Nucleophilic Attack on Iodonium Ion Intermediate. "Real" Regiochemistry of the Iodo Azide Adduct of 1-Phenylcyclohexene and of Its Dehydrohalogenation Product

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The regiochemistry of the anti iodo azide adduct (IAA) of 1-phenylcyclohexene (1), originally reported as 3, was reexamined and proposed to be the reversed one 4 on the basis of its dehydrohalogenation to an unsaturated compound, which was supposed to be the azido olefin 8. Structural data on the anti iodo isocyanate adduct of 1 (5) prompted us to further verify the regiochemistry of the IAA. Comparison of NMR data (^1H and ^{13}C) of the IAA with corresponding ones of analogous compounds of proved structures and the absence of any coupling in the ^{15}N NMR of the IAA led us to reverse further the regiochemistry of the IAA to the original one 3. The dehydrohalogenation product of the IAA was proven to be different from 8 and was unequivocally shown to be the isomeric azido olefin 14. The formation of 14 from 3 (IAA) was rationalized through the initial formation of the azido olefin 16, followed by a [3,3] sigmatropic rearrangement to the more stable isomeric 14.

It is well established[1,2] that electrophilic additions to olefinic double bonds initiated by positive halogens proceed through the formation of halonium-type intermediates, which, on attack of the nucleophile, usually afford anti adducts. In unsymmetrical olefins, Markovnikov- and contra-Markovnikov-type[3] addition products can be obtained; the product distribution is strictly linked to the nature of the halogen, the steric and electronic effects of the substituents on the double bond, the nucleophile, and the reaction conditions in general.[1,2]

Some years ago, Hassner[4] reported that the addition reaction of iodine azide to 1-phenylcyclohexene (1) yielded, with complete regio- and stereoselectivity, the anti-Markovnikov-type adduct 3, which can be considered to arise from the attack of the N_3 nucleophile on the tertiary benzylic carbon of the intermediate iodonium ion 2 (Scheme I, route 1). Whereas the anti nature of the adduct 3 was shown through its conversion into the aziridine 7, the regiochemistry was based only on the ^1H NMR spectrum (Scheme I).[4]

Recently[5] the regiochemistry of the anti addition product[6] (IAA) obtained from 1 and iodine azide was reexamined[5] on the basis of a dehydrohalogenation reaction, carried out on this adduct, which yielded an unsaturated compound (DHP), presumed to be 3-azido-2-phenylcyclohexene (8) (Scheme II).[5] Following these results it was "unequivocally" assumed[5] that the structure of the IAA was 2-azido-1-iodo-1-phenylcyclohexane (4) rather than 1-azido-2-iodo-1-phenylcyclohexane (3) as originally reported.[4] The authors[5] envisaged that, as a result of steric considerations, the attack of the azide ion on the stable iodonium ion intermediate 2 would be expected to occur on the less substituted carbon of 2, thus yielding the adduct 4 (Scheme I, route 2).[5] The structure assigned to the DHP (presumably 8, Scheme II) was based on the presence in its ^1H NMR spectrum of one methine proton (H_6) and of only one olefinic proton (H_2) and on decoupling studies.[5] Double resonance experiments carried out on both the signals did not result "in any significant change" in the other signal, leading to the conclusion that the two protons (H_2 and H_6) were not coupled and therefore not on adjacent carbons.[5]

A previous paper from our laboratories concerned the reaction of 1-phenylcyclohexene (1) with iodine isocyanate,[7] which yields only the adduct 5. Whereas the stereochemistry of the adduct 5 was proven by its conversion to the aziridine 7, its regiochemistry was assumed mainly on the basis of a Markovnikov-type attack of the ^-NCO nucleophile on the benzylic carbon of the intermediate iodonium ion 2, analogously to what was originally suggested by Hassner for the reaction of 1 with iodine azide.[4]

The results obtained in ref 5 prompted us to verify if a regiochemistry different from that originally hypothesized,[7] but not proven, could have taken place also in the nucleophilic attack of ^-NCO on the intermediate 2[8] (Scheme I). However, an X-ray crystal structure determination carried out on the iodoisocyanate adduct of 1 unequivocally confirmed the structure and the regiochemistry previously assigned[7] and shown in 5, ruling out, in this case, the possibility of a contra-Markovnikov-type nucleophilic attack on 2, which would have yielded anti adduct 6 (Scheme I).[8]

From all these data[5,8] it appeared that the IAA (proposed to be 4[5]) and the iodo isocyanate adduct (demonstrated to be 5[8]) of 1-phenylcyclohexene (1) exhibit an opposite regiochemistry in spite of the fact both should arise by attack of the two nucleophiles, N_3^- and ^-NCO, respectively, on the very same iodonium ion-type intermediate 2. The two adducts of 1 (the iodo azide and the iodo isocyanate) should reasonably be expected to have the same regiochemistry. We therefore decided to further check the regiochemistry of the IAA and find out whether the actual structure is 4, as recently reported,[5] or if it must be changed to the original proposed[4] 3, corresponding to 5[8] (Scheme I). The most direct and unequivocal route ap-

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(1) Fahey, R. C. *Top. Stereochem.* **1968**, *3*, 286.
(2) De La Mare, P. B. D.; Bolton, R. *Electrophilic Additions to Unsaturated Systems*; Elsevier Scientific: Amsterdam, 1982.
(3) According to ref 2 the term "contra-Markovnikov" is preferred to "anti-Markovnikov" in order to avoid confusion with the stereochemical use of the prefix anti.
(4) Hassner, A.; Matthews, G. J.; Fowler, W. F. *J. Am. Chem. Soc.* **1969**, *91*, 5046.
(5) Sivasubramaniam, S.; Aravind, S.; Kumarasingh, L. T.; Arumulgam, N. *J. Org. Chem.* **1986**, *51*, 1985.
(6) In order to simplify the discussion about their real structures, we will refer to the anti iodo azide adduct of 1 simply as IAA and to the dehydrohalogenated product derived from IAA simply as DHP (see Scheme II).
(7) Anselmi, C.; Camici, G.; Macchia, F.; Monti, L. *Gazz. Chim. Ital.* **1972**, *102*, 1129.
(8) Chini, M.; Crotti, P.; Macchia, F.; Domiano, P.; Monti, L. *Gazz. Chim. Ital.* **1988**, *118*, 123.

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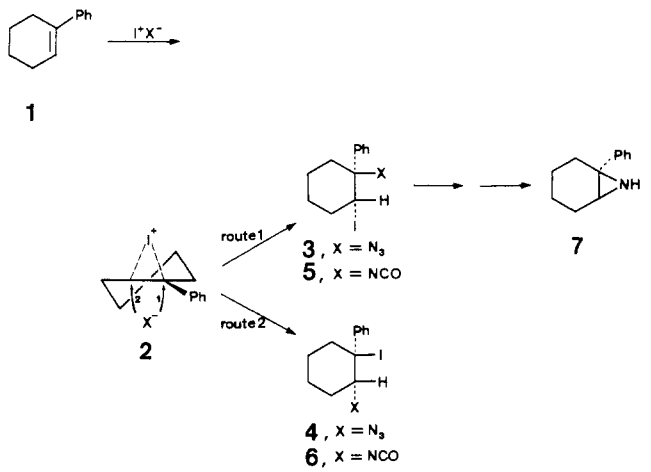
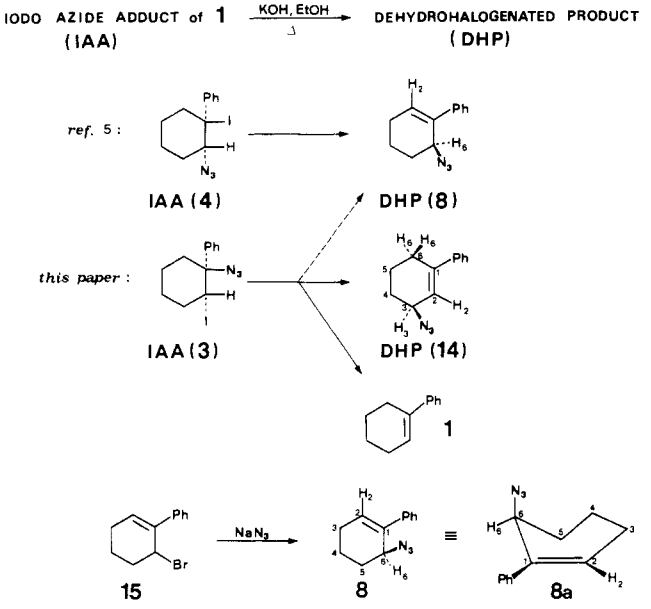
Scheme I

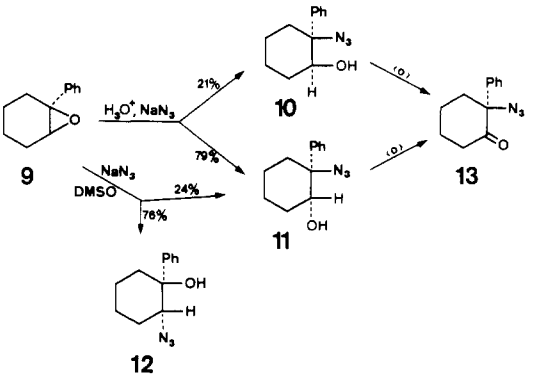


Scheme II



peared to be an X-ray crystal structure determination of the IAA, as previously done in the case of the iodo isocyanate adduct **5**.[8] Unfortunately, we were not able to obtain crystals of the IAA suitable for X-ray analysis. On the other hand, attempts to transform the IAA into derivatives which could be useful for the determination of the regiochemistry of the starting compound were completely unsuccessful. As an example, the tentative reduction of the azido group present in the IAA with BH_3·Me_2S in THF, even for a long period (30 days), led to the complete recovery of the starting product (IAA), whereas when the reduction was carried out with hydrogen in the presence of Pd/C, mixtures consisting of the starting compound (IAA), 1-phenylcyclohexene (1), and phenylcyclohexane were obtained; on the other hand, attempts to dehalogenate the IAA with Bu_3SnH led only to 1-phenylcyclohexene (1). Therefore, the only promising approach to the "real" structure (regiochemistry) of the IAA appeared to be an exhaustive NMR study including ^1H, ^{13}C, and ^{15}N spectroscopy. In order to make the NMR study more efficient the ^1H and ^{13}C NMR spectra of the IAA were compared with those of analogous compounds of proven structure: the iodo isocyanate adduct **5**[7,8] and

Scheme III



the newly prepared azido alcohols **10**, **11**, and **12** (Scheme III). In **10** and **11** the azido group is on the tertiary benzylic carbon as in structure **3**, while in **12** the same group is on the adjacent non benzylic secondary carbon, as in structure **4**. The diastereoisomeric cis (**10**) and trans (**11**) azido alcohols were formed as a 21:79 mixture in the reaction of the epoxide **9** with aqueous NaN_3 solution in the presence of acid. The reaction of the same epoxide **9** with NaN_3 in DMSO yielded a mixture of the two regioisomeric trans azido alcohols **11** and **12** in which the latter largely predominated (24:76) (Scheme III). The formation of the azido alcohols **10**–**12** from epoxide **9** agrees with the expectations of epoxide **9** under the specified conditions:[9,10] in this way, while the reaction carried out in the presence of acid yielded a mixture consisting of the *syn*-**10** and *anti*-**11** addition products with attack of the nucleophile on the benzylic carbon, the strongly nucleophilic nonacidic conditions (DMSO–NaN_3) led to the formation of only the anti adducts **11** and **12**. In these latter conditions the attack of the nucleophile on the least substituted carbon must predominate,[9,10] as observed. The diastereoisomeric nature of **10** and **11** and the regiochemistry of all the azido alcohols **10**–**12** was proven by the oxidation of **10** and **11** to the same ketone **13**, whereas **12** was stable under the same experimental oxidation conditions. On the other hand, the formation of **11** and **12** in the nonacidic azidolysis of **9** defines their trans configurations.[9,10] The configurations of compounds **10**–**12** were confirmed on the basis of the half-band widths[9-11] of the signals of the methyne proton in their ^1H NMR spectra, on the logical assumption that the large phenyl group occupies an equatorial position in the most stable conformation (see Table I).

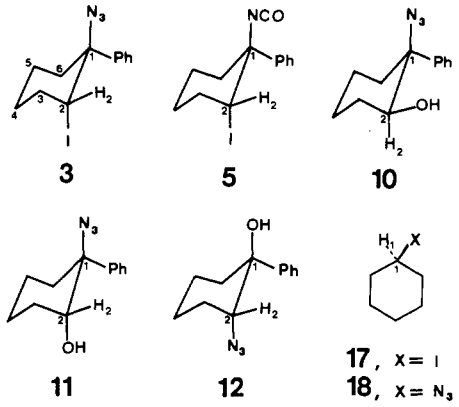
Going on to the demonstration of the actual structure of the IAA, let us first examine the ^{13}C NMR data (see Table I) obtained from this adduct and from the other structurally correlated compounds (**5** and **10**–**12**): the chemical shift of the quaternary carbon (C_1 in Table I) of the IAA is quite similar to that of the azido alcohol **11**, while the value for the methyne carbon (C_2 in Table I) of the IAA is very close to the one observed in the iodo isocyanate adduct **5**, and at the same time very different from the C_2 value of the azido alcohol **12**. Analogously, the

(9) See for example: Crotti, P.; Dell'Omodarme, G.; Ferretti, M.; Macchia, F. *J. Am. Chem. Soc.* **1987**, *109*, 1463 and references cited therein.

(10) Battistini, C.; Crotti, P.; Macchia, F. *Gazz. Chim. Ital.* **1977**, *107*, 153.

(11) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon Press: New York, 1969; p 288.

Table I. ^1H and ^{13}C NMR Data for Compounds 3, 5, 10–12, 17, and 18



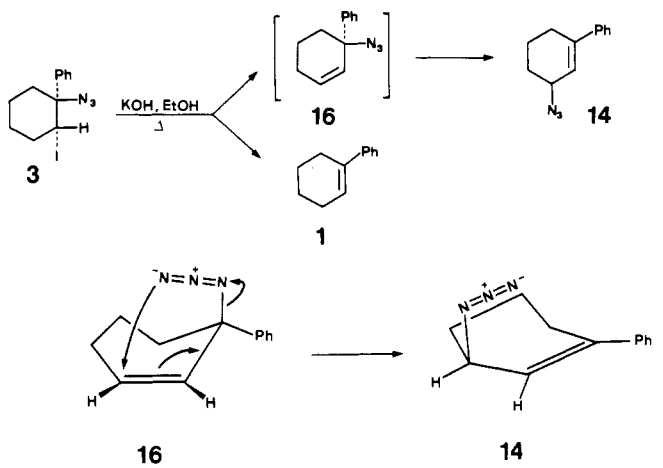
compd	^1H NMR, δ CHX[a] ($W_{1/2}$, Hz)	^{13}C NMR, ppm C_1	C_2
IAA[b]	4.75 (6.0)	67.9	41.1
5	4.72 (6.1)	64.8	42.4
10	3.90 (16.0)	70.9	74.8
11	3.76 (7.2)	68.2	71.6
12	3.86 (7.0)	73.4	66.2
17	4.40	31.8	
18	3.32	59.9	

[a] H_2 in the formulas. [b] IAA = compound 3, and see ref 6.

chemical shift of C_2 in the IAA (41.1 ppm) is closer to the corresponding shift (C_1) of the iodocyclohexane (17) (31.8 ppm)[12a] than to that of azidocyclohexane (18) (C_1 = 59.9 ppm, see the Experimental Section, and Table I). Furthermore, the three ^{15}N NMR resonances of the IAA do not show any proton coupling. Therefore, all the ^{13}C and ^{15}N data speak in favor of structure 3. The same structure 3 is also inferred by the ^1H NMR studies; the half-band widths[9-11] of the methyne proton of the IAA, of 5, and of 12 (see Table I) indicate that all these compounds exist preferentially in the conformations shown in the table, with the phenyl group equatorial. As for the chemical shift, the value found for the methyne proton in the IAA is almost identical with that of the structurally related iodo isocyanate 5, and at the same time quite different from that of the azido alcohol 12 (see Table I). Moreover, the value found for CHX in the IAA (δ 4.75) is much closer to the one found for the corresponding proton in 17 (δ 4.40)[12b] than in 18 (δ 3.32).

Once we had firmly established that the actual structure of the iodo azide adduct (IAA) of 1-phenylcyclohexene (1) is as shown in 3, it appeared unlikely that the dehydrohalogenation of the IAA (that is 3) could lead to the azido olefin 8, as affirmed[5] (Scheme II). Therefore, we also decided to check this reaction. Actually, when compound 3 is refluxed with 20% KOH in EtOH as described,[5] in addition to a compound (DHP)[6] corresponding to the *supposed azido olefin 8*,[5] substantial amounts (30%, see the Experimental Section) of 1, not previously[5] detected, were obtained. However, the DHP was different from an authentic sample of 8 prepared by simple substitution of the known allylic bromide 15[13] with sodium azide in acetone (Scheme II). NMR studies were therefore carried out in order to confirm the structure of the newly synthesized

Scheme IV



azido olefin 8 and to demonstrate that the DHP previously identified with 8[5] had to have some different structure. The ^1H NMR spectrum of 8 exhibits an olefinic proton (H_2) and a methyne proton (H_6) that double-resonance experiments show to be not coupled, according to its structure (Scheme II). The lack of any appreciable allylic coupling constant between the H_2 and H_6 protons appears to be due to the unfavorable conformational arrangement. As can be inferred from the half-band width value[11] of the methyne proton (9.4 Hz), compound 8 largely exists in the conformation 8a having the methyne proton pseudoequatorial (Scheme II). In this situation, the "allylic" angle for that proton is very small, predicting an allylic coupling constant near zero.[14] As for the DHP the ^1H NMR data make it possible to assign to it unequivocally the structure of the azido olefin as shown in 14. As previously reported,[5] the ^1H NMR spectrum of the DHP (14, supposed to be 8[5]) shows an olefinic proton (H_2, as a doublet of triplets) and a methyne proton (H_3, as a multiplet). However, contrary to the previous report,[5] double-resonance experiments indicate a coupling constant of 3.85 Hz ($J_{2,3}$) between the two protons. The same type of experiment indicates an allylic coupling constant ($J_{2,6}$ = 1.77 Hz) between proton H_2 and the allylic H_6 protons and a coupling between H_3 and the H_4 protons. Furthermore, the H_4 and H_6 protons were shown to be coupled with the H_5 protons.

Clearly the azido olefin 14 cannot be imagined to be the primary product of dehydrohalogenation of 3. A logical rationalization of the reaction could be that the initially formed azido olefin 16 undergoes a [3,3] sigmatropic rearrangement,[15] as shown in Scheme IV,[16] through a concerted transition state to yield the more stable azido olefin 14. It may be pointed out that in the dehydrohalogenation–rearrangement sequence leading to 14 from 3, no incorporation of solvent moiety (EtOH) occurs. The rearrangement of allylic azides through sigmatropic [3,3] shifts is a well-known process.[18,19] However, a simple

(12) (a) Pretsch, C.; Seibel, S. *Tabellen zur Strukturaufklärung Organischer Verbindungen mit Spektroskopischen Methoden*; Springer-Verlag: Berlin, 1981; p C70. (b) Pouchert, C. J. *The Aldrich Library of NMR Spectra*, 2nd ed.; Aldrich: Milwaukee, WI, 1981; Vol. 2, 1, 95C.

(13) Barili, P. L.; Bellucci, G.; Marioni, F.; Morelli, I.; Scartoni, V. *J. Org. Chem.* **1973**, *38*, 3472.

(14) Reference 11, p 316.

(15) March, J. *Advanced Organic Chemistry*, 3rd ed.; J. Wiley and Sons: New York, 1985; p 1028.

(16) In order to avoid unnecessary complication of the formulas 16 and 14 in Scheme IV, we have depicted only one of the two resonating structures of azido group: R—N=$^+$N=$^-$N↔R—$^-$N—N≡N$^+$.[17]

(17) *The Chemistry of the Azido Group*; Patai, S., Ed.; Interscience: London, 1971; p 4.

(18) Reference 17, p 84.

(19) (a) McManus, M. J.; Berchtold, G. A.; Jerina, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 2977. (b) Cleophax, J.; Olesker, A.; Rolland, A.; Gero, S. D.; Forchioni, A. *Tetrahedron* **1977**, *33*, 1303. (c) Ferrier, R. J.; Vethaviyaser, N. *J. Chem. Soc. C* **1971**, 1907. (d) VanderWerf, C. A.; Heasely, V. L. *J. Org. Chem.* **1966**, *31*, 3534. (e) Gagneux, A.; Winstein, S.; Young, W. G. *J. Am. Chem. Soc.* **1960**, *82*, 5956.

ionization process proceeding through intimate ion pairs cannot be completely excluded in the rearrangement pathway **16** → **14**.

In conclusion the regiochemistry of the iodo azide adduct of 1-phenylcyclohexene (IAA), recently reassigned to be **4**, must be reversed to **3**, as originally proposed by Hassner.[4] Also the structure of the dehydrohalogenation product of the IAA (**3**), which was proposed to be **8**,[5] must be corrected to **14**. In the same paper[5] a series of iodine azide adducts of 1-arylcyclohexenes (*p*-Me, 3,4-Me_2, *p*-OCH_3, *p*-*t*-Bu) were also prepared, and the configurations were assigned on the same basis. It appears that also for these derivatives the structure of the adducts and that of the dehydrohalogenation product must be corrected to those corresponding to **3** and **14**, respectively.

As for the attack of the nucleophile on the iodonium ion-type intermediate **2**, it may be concluded that this occurs on the tertiary benzylic carbon by both the nucleophile N_3^- and ^-NCO, according to a Markovnikov-type regiochemistry.

Experimental Section

Melting points were determined on a Kofler apparatus and are uncorrected. IR spectra for the comparison of compounds were taken as films (liquids) or as paraffin oil mulls (solids) on a Perkin-Elmer Infracord Model 137. ^1H NMR spectra for all compounds were taken on a Varian EM-360 spectrometer using Me_4Si as an internal standard; ^{13}C NMR spectra for all the described compounds and ^{15}N NMR spectrum for compound **3** (IAA) were obtained, and decoupling experiments on **8** and **14** were performed in $CDCl_3$ as solvent at 25 °C on a Varian VXR 300 spectrometer, operating at 300 MHz for ^1H, 75 MHz for ^{13}C, and 30 MHz for ^{15}N. Proton and carbon chemical shifts are given in ppm referred to TMS as an internal standard; the number of hydrogens attached to each carbon was determined by the DEPT technique. GLC analyses, in all cases, were performed on a Dani Gas Chromatograph 3800 apparatus with a flame ionization detector and a capillary column (25 m × 0.22 mm) packed with CP Wax 57 CB. Preparative and semipreparative TLC were performed on 2-mm and 0.5-mm silica gel plates (Merck F_{254}), respectively, containing a fluorescent indicator. Petroleum ether refers to the fraction with bp 40–70 °C.

Iodine Azide Addition Reaction to 1-Phenylcyclohexene. This reaction was repeated as previously described[5] to give a solid product which turned out to be ***t*-*r*-1-azido-2-iodo-1-phenylcyclohexane (3)**: mp 75.5–76 °C [lit.[4] mp 75–76 °C; lit.[5] (designated as the regioisomer **4**, see Discussion) mp 75 °C]; IR 2120 cm^{-1} (N_3); ^1H NMR δ 7.60–7.35 (m, 5 H, aromatic protons), 4.75 [m, 1 H, $W_{1/2}$ = 6.0 Hz, CHI (H_2)]; ^{13}C NMR 143.0, 128.3, 128.2, 125.4 (aromatic carbons), 67.9 (C_1), 41.1 (C_2), 32.2, 27.8, and 21.2 ppm (methylenic carbons).

***t*-2-Iodo-1-phenyl-*r*-1-cyclohexylisocyanate (5)** was prepared as previously described:[7,8] ^1H NMR δ 7.48–7.32 (m, 5 H, aromatic protons), 4.72 [m, 1 H, $W_{1/2}$ = 6.1 Hz, CHI (H_2)]; ^{13}C NMR 145.6, 128.5, 128.3 and 124.9 (aromatic carbons), 64.8 (C_1), 42.4 (C_2), 33.0, 31.5, 21.7, and 21.3 ppm (methylenic carbons).

3-Bromo-2-phenylcyclohexene (15) was prepared as previously described.[13]

3-Azido-2-phenylcyclohexene (8). Bromo derivative **15** (0.47 g, 2 mmol) was added to a stirred suspension of NaN_3 (0.65 g, 10 mmol) in dry acetone (10 mL). After 15 min of stirring at room temperature, the reaction mixture was gently refluxed for 30 min. After cooling, the organic solution was diluted with water and extracted with ether. Evaporation of the washed (water) ether extracts afforded an oily residue consisting of crude **8** (0.35 g), which was purified by preparative TLC (a 8:2 mixture of petroleum ether and ether was used as the eluant; only one elution). Rapid extraction, with $CHCl_3$ at room temperature, of the most intense band afforded pure **8** as a liquid: IR 2085 cm^{-1} (N_3); ^1H NMR δ 7.76–7.36 (m, 5 H, aromatic protons), 6.36 [dd, 1 H, $J_{2,3}$ = 4.3 and 3.4 Hz, =CH (H_2)], 4.37 [m, 1 H, $W_{1/2}$ = 9.4 Hz, CHN_3 (H_6)]; double-resonance experiments show no coupling between protons H_2 and H_6; ^{13}C NMR 139.8, 134.4, 128.3, 127.2, 125.5 (aromatic carbons), 130.3 [=CH (C_2)], 56.7 [CHN_3 (C_6)], 29.5, 25.6, 17.5 ppm (methylenic carbons). Anal. Calcd for $C_{12}H_{13}N_3$: C, 72.33; H, 6.57. Found: C, 72.60; H, 6.85.

Cleavage Reaction of Epoxide 9 with NaN_3 in the Presence of Acid. 1-Phenyl-1,2-epoxycyclohexane (**9**, 0.35 g, 2 mmol) was added to a stirred suspension of NaN_3 (7.8 g, 120 mmol) in a 1:1 acetone/water mixture (40 mL) containing concentrated H_2SO_4 (0.2 mL), and the reaction mixture was stirred at room temperature for 3 h. Then 10% aqueous H_2SO_4 was added in order to slightly reduce the basicity of the reaction medium, and stirring was continued overnight. Dilution with ether (100 mL) and evaporation of the washed (water) organic layer afforded an oily residue (0.36 g) consisting of a 21:79 (GLC) mixture of azido alcohols **10** and **11**, which was subjected to preparative TLC (a 9:1 mixture of petroleum ether and ethyl acetate was used as the eluant; elution was repeated three times). Extraction of the two most intense bands (the faster moving band contained **11**) afforded ***c*-2-azido-2-phenyl-*r*-1-cyclohexanol (10)** (0.040 g) as a solid: mp 62–63 °C; IR 3440 (OH), and 2100 cm^{-1} (N_3); ^1H NMR δ 7.70–7.36 (m, 5 H, aromatic protons), 3.90 [m, 1 H, $W_{1/2}$ = 16.0 Hz, *CH*OH (H_2)]; ^{13}C NMR 141.3, 128.6, 127.9, 127.4, 126.4, 125.6 (aromatic carbons), 74.8 (C_2), 70.9 (C_1), 35.4, 30.1, 23.7, 21.3 ppm (methylenic carbons). Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.33; H, 6.95. Found: C, 66.21; H, 7.10. ***t*-2-Azido-2-phenyl-*r*-1-cyclohexanol (11)** (0.15 g) was obtained as a solid: mp 53–54 °C; IR 3460 (OH), and 2090 cm^{-1} (N_3); ^1H NMR δ 7.66–7.30 (m, 5 H, aromatic protons), 3.76 [m, 1 H, $W_{1/2}$ = 7.2 Hz, *CH*OH (H_2)]; ^{13}C NMR 140.9, 128.52, 128.51, 127.9, 127.8, 126.4 (aromatic carbons), 71.6 (C_2), 68.2 (C_1), 27.8, 26.8, 21.1, and 18.5 ppm (methylenic carbons). Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.33; H, 6.95. Found: C, 66.65; H, 7.15.

2-Azido-2-phenylcyclohexanone (13). A solution of **11** (0.050 g, 0.23 mmol) in acetone distilled from $KMnO_4$ (10 mL) was treated with stirring with Jones reagent (0.06 mL, 0.50 mequiv). After 5 min at room temperature, the reaction mixture was diluted with water and extracted with ether. Evaporation of the washed (saturated aqueous $NaHCO_3$ solution, and water) and dried ether extracts afforded an oily residue (0.045 g) consisting of crude **13**, which was subjected to semipreparative TLC (a 9:1 mixture of petroleum ether and ether was used as the eluant; elution was repeated twice). Extraction of the most intense band afforded pure **13** (0.020 g) as a liquid: IR 2095 (N_3), 1725 cm^{-1} (C=O). Anal. Calcd for $C_{12}H_{13}N_3O$: C, 66.95; H, 6.08. Found: C, 66.70; H, 6.25.

Analogous reaction carried out on the stereoisomeric azido alcohol **10** gave the same azido ketone **13**.

Opening Reaction of Epoxide 9 with NaN_3 in DMSO. Epoxide **9** (0.43 g, 2.5 mmol) was added to a stirred suspension of NaN_3 (0.78 g, 12 mmol) in DMSO (25 mL), and the reaction mixture was heated at 120 °C for 24 h. After cooling, ether was added and the organic solution was washed (water) and evaporated to give an oily residue (0.45 g) consisting of a 24:76 mixture of **11** and **12** (GLC), which was subjected to preparative TLC (a 9:1 mixture of petroleum ether and ethyl acetate was used as the eluant; elution was repeated three times). Extraction of the two most intense bands (the faster moving band contained **11**) afforded **11** (0.045 g) and ***t*-2-azido-1-phenyl-*r*-1-cyclohexanol (12)** (0.19 g) as a liquid: IR 3440 (OH), 2110 cm^{-1} (N_3); ^1H NMR δ 7.93–7.53 (m, 5 H, aromatic protons), 3.86 [m, 1 H, $W_{1/2}$ = 7.0 Hz, CHN_3 (H_2)]; ^{13}C NMR 145.4, 129.1, 128.0, 127.5, 125.6 (aromatic carbons), 73.4 (C_1), 66.2 (C_2), 31.4, 26.3, 20.5, and 19.4 ppm (methylenic carbons). Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.33; H, 6.95. Found: C, 66.25; H, 6.82.

Azido alcohol **12** was completely stable under oxidation conditions and was recovered completely unchanged when an acetone solution was treated with Jones reagent as described for **10** and **11**.

Treatment of Iodo Azide 3 with 20% KOH in EtOH. The reaction described in ref 5 on iodo azide **3** (reported[5] to be **4**, see Discussion) was repeated using the same experimental conditions: compound **3** (0.60 g) was added to 20% ethanolic KOH (4 mL) and the reaction mixture was refluxed for 1 h. After cooling, ether was added and the organic solution was washed (water) and evaporated to give an oily residue (0.31 g) consisting of a 70:30 (GLC) mixture of azido olefin **14** and 1-phenylcyclohexene (**1**), which was subjected to preparative TLC (a 9:1 mixture of petroleum ether and ether was used as the eluant; elution was

repeated twice). Extraction of the two most intense bands (the fastest moving band contained 1) afforded 1 (0.060 g) and pure **3-azido-1-phenylcyclohexene (14)** (0.16 g) as a liquid: IR 2100 cm^{-1} (N_3); ^1H NMR δ 7.50–7.30 (m, 5 H, aromatic protons), 6.10 [dt, 1 H, $J_{2,3}$ = 3.85, and $J_{2,6}$ = 1.77 Hz, =CH (H_2)], 4.12 [m, 1 H, CHN_3 (H_3)], 2.60–2.40 (m, 2 H, methylenic H_6), 2.05–1.90 (m, 2 H, methylenic H_4), 1.87–1.78 (m, 2 H, methylenic H_5); double-resonance experiments showed coupling between H_2 and H_3, H_2 and H_6, H_3 and H_4, H_6 and H_5, H_4 and H_5; ^{13}C NMR 142.3, 140.7, 128.2, 127.6, 125.3 (aromatic carbons), 121.2 (C_2), 56.8 (C_3), 28.3, 27.4, and 19.8 ppm (methylenic carbons). Anal. Calcd for $C_{12}H_{13}N_3$: C, 72.33; H, 6.57. Found: C, 72.42; H, 6.70.

The above described reaction was also repeated in some different experimental conditions in order to evaluate the importance of the temperature and of the temperature-increasing rate on the dehydrohalogenation process leading to the azido olefin 14 vs the elimination process leading to olefin 1. In any case the proceeding reactions were followed by GLC. The slower the temperature of the reaction mixture increases in order to reach the refluxing temperature, the higher the percentages of olefin 1 that are obtained. In a run, for example, after 3 h at 50 °C, the reaction mixture had the following composition: 1 60%, 14 10%, starting product 30%. The same mixture after 15 min at 80 °C gave the following result: 1 80%, 14 15%, starting product 5%. In a different run the iodo azide 3 was directly added to the boiling ethanolic KOH: the reaction is complete in 15 min, yielding a mixture of 1 and 14 in a ratio about 70:30.

1-Azidocyclohexane (18). A pure sample of 18 was prepared by heating at 120 °C for 15 h a solution of bromocyclohexane (0.30 g, 1.84 mmol) in DMSO (10 mL) in the presence of NaN_3 (0.61 g, 9.4 mmol). Crude 18 was distilled to give pure 18 as a liquid: bp 38 °C (15 mmHg) [lit.[20] 68.5–69 °C (21 mmHg)]; IR 2095 cm^{-1} (N_3); ^1H NMR δ 3.32 [m, 1 H, CHN_3 (H_1)]; ^{13}C NMR 59.9 (C_1), 31.7, 25.4, and 24.3 ppm (methylenic carbons). Anal. Calcd for $C_6H_{11}N_3$: C, 57.57; H, 8.85. Found: C, 57.60; H, 8.95.

Attempts To Reduce the N_3 Group of 3 to an Amino Group. The following reactions were carried out:

(a) Iodo azide 3 (0.10 g, 0.3 mmol) in anhydrous THF (3 mL) was treated with BH_3-Me_2S complex (1 mL, 10 mmol), and the resulting mixture was left stirring at room temperature. After 30 days, the unreacted iodo azide 3 was completely recovered.

(b) Iodo azide 3 (0.165 g, 0.5 mmol) in EtOH (10 mL) was hydrogenated at room pressure for 12 h at 20 °C in the presence of 10% Pd/C (0.20 g). The analysis (GLC) of the crude reaction mixture showed the presence of 1 (40%), 1-phenylcyclohexane (20%), and starting material (40%).

(c) Treatment of a solution of 3 (0.10 g, 0.3 mmol) in anhydrous ether (15 mL) with $LiAlH_4$ (0.050 g) yielded almost completely olefin 1 (^1H NMR).

Dehalogenation Attempt. In order to remove selectively the iodine atom, iodo azide 3 (0.10 g, 0.3 mmol) in anhydrous THF (5 mL) was treated with Bu_3SnH (0.2 mL). After 4 h at room temperature, the reaction mixture consisted of a 30:70 mixture of olefin 1 and starting material 3 (^1H NMR and GLC).

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Effect of the Side Chain on the Racemization of Amino Acids in Aqueous Solution[1]

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The rate of racemization of 13 amino acids possessing hydroxy, carboxy, alkoxy, carboalkoxy, alkyl, aryl, and thioether side chains were compared. Reaction conditions were identical for all amino acids studied. Gas chromatography was used to determine the percent of D isomer present. Hydroxy amino acids racemized most rapidly, but conversion to an ether function reduced the rate considerably. The increased racemization rate of methionine (R = $CH_2CH_2SCH_3$) over Ala (R = CH_3) has been attributed to orbital overlap from the sulfur. Asp racemized faster than Glu, α-aminoadipic acid, and pyroglutamic acid. β- and γ-monomethyl esters of aspartic and glutamic acids, respectively, racemized only slightly faster than the corresponding free acids. The slight increase in rate appears attributable to a solvent change brought on by ester hydrolysis. Under the reaction conditions, pH 8 and 140 °C, hydrolysis of the esters competed favorably with racemization at the methine carbon. The relatively lower racemization rate observed in the case of Glu compared with Asp resulted from the slow formation of pyroglutamic acid. Pyroglutamic acid racemized at a considerably slower rate than acidic amino acids. The differences in the racemization rates with changes in the R group are discussed in terms of several factors, including intramolecular reactions, direct field effects, orbital overlap, and solvation effects, as well as inductive, resonance, and steric factors.

Introduction

Amino acid racemization studies are of interest in peptide synthesis,[2] geochronology,[3] geothermometry,[3] and nutrition.[4] They provide a system in which to study structure vs reactivity relationships and afford a method

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