temperature controller, and an Autolab 6300 digital integrator, on a 3-mm SE-30 column at 120 °C with flame ionization detection. Pyrolyses were done in a molten potassium nitrite–sodium nitrate bath controlled with a Bailey Instruments Model 253 precision temperature controller. A Hewlett Packard Model 2802A digital thermometer was used to measure the bath temperature.

Low-resulution mass spectra and GLC analyses were taken as adequate evidence of molecular formula and purity for new substances; structural assignments were based on IR and ^1H NMR spectra and on the synthetic sequences linking new and previously established structures.

Bicyclo[4.2.0]oct-1(6)-ene (8) was prepared from commercial *cis*-4-cyclohexene-1,2-dicarboxylic anhydride through esterification,[16] catalytic hydrogenation,[16] reduction with lithium aluminum hydride,[17] conversion of the *cis*-1,2-bis(hydroxymethyl) compound 6 to the corresponding *cis*-1,2-bis(iodomethyl) intermediate,[18] dehydrohalogenation with alcoholic potassium hydroxide,[18] and photochemical isomerization.[20-22] The photolysis, accomplished in 9–12 h with use of a Hanovia 450-W high-pressure lamp, Vycor filter, nitrogen atmosphere, and pentane solution of 1,2-dimethylenecyclohexane (7) at 0 °C, was followed by NMR spectroscopy; the narrow multiplets at δ 4.6 and 4.9 from the exocyclic vinyl methylene protons and the allylic proton resonance centered at δ 2.25 diminished in intensity as the methylene proton multiplet of the cyclobutene moiety at 2.45 ppm increased. The bicyclo[4.2.0]oct-1(6)-ene (8), isolated through concentration and vacuum transfer (25 °C, 20 mm), was found to be homogeneous through GLC and NMR analyses.

9-(Carboethoxy)bicyclo[4.2.1.$0^{1,6}$]nonanes.[24] Ethyl diazoacetate (2.91 g, 69 mmol) in 30 mL of cyclohexane was added dropwise over a 2.5-h period to a stirred mixture of cupric sulfate (1.0 g) and bicyclo[4.2.0]oct-1(6)-ene (8; 2.27 g, 21 mmol) in 5 mL of cyclohexane heated to reflux. The reaction mixture was stirred at reflux an additional 15 min, cooled, and filtered. Concentration of the deep-burgundy filtrate and distillation of the residue gave 1.64 g (41% yield) of the two 9-(carboethoxy)bicyclo[4.2.1.$0^{1,6}$]-nonanes: bp 43–68 °C (1 mm); IR 1700, 1730 cm^{-1}; mass spectrum, *m/e* 194 (M^+), 82 (base peak).

9-(Hydroxymethyl)bicyclo[4.2.$0^{1,6}$]nonanes (9). A solution of the two 9-(carboethoxy)bicyclo[4.2.1.$0^{1,6}$]nonane isomers (1.56 g, 8 mmol) in 15 mL of ether was added dropwise under nitrogen to a stirred slurry of $LiAlH_4$ (0.30 g, 8 mmol) in 25 mL of ether at reflux. The reaction mixture was stirred at reflux another 1.5 h and then cooled and hydrolyzed.[35] The dried ($MgSO_4$) and filtered ethereal solution was concentrated at reduced pressure to give 0.91 g (74% yield) of the hydroxymethyl isomers as a clear oil: NMR, HC(9)CH_2OH doublets (*J* = 8 Hz) at δ 3.85 and 3.69 (3:1 ratio); IR 3600, 3440 cm^{-1}; mass spectrum, *m/e* 152 (M^+), 79 (base peak).

Tricyclo[4.2.1.$0^{1,6}$]nonane-9-carboxaldehyde Tosylhydrazone (10). In a 250-mL, three-necked, round-bottomed flask equipped with an overhead stirrer and a reflux condenser was placed dry pyridine (5.68 g, 72 mmol) and 90 mL of dry methylene chloride. Under a nitrogen atmosphere and with stirring was added in several portions chromium trioxide (3.6 g, 36 mmol, dried over phosphorus pentoxide); the dark-red suspension was stirred another 15 min and then a mixture of epimeric 9-(hydroxymethyl)tricyclo[4.2.1.$0^{1,6}$]nonanes (9; 0.91 g, 36 mmol) was added. The black reaction mixture was stirred for 15 min and filtered through Florisil. The Florisil was washed with 200 mL of CH_2Cl_2, and the methylene chloride solutions were combined, extracted with dilute HCl and saturated $NaHCO_3$, washed with water and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure to give the crude aldehydes as a yellow oil (0.69 g, 77%). This oil was added to (*p*-tolylsulfonyl)hydrazine (0.93 g, 5 mmol) dissolved in a minimum of ethanol at 50 °C. The reaction mixture was cooled in an ice bath and then allowed to stand at room temperature overnight. The collected, washed, and dried tosylhydrazone (0.39 g, 20% from the mixture of alcohols) had mp 136.5–138.0 °C; mass spectrum, *m/e* 318 (M^+), 290, 262, 171, 163 (base peak).

Tricyclo[4.2.2.$0^{1,6}$]dec-7-ene (1). In a 15-mL, one-necked, round-bottomed flask under nitrogen was placed sodium hydride

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(0.042 g, 1.75 mmol) in 2 mL of dry tetrahydrofuran. The tosylhydrazone prepared above (0.39 g, 1.2 mmol) was added, and the reaction mixture was stirred for 15 min. The solvent was removed by distillation at reduced pressure, and the reaction flask was connected through a trap to a vacuum line. The system was evacuated to 0.2 mm and the flask was heated; at a bath temperature of 120–130 °C, the pale-yellow sodium salt turned pink, and liquid began to collect in the liquid-nitrogen-cooled trap. The bath temperature was brought to 180–190 °C for 1.5 h to complete the reaction. Purification of the liquid collected in the cold-finger trap by preparative GLC (SE-30, 120 °C) gave 30 mg (19% yield) of tricyclo[4.2.2.0^{1,6}]dec-7-ene: NMR 6.25 (2 H, s), 1.82 (6 H, br s), 1.50 (2 H, m), 1.35 (4 H, m); mass spectrum, *m/e* 134 (M^+), 119, 106, 105, 91 (base peak).

Tricyclo[4.2.2.0^{1,6}]decane (11). Atmospheric hydrogenation of 5 mg of tricyclo[4.2.2.0^{1,6}]dec-7-ene in ethyl acetate with the aid of Adams catalyst gave a colorless low-melting solid. Its NMR spectrum matched the published spectrum of [4.2.2]propellane (tricyclo[4.2.2.0^{1,6}]decane).[27]

3,8-Dimethylenecyclooctene (2). A 5-mg sample of tricyclo[4.2.2.0^{1,6}]dec-7-ene in 0.5 mL of benzene-d_6 was thoroughly degassed, sealed in vacuo, and heated in a salt bath maintained at 221.4 °C. After 10 min, new NMR signals had appeared at δ 6.15 (s), 4.95 (s), 2.4 (br m), and 1.4 (m), with relative intensities 1:2:2:2. After 60 min of thermolysis, more than 90% of the starting material had been converted to this new product. On an SE-30 column at 120 °C, it had a longer retention time than the starting material; mass spectrum, *m/e* 134 (M^+), 119, 106, 91 (base peak).

Kinetics of the Tricyclo[4.2.2.0^{1,6}]dec-7-ene to 3,8-Dimethylenecyclooctene Rearrangement. Open-ended glass capillary tubes were soaked for several hours in dilute HCl and again in an NH_4OH/EDTA solution and then thoroughly washed with distilled water and dried overnight in an oven at 140 °C. One end of each tube was sealed. A benzene solution approximately 0.8 M in tricyclodecene and containing dodecane as internal standard was prepared; 5-μL portions of this solution were placed in each capillary tube with a syringe. These capillary-tube ampules were flushed gently with nitrogen, frozen, sealed, and heated in the salt bath; after pyrolyses the reaction mixtures were analyzed by GLC. The observed first-order rate constants for the thermal conversion of tricyclodecene to 3,8-dimethylenecyclooctene were $(2.52 \pm 0.15) \times 10^{-5}$ s^{-1} at 181.1 °C, $(2.51 \pm 0.24) \times 10^{-4}$ s^{-1} at 211.2 °C, and $(2.31 \pm 0.06) \times 10^{-3}$ s^{-1} at 240.3 °C. The kinetic work at 211.2 °C was done several months after the other two sets of pyrolyses were completed. An Arrhenius plot based on the three rate constants gives the activation parameters $E_a = 35.8 \pm 1.3$ kcal/mol and log $A = 12.6 \pm 0.6$.

Acknowledgment. We are indebted to the National Science Foundation for partial support of this work and to Professors S. Masamune, M. Goldstein, and H.-D. Martin for helpful correspondence.

Discrimination between Alternative Pathways of Aqueous Decomposition of Antitumor (2-Chloroethyl)nitrosoureas Using Specific ^{18}O Labeling†

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The synthesis of certain specifically ^2H- and ^{18}O-labeled 1-(2-chloroalkyl)-3-alkyl-1-nitrosoureas is described. When BCNU-β,β'-d_4 (2) was allowed to decompose in phosphate buffer at pH 7.1 and 25 °C in 99% $H_2{}^{18}O$ in the presence of liver alcohol dehydrogenase and NADH, the acetaldehyde initially produced is immediately reduced to ethanol. Gas chromatographic mass spectral analysis of the positions of ^2H and ^{18}O labels in the ethanol permitted a discrimination between competing pathways of decomposition, indicating in this case ca. 21% contribution via a postulated 1,2,3-oxadiazoline intermediate. The observation of $CH_2DCDH^{16}OH$ in addition to $CH_3CDH^{16}OH$ indicates the 1,2,3-oxadiazoline intermediate may decompose partly by a concerted pathway requiring a 5 to 4 deuterium shift. In contrast decomposition of BCNU-α,α'-diMe (3) in 99% $H_2{}^{18}O$ containing phosphate buffer at pH 7.1 and 25 °C in the presence of the alcohol dehydrogenase afforded labeled propanol corresponding to ca. 89% contribution via the 1,2,3-oxadiazoline intermediate. The result was substantiated by the reverse decomposition of BCNU-β,β'-d_4-α,α'-diMe-*N*-^{18}O in $H_2{}^{16}O$, GC–MS analysis of which afforded $CH_3CDHCDH^{18}OH$ and $CH_3CH_2CDH^{18}OH$ corresponding to ca. 88% contribution of the 1,2,3-oxadiazoline pathway. The preference for this pathway in the latter case may be due to the increased stabilization the α-Me group affords the intermediate cation. This would tend to disfavor the two alternative mechanisms which require a hydride shift in the cationic intermediate.

Introduction

The (2-chloroethyl)nitrosoureas (CENUs) such as BCNU, CCNU, and MeCCNU, and chlorozotocin are of clinical value in the treatment of a wide range of neoplasma.[1,2] Pharmacologial evidence indicates that CENUs decompose spontaneously under physiological conditions, giving rise to electrophiles including isocyanate, 2-chloroethyldiazohydroxide, or the 2-chloroethyl cation, and that the latter two species both alkylate and form interstrand cross-links in DNA and between DNA and proteins.[3–10]

† CENU, 1-(2-chloroethyl)-3-alkyl-1-nitrosourea; BCNU, bis(2-chloroethyl)-1-nitrosourea; BCNU-β,β'-d_4, bis(2-chloro-2,2-dideuterioethyl)-1-nitrosourea; BCNU-α,α'-diMe, bis(2-chloro-1-methylethyl)-1-nitrosourea; BCNU-β,β'-d_4-α,α'-diMe, bis(2-chloro-2,2-dideuterio-1-methylethyl)-1-nitrosourea; BCNU-β,β'-d_4-α,α'-diMe-*N*-^{18}O, bis(2-chloro-2,2-dideuterio-1-methylethyl)-1-[^{18}O]-nitrosourea.

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