produced from the set of phases with the best combined figure of merit yielded the positions of all non-hydrogen atoms. A full-matrix, least-squares refinement with calculated and fixed positions of hydrogen atoms and anisotropic thermal parameters for non-hydrogen atoms was carried out. The quantity minimized by a normal unconstrained least-squares refinement was $\sum w(|F_o| - |F_c|)^2$ where $w = (\sigma^2(F_o) + (0.02F_o)^2)^{-1}$. The refinement converged to $R = 0.045$ and $R_w = 0.043$ with the highest maximum on the final difference Fourier map 0.26 e Å^{-3}.[41]

The structure of **60** was solved by means of MULTAN 11/82[40] using 450 structure amplitudes with $E > 1.45$. The knowledge of structure of **48** was utilized to normalize structure factors by assuming two symmetry-independent, randomly oriented molecules in the unit cell. Earlier attempts to solve the structure with the structure factors normalized on the assumption of randomly distributed atoms were not successful. The E map produced from the set of phases with the best combined figure of merit yielded the positions of almost all atoms. The two missing, one in each molecule, were revealed in a subsequent difference Fourier map. A full-matrix least-squares refinement was then carried out based on the assumption of two ordered molecules A and B in the unit cell. Calculated positions of hydrogen atoms with the C-H distance of 1.00 Å were periodically updated and used in structure factors calculations. The refinement with isotropic atomic temperature factors converged at $R = 0.22$, with anisotropic at $R = 0.16$. At this stage it was apparent that the structure was partially disordered. We again carried out refinement with isotropic temperature factors, but this time we used elastic restraints on bond lengths and some of the angles utilizing the program SHELX-76.[42] The target values for the bond lengths were those given by Ermer[43] with $\sigma = 0.004$ Å. The angles were restrained only in the macrocycle by targeting the distance between the second neighboring carbon atoms with the average value of 2.558 Å and $\sigma = 0.010$ Å found in **48**. The angles at C(1) and C(12), atoms which also form the strained cyclopropane ring, were not restrained. After several refinement/difference Fourier calculations we were able to find molecule C overlapping with B by connecting peaks in the difference Fourier maps and atoms with unusually low-temperature factors. Molecule C as discussed above is essentially the enantiomer of molecule A. In the final model only one atom C(17) was common to molecules B and C. There is also a partial disorder in the site occupied by molecule A, but this is just the superposition of two different conformers. We allowed for it by introducing molecule D with nine separate atoms and 14 atoms common with molecule A. The same restraints were used for molecules C and the independent part of D as for molecules A and B; however, we did not introduce any restraints at the joints of A and D. The refinement of the model with isotropic thermal parameters for all atoms converged at $R = 0.120$. At this stage we introduced anisotropic thermal parameters for 15 atoms with full occupancy. The refinement of this model with 77 isotropic and 15 anisotropic atoms and 446 parameters against 1973 observations and 116 restraints were carried out in two blocks that included the pairs of overlapping molecules. The occupancies of the molecules were allowed to refine with the sums A + D and B + C constrained to 1.0. Their final values were 0.600 (21) and 0.662 (6) for A and B, respectively. The quantity minimized was $\sum w(|F_o| - |F_c|)^2$ where $w = (\sigma^2(F_o) + 0.0004F_o^2)^{-1}$ and $\sigma(F_o)$ is from the counting statistics. The refinement converged except for strongly correlated temperature factors of C(2B) and C(2C) that had in the last cycle shift/esd ratios of 1.6. The average shift/esd ratio was <0.1, final $R = 0.108$, $R_w = 0.131$, and the highest peak on the difference Fourier map was 0.44 e Å^{-3}. The largest violation of a bond length restraint was 0.005 Å and of a second neighbor distance was 0.04 Å. A series of Laue photographs did not show significant diffuse scattering that would indicate short term order.

(41) Calculations were carried out by using: Frenz, B. A., Ed. "Enraf-Nonius Structure Determination Package", 1982.
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Acknowledgment. Support from the National Science Foundation through a research grant (CHE-8026013) is gratefully acknowledged.

Registry No. 13, 4834-94-4; **13**, 4834-94-4; **14**, 76128-04-6; **15**, 76128-06-8; **16**, 76128-08-0; **17**, 91410-29-6; **18**, 91410-30-9; **19**, 91410-34-3; **20**, 91410-31-0; **21**, 91410-32-1; **22**, 91410-33-2; **23**, 91410-35-4; (*E*)-**25**, 91410-37-6; (*Z*)-**25**, 91410-36-5; **26**, 87336-89-8; **27**, 91464-50-5; **28**, 91464-51-6; **29**, 91464-52-7; **30**, 63240-90-4; **30** (diacid), 63240-88-0; **31**, 63240-92-6; **31** (enediol disilyl ether), 91410-38-7; **32**, 91410-39-8; **33**, 91410-40-1; **34**, 91410-41-2; (*E,E*)-**35**, 91410-43-4; (*Z,E*)-**35**, 91410-42-3; (±)-**37**, 91410-44-5; (+)-**37**, 91464-54-9; (*Z*)-**37**, 91443-16-2; (+)-**37** ((+)-Mosher ester), 91423-99-3; (*Z*)-**37** ((+)-Mosher ester), 91465-55-3; **38**, 91410-45-6; **39**, 91410-46-7; **41**, 91410-47-8; **42**, 91410-48-9; **43**, 91410-49-0; **44**, 91410-50-3; **45**, 91410-54-7; **45** (diacid), 91410-55-8; **46**, 91410-56-9; **47**, 91410-57-0; **48**, 91410-58-1; *cis*-**49**, 91410-53-6; *trans*-**49**, 91464-55-0; **50**, 91410-51-4; **50** (diester), 91410-52-5; **51**, 91410-59-2; **52**, 87336-92-3; **53**, 91410-60-5; **54**, 87336-93-4; **55**, 87336-95-6; **55** (diacid), 87336-94-5; **56**, 87336-96-7; **57**, 91464-53-8; **58**, 87350-59-2; **59**, 87336-98-9; (±)-**60**, 87336-99-0; (+)-**60**, 91465-56-4; $BrMg(CH_2)_9CH{=}CH_2$, 88476-93-1; *p*-$TsNHNH_2$, 1576-35-8; $CH_2{=}CH(CH_2)_2MgBr$, 7103-09-5; $(EtO)_2POCl$, 814-49-3; $CH_3CH{=}C(CH_3)_2$, 513-35-9; $(i\text{-}Pr)_3SiC{\equiv}CCH_2MgBr$, 87350-60-5; $(CH_3)_3SiCl$, 75-77-4; $(PhO)_2POCl$, 2524-64-3; $CH_3COCH_2CO_2CH_3$, 105-45-3; *p*-TsN_3, 941-55-9; 1-methylene-2-(3-butenyl)-2-(4-pentenyl)-cyclododecane, 91423-98-2; (+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride, 20445-33-4.

Ylide vs. 1,4-Cycloaddition in the Interaction of an Alkylidenecarbene with Azoarenes and the Formation of 2*H*-Indazoles and Tetrahydrotetrazoles[1]

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Contribution from the Department of Chemistry, University of Utah, Salt Lake City, Utah 84112. *Received February 9, 1984*

Abstract: Reaction of substituted azobenzenes with isopropylidenecarbene $(CH_3)_2C{=}C$:, generated from either 2-methyl-1-propenyl triflate and *t*-BuOK or silylvinyl triflate $(CH_3)_2C{=}C(OTf)SiMe_3$ and benzyltrimethylammonium fluoride (BTAF), gave 2*H*-indazoles in moderate yield. Indazoles were identified by spectral means as well as independent synthesis. A two-step mechanism, involving an ylide-type intermediate, is proposed for these reactions. Interaction of 3,3′,5,5′-tetrakis(trifluoromethyl)azobenzene and 4,4-bis(trifluoromethyl)azobenzene with the carbene derived from silylvinyl triflate gave tetrahydrotetrazoles, a new class of compounds, consistent with trapping of the proposed ylide. 2*H*-Indazoles react with methyl triflate to form the N-methylated salt, but they do not undergo Diels-Alder reactions.

We had previously reported[3] that the reaction of isopropylidenecarbene **2** with azobenzene gave 2-phenyl-3-isopropylindazole (**3**), an unusual and little known heterocyclic ring system. In order to provide further mechanistic insight as well

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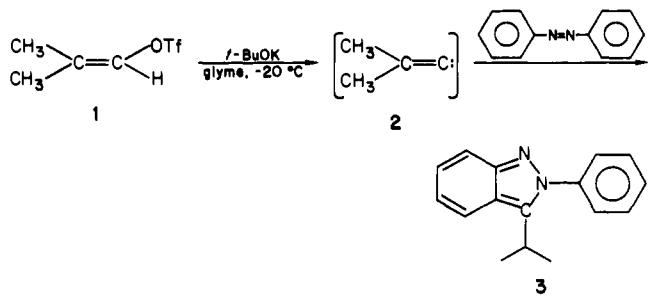


as to establish the generality of this reaction, we decided to investigate the reaction of carbene **2** with a variety of ring-substituted azobenzenes. To unambigiously establish the structure of these adducts, they were also prepared by an independent synthesis. Some chemistry of 2*H*-indazoles was examined as well.

Results and Discussion

Isopropylidenecarbene was generated from either vinyl triflate **1** and *t*-BuOK[4] or from silylvinyl triflate **4**, and benzyltrimethylammonium fluoride.[5] Both procedures give a carbene that is free of association with the leaving group (OTf) or the respective cation (K^+, NR_4^+),[5,6] but there are some minor differences between the two methods, presumably due to the reaction medium differences.

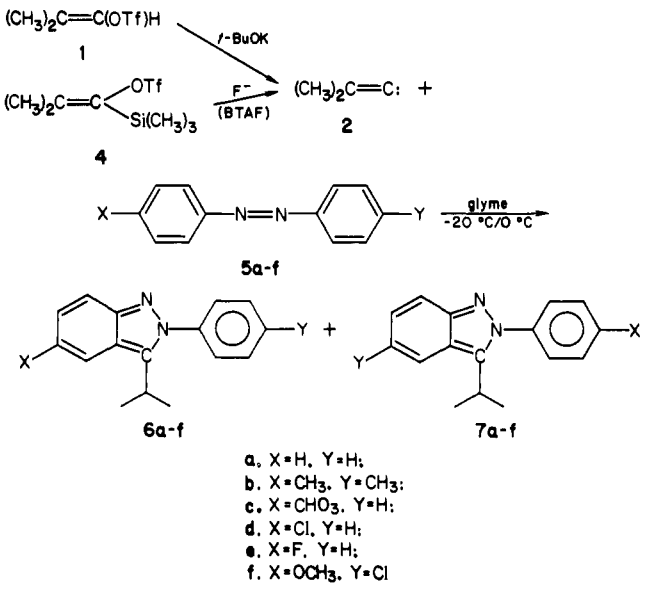
We first investigated the reaction of several para-substituted azobenzenes **5** with carbene **2**. 4,4′-Dimethylazobenzene (**5b**) was prepared from *p*-toluidine by a known procedure,[7] the monosubstituted azobenzenes **5c–e** were prepared by condensation of nitrosobenzene with the appropriate aniline,[8] and 4-chloro-4-methoxyazobenzene[9] (**5f**) was prepared by condensation of 4-chloronitrosobenzene[10] and *p*-anisidine.[8] Reaction is carried out by dissolving 4–5 equiv of azobenzene **5** along with 1.1 equiv of either *t*-BuOK or benzyltrimethylammonium fluoride (BTAF) in glyme either at −20 or 0 °C, and then 1 equiv of vinyl triflate **1** or **4** is added dropwise with stirring. The reaction progress can be monitored by TLC and GC, and after workup the residue is chromatographed on silica gel, yielding the isomeric 2*H* indazoles **6** and **7** as seen in Scheme I.

In the case of the dissymetrically substituted azobenzenes the ratio of product isomers **6** and **7** was determined by GLC. The pure isomers can be obtained by MPLC. Table I gives the overall yields, isomer ratios, and spectral properties of the products.

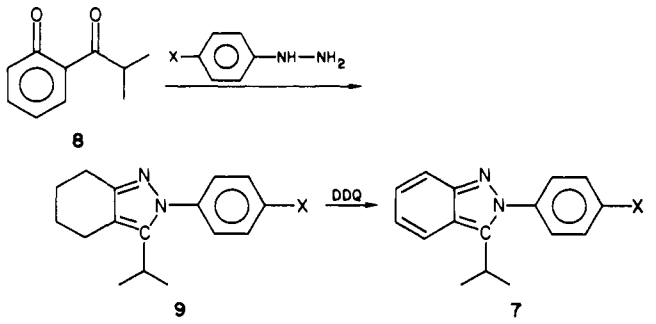
The molecular ion ion the mass spectrum of the products confirms a 1:1 adduct between azoarene and carbene, and the spectral properties are consistent with the 2*H*-indazole skeleton. To confirm this structure assignment, as well as to provide authentic sample for GC analysis, some 2*H*-indazoles were prepared by an unambiguous independent synthesis as shown in Scheme II.

Condensation of dione **8** with the appropriately substituted phenylhydrazine gave **9** that upon DDQ oxidation gave 2*H*-indazoles **7**. GC coinjection and spectral comparison unambiguously established the identity of the carbene azoarene adducts as **7**. The remainder of the structure assignments in Table I were made by spectral comparison and similarity of GC retention times. In particular in the mass spectrum all 2*H*-indazoles readily lose the *N*-aryl group. In the case of isomers **6** this corresponds to loss of *m/z* 77 whereas in isomer **7** to loss of *m/z* C_6H_4X.

Scheme I

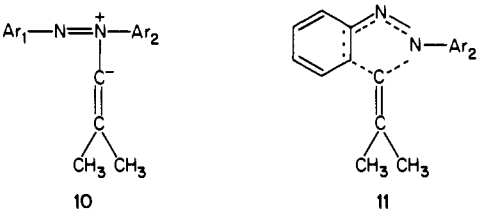


Scheme II



Compared to the additon of alkylidenecarbenes to carbon–carbon double bonds[4] the yields in this reaction are relatively low. This is somewhat surprising yet in accordance with other work reported on the reaction of carbenes in general with azo compounds[11-13] and may be an indication that the reaction of alkylidenecarbenes with N–N double bonds is mechanistically different from the reaction of carbenes with C–C double bonds.

As we previously mentioned,[3] there are two reasonable mechanistic pathways involving either a carbene–nitrogen zwitterionic ylide **10** as the first intermediate or a concerted 1,4-addition via **11**.



Normally carbenes add to 1,3-dienes in a 1,2-fashion[14] and despite numerous attempts to achieve 1,4 addition only very few such examples are known.[15] In a molecular orbital study on the addition of singlet methylene to butadiene Hoffman and co-

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Table I. Yields and Spectral Features of 2*H*-Indazoles 6 and 7

compd	mp, °C	yield, % (6 and 7)	ratio 6/7	MS, *m/z* (rel int)	UV,[a] λ_{max}, nm (log ϵ)	^{1}H NMR,[b] δ (H's m, Hz)	IR,[d] cm^{-1}
6a, 7a: X, Y = H	121–122	43		237 (9), 236 (M^+, 46), 222 (17), 221 (100), 77 (34), 51 (20), 44 (12)	278 (3.8), 303 (3.8)	1.44 (6, d, 7.0), 3.33 (1, sept, 7.0), 7.42 (5, s), 7.0–7.9 (4, m)	1600, 1501, 1389, 1119, 702
6b, 7b: X, Y = CH_3	106–108	38		265 (10), 264 (M^+, 52), 250 (15), 249 (100), 165 (14), 131 (16), 109 (25), 91 (7)		1.45 (6, d, 7.0),[c] 2.43 (6, s), 3.33 (1, sept, 7.0), 7.33 (4, s), 7.1–7.7 (3, m)	2960, 1605, 1512, 1342, 1319, 1310, 1102, 1085
6c: X = OCH_3; Y = H	148–149			267 (11), 266 (M^+, 63), 252 (17), 251 (100), 77 (36), 51 (10)	299 (4.6), 225 (4.5), 276 (4.0), 317 (4.0)	1.50 (6, d, 9.0), 3.40 (1, sept, 9.0), 3.97 (3, s), 7.0–7.8 (3, m), 7.66 (5, s)	1630, 1600, 1520, 1455, 1220, 827, 781, 712
		36	63/37				
7c: X = OCH_3; Y = H	132–134			267 (13), 266 (M^+, 69), 252 (18), 251 (100), 77 (8)	210 (4.6), 223 (4.4), 278 (4.2), 301 (4.1)	1.5 (6, d, 7.0), 3.42 (1, sept, 7.0), 3.97 (3, s), 7–8 (8, m)	1600, 1508, 1465, 1255, 847, 765
6d: X = Cl; Y = H	107–109			272 (M^+ ^{37}Cl, 18), 271 (11), 270 (M^+ ^{35}Cl, 53), 257 (33), 256 (17), 255 (100), 219 (15), 77 (42)	212 (4.5), 227 (4.5), 284 (3.9), 311 (3.9)	1.41 (6, d, 6.7), 3.33 (1, sept, 6.7), 7.35 (5, s), 7.0–7.7 (3, m)	1598, 1505, 1221, 1110, 775, 749, 709
		20	64/36				
7d: X = Cl; Y = H	123–124			272 (M^+ ^{37}Cl, 20), 271 (11), 270 (M^+ ^{35}Cl, 64), 267 (14), 257 (33), 256 (17), 220 (28), 219 (21), 205 (25), 115 (15), 113 (6), 111 (15), 77 (36), 75 (19)	208 (4.4), 230 (4.3), 283 (3.9), 304 (3.8)	1.45 (6, d, 6.6), 3.36 (1, sept, 6.6), 7.60 (5, s), 6.9–7.4 (3, m)	1621, 1500, 1389, 1082, 850, 752
6e: X = F; Y = H	101–106			255 (11), 254 (M^+, 52), 239 (17), 238 (100), 224 (17), 77 (19)	205 (4.5), 217 (4.4), 274 (4.0), 308 (4.0)	1.46 (6, d, 7.5), 3.37 (1, sept, 7.5), 7–8 (3, m), 7.6 (5, s)	1632, 1597, 1517, 1500, 1185, 821, 770
		18	53/47				
7e: X = F; Y = H	121–126			255 (14), 254 (M^+, 51), 239 (17), 238 (100), 244 (15), 95 (18), 75 (11)	209 (4.1), 223 (4.1), 280 (3.8)	1.53 (6, d, 7.0), 3.41 (1, sept, 7.5), 7–8 (8, m)	1628, 1601, 1520, 1230, 859, 751
6f: X = OCH_3; Y = Cl	163–165			302 (M^+ ^{37}Cl, 24), 301 (13), 300 (M^+ ^{35}Cl, 66), 287 (33), 286 (18), 285 (100), 250 (31), 235 (28), 113 (4), 111 (12), 77 (9)	215 (4.6), 287 (3.9), 316 (3.8)	1.45 (6, d, 7.5), 3.28 (1, sept, 7.5), 3.91 (3, s), 6.8–7.8 (7, m)	1501, 1465, 1183, 1170, 1041, 699
		31	64/36				
7f: X = OCH_3; Y = Cl	173–175			302 (M^+ ^{37}Cl, 301 (12), 300 (M^+ ^{35}Cl, 63), 287 (34), 286 (18), 285 (100)	213 (4.5), 283 (3.8), 310 (3.8)	1.48 (6, d, 7.0), 3.33 (1, sept, 7.0), 3.82 (3, s), 6.8–7.1 (2, m), 7.5–7.7 (5, m)	1610, 1510, 1300, 1170, 1040

[a] In Ethanol. [b] In CCl_4, Me_4Si internal standard. [c] In $CDCl_3$, Me_4Si internal standard. [d] KBr.

workers[16] have shown that the 1,4 addition is discriminated against the 1,2 addition by excessive closed-shell interaction, a fact which cannot be compensated by introduction of substituents. The addition of dichlorocarbene to 1,2-bis(methylene)cycloheptane gives a mixture of 1,2- and 1,4-addition products in a ratio of 99:1.[15b] Anastassiou et al.[15a] report the 1,4 addition of dicyanocarbene to cyclooctatetraene, yet the predominant product is again the 1,2-addition product. Finally Franzen[15c] reports on the 1,4 addition of photochemically generated triplet methylene to butadiene, and again 1,2-addition products are also observed. One can generally conclude that for 1,4 addition to occur the diene must have a rigid cisoid conformation and more electron-deficient carbenes, which are more easily converted into triplet carbene[14b,d] are involved.

Our reactants do not meet these requirements; the isopropylidenecarbene **2** has been shown to be a singlet[17] and in the azo compound one portion of the 1,3-diene is part of the delocalized aromatic ring. Hence, these considerations and the absence of any 1,2 addition product make the concerted 1,4-cycloaddition process highly unlikely.

We hoped to gain further insight into the mechanisms by means of substituent effects. As indicated in Scheme III electron-donating substituents favor electrophilic attack on the β-nitrogen rather than α-attack due to the resonance involvement of the substituent. Likewise, electron-withdrawing substituents such as F and Cl inductively deactivate the α-nitrogen, thereby once again favoring β-attack. As the ratio of isomers in Table I shows the product resulting from such β-adduct is indeed found to predominate. However, the difference in isomer ratios corresponds to a $\Delta G^{\ddagger}$ of about 200 kcal/mol, a surprisingly small substituent effect for an ylide-type mechanism with an ionic intermediate. Since it is very difficult to predict what the expected substituent effects would be in a concerted cheleotropic cycloaddition proces, these observations are consistent with but by no means prove the proposed ylide mechanism. It should be mentioned that alkylation of *p*-methoxyazobenzene with methyl triflate[19] gives both N-alkylated products in nearly equal amount, and thus no major substituent effect is observed, despite an electrophilic attack by a reagent which should clearly favor β-attack. Besides differ-

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Scheme III

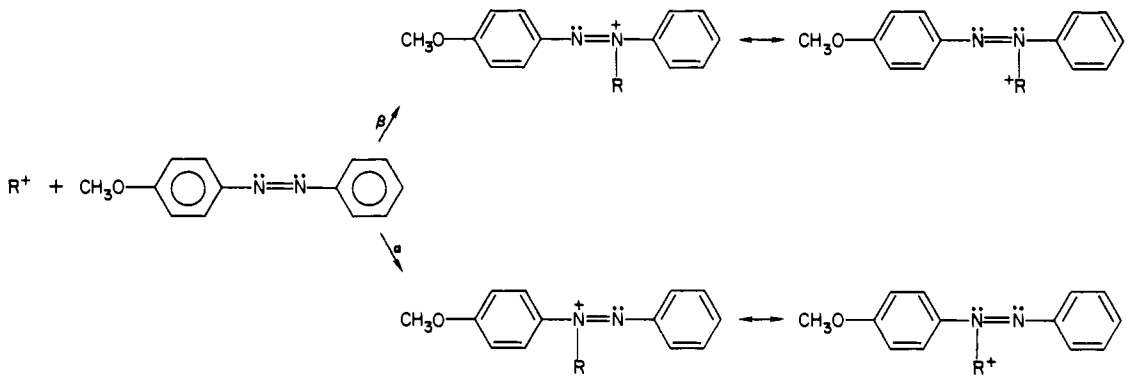


Table II. Yields, Melting Points, and Spectral Properties of Compounds **13** and **14**

compd	mp, °C	yield,[a] %	MS, *m/z* (rel int)	^{1}H NMR,[b] δ (H, s, m, Hz)	^{13}C NMR,[c] δ (m, Hz)	^{19}F NMR,[d] δ (m)	IR,[e] cm^{-1}
13	140–142	10	964 (M^+, 0.6), 736 (2.4), 735 (7.1), 525 (1.6), 524 (6.0), 509 (2.7), 508 (3.6), 507 (3.8), 454 (7.9), 281 (25.8), 213 (41), 72 (98), 59 (85)	1.93 (6 H, s, CH_3), 6.32 (2 H, s, NH), 6.90, 7.07, (4 H, 4 H, s, s, *o*-H, *o*′-H), 7.33, 7.38 (2 H, 2 H, s, s, *p*-H, *p*′-H)	20.3 (s, CH_3), 108.4 (s, CCH_3), 111.8–112.8 (m, *o*-C, *o*′-C), 114.3–115.3 (m, *p*-C, *p*′-C), 122.8[h] (q, 273, CF_3, CF_3′), 130.4 (s, C≡CN), 133.2, 133.4 (q, q, 34, *m*-C, *m*′-C), 146.7, 148.4 (s, s, NC_{Ar}, NC_{Ar}′)	52.6 (s), 53.7 (s)	3314, 1699 (C=C), 1617 (Ar), 1472, 1377, 1280, 1179, 1128, 999, 952, 878, 702, 684
14a	164–166	15	962 (M^+, 2.3), 943 (0.6), 720 (0.4), 508 (1.6), 493 (7.5), 489 (7.5), 454 (1.4), 282 (13), 281 (100), 269 (32), 254 (41), 213 (31)	1.87 (6 H, s, CH_3), 7.15, 7.69 (4 H, 4 H, s, s, *o*-H, *o*′-H), 7.45, 7.52 (2 H, 2 H, s, s, *p*-H, *p*′-H)	21.1 (s, CH_3), 109.5 (s, CCH_3), 118.2–118.4 (m, *o*-C, *o*′-C), 119.6–119.8 (m, *p*-C, *p*′-C), 122.8 (q, 274, CF_3, CF_3′), 133.3 (s, C≡CN), 133.0, 133.4 (q, q, 33, 34.6, *m*-C, *m*′-C), 147.8, 150.6 (s, s, NC_{Ar}, NC_{Ar}′)	62.4 (s), 62.6 (s)	1709, 1617, 1466, 1380, 1368, 1282, 1174, 1137, 950, 888, 785, 722, 700, 685
14b	131–132	10	690 (M^+, 32), 662 (24), 517 (75), 516 (100), 372 (23), 213 (75)	1.81 (6 H, s, CH_3),[g] 7.14, 7.45, 7.48, 7.58 (all 4 H, d, 9)	21.4 (s, CH_3), 105.2[i] (s, CCH_3), 119.3, 121.3 (s, s, *o*-C, *o*′-C), 125.5, 125.55 (q, q, 271, CF_3, CF_3′); 125.8 (q, 33, *p*-C, *p*′-C), 126.6, 127 (q, q, 3.5, *m*-C, *m*′-C), 134.9 (s, C≡CN), 151.1, 154.3 (s, s, NC_{Ar}, NC_{Ar}′)	63.05 (s), 63.01 (s)	2930, 1698 (C=C), 1610 (Ar), 1512, 1418, 1325, 1160, 1120, 1068, 1012, 890, 848, 840, 775, 712

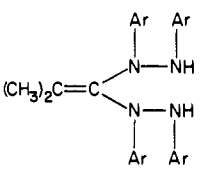
[a] Isolated, purified yields. [b] In $CDCl_3$, Me_4Si internal standard. [c] In $CDCl_3$, $CDCl_3$ center line 77 ppm. [d] In acetone-d_6, $CFCl_3$ internal standard. [e] KBr. [f] Exchangeable in D_2O. [g] In acetone-d_6, Me_4Si internal standard, 300 MHz. [h] In acetone-d_6 two signals at 124.5 and 124.6 ppm. [i] In acetone-d_6, acetone-d_6 center line 29.8 ppm.

entiating between α- and β-attack, substituents of course also affect the overall rate of reaction. Hence, electron-withdrawing substituents that inductively decrease the nucleophilicity of the nitrogen lone pairs should decrease the rate of reaction. Indeed the introduction of F and Cl results in a considerable decrease in adduct yield compared to activated substituents such as CH_3O and CH_3. Thus rearrangement of the carbene **2** to 2-butyne[4] becomes more competitive and results in a lower yield of the adduct indazoles **6** and **7**. Once again consistent with the ylide pathway.

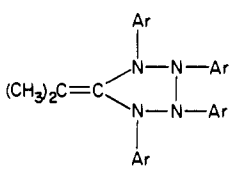
To further test this hypothesis, we decided to examine the behavior of even more strongly deactivated systems. The molecule of choice was 3,3′,5,5′-tetrakis(trifluoromethyl)azobenzene (**12a**) as it is easily prepared by sodium hypochlorite oxidation of 3,5-bis(trifluoromethyl)aniline.[20]

(20) Burdon, M. J.; Morton, C. J.; Thomas, D. F. *J. Chem. Soc.* **1965**, 2621.

Interaction of isopropylidenecarbene, generated from vinyl triflate **1** and *t*-BuOK with excess azobenzene **11a** in glyme, gave a new ring-opened adduct **13**, whereas reaction of the carbene generated from silylvinyl triflate **4** via F^- gave the novel cyclic product **14a**. Likewise, reaction of silylvinyl triflate **4** derived carbene with excess 4,4′-bis(trifluoromethyl)azobenzene **12a** gave adduct **14b**.



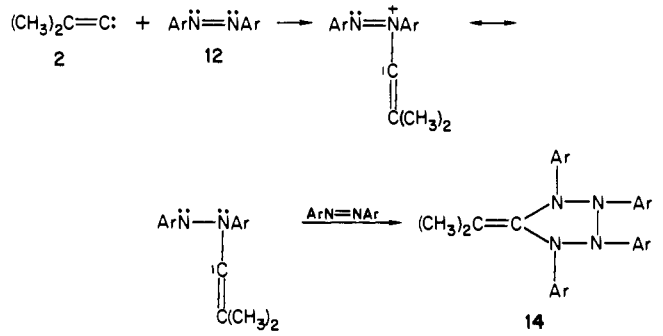
13. Ar = 3,5-di-$CF_3C_6H_3$



14a. Ar = 3,5-di-$CF_3C_6H_3$
b. Ar = *p*-$CF_3C_6H_4$

The physical and spectral properties of adducts **13** and **14** are summarized in Table II. Mass spectrum clearly indicates a 2:1

Scheme IV



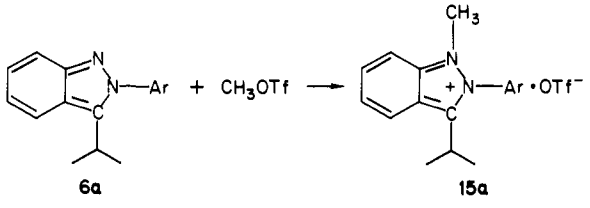
adduct, and the ^{19}F NMR shows two distinct signals as expected for these adducts. The IR displays a double-bond absorption between 1698 and 1709 cm^{-1} along with appropriate C–N absorptions and in the case of **13** the N–H stretch at 3314 cm^{-1}. Most characteristic are the ^1H and ^{13}C NMR spectra, completely consistent with the proposed structures.

Adducts **14a** and **14b**, to our knowledge, represent the first examples of the hitherto unknown class of compounds, namely, tetrahydrotetrazoles. They are stable crystalline compounds and do not react with dilute aqueous HCl or aqueoous KOH. Further proof of structure assignment comes from the ready interconversion of **13**–**14a**. Sodium hypochlorite oxidation of **13** quantitatively converts it to **14a**. In turn, $LiAlH_4$ reduction of **14a** in THF gives **13**.

There are two noteworthy features to the interaction of isopropylidenecarbene with these highly deactivated azoarenes. Only 2:1 adducts were isolated with no 2*H*-indazole like products being observed at all. The yields of adduct were very low (10–15%) with the bulk of the reaction proceeding to intramolecularly rearranged 2-butyne. Both of these observations are consisted with and provide further support for the proposed ylide-type mechanism. The very low yield of trapping products is the consequence of the greatly diminished nucleophilicity of the nitrogen lone pairs due to the strong inductive effect of the CF_3 group. Likewise, ring closure to the precursor of the 2*H*-indazole would be disfavored by the destabilizing influence of the CF_3 groups.

In contrast, trapping of the ylide as a 1,3-dipolarophile by excess starting material, as shown in Scheme IV, nicely accounts for the formation of the observed 2:1 adducts. That dipolarophiles readily undergo 1,3 cycloadditions has been amply demonstrated by Huisgen and co-workers.[21]

Finally, since little is known about the chemistry of 2*H*-indazoles, we investigated two types of reactions of these novel aromatic heterocycles. In analogy with the alkylation of benzisoxazoles with methyl triflate by Haley,[22] 2*H*-indazoles readily react with CH_3OTf to give salts **15**. Since 2*H*-indazoles possess



a rigid cisoid-diene moiety, it was interesting to see if they would undergo Diels–Alder reactions. However, treatment of indazole **6a** with several dienophiles gave only recovered starting materials even under forcing conditions. This lack of Diels–Alder reactivity confirms the highly aromatic character of these novel 10π-electron heterocyclic systems.

Summary

We have demonstrated that the reaction of isopropylidenecarbene with substituted azobenzenes to give 2*H*-indazoles is a general process. Substituent effects as well as trapping studies are strongly suggestive of an ylide-type mechanism for the interaction of alkylidenecarenes with azoarenes.

Reaction with highly deactivated systems does not give any 2(*H*)-indazole product but only a 2:1 adduct, namely, a substituted tetrahydrotetrazole. The isolated 2*H*-indazoles are members of a little known novel 10π-electron heterocyclic system, whereas the tetrahydrotetrazoles are the first isolated members of this hitherto unknown class of compounds. The aromatic nature of 2(*H*)-indazoles is confirmed by their lack of Diels–Alder reactivity, whereas they readily undergo alkylation with CH_3OTf.

Experimental Section

General Data. In all carbene reactions dry argon or nitrogen was used as the reaction atmosphere, and all glassware was baked at 130–140 °C for a minimum of 1 h before being used. All boiling and melting points are uncorrected.

^1H NMR spectra are given in δ (ppm) relative to internal tetramethylsilane (Me_4Si, δ 0) except where indicated, ^{19}F NMR are reported in δ (ppm) relative to trichlorofluoromethane, and ^{13}C are reported in δ (ppm) downfield from internal tetramethylsilane, unless otherwise noted. Analytical gas chromatography was performed on a flame ionization gas chromatograph connected to an integrator. Two types of columns were used: column A, 6 ft × 0.125 in. 10% UCW-982 on 100-120 Chromosorb W; column B, 11 ft × 0.125 in. 10% FFAP on 100-120 Chromosorb W. Combustion analysis were done by Galbraith Laboratories, Knoxville, TN.

1,2-Dimethoxyethane (glyme) and tetrahydrofuran were distilled from potassium benzophenone ketyl. Methylene chloride was distilled over P_2O_5 and pentane over $LiAlH_4$. Potassium *tert*-butoxide was doubly sublimed at 165 °C (0.05 mm) and stored under argon. *N,N*-Diisobutyl-2,4-dimethyl-3-pentylamine was distilled from CaH_2. Benzyltrimethylammonium fluoride (BTAF) was prepared from benzyltrimethylammonium hydroxide[23] and was stored and weighed out under argon. 2-Methyl-1-propenyl triflate (**1**) was prepared from isobutyraldehyde.[24] Known procedures were used to prepare triflic anhydride,[25] 1-(trimethylsilyl)-2-methyl-1-propenyl triflate (**4**),[5] and 4,4′-dimethylazobenzene (**5b**).[7] Azobenzenes were recrystallized from either ethanol (compounds **5**) or benzene (compounds **11**) and then dried in vacuo.

General Procedure for the Preparation of Monosubstituted Azobenzenes 5c–e.[8] ***p*-Chloroazobenzene (5c).** A 10-g (94-mmol) sample of nitrosobenzene[25] was added to a solution of 12 g (94 mmol) of *p*-chloroaniline in 94 mL of glacial acetic acid, and the mixture was shaken until all the nitrosobenzene was dissolved. The flask was stoppered, and the solution was allowed to stand for 12 h at room temperature. The solution was filtered, and the precipitate was recrystallized from 95% ethanol to yield 14.1 g (69%) of *p*-chloroazobenzene **5c**, mp 87–88 °C [lit.[26] 88–89 °C].

***p*-Methoxyazobenzene (5d).** *p*-Anisidine (57 g, 0.46 mol) and nitrosobenzene (51 g, 0.51 mol) gave after evaporation of the actic acid and recrystallization from 95% ethanol 30 g (14%) of *p*-methoxyazobenzene (**5d**); mp 54–56 °C [lit.[26] 54–55 °C].

***p*-Fluoroazobenzene (5e).** *p*-Fluoroaniline (30 g, 0.27 mol) and nitrosobenzene (26 g, 0.27 mol) yielded 25 g (40%) of *p*-fluoroazaobenzene (**5e**); mp 82–84 °C [lit.[26] 82.5 °C].

4-Chloro-4′-methoxyazobenzene (5f). The azobenzene is prepared in the same maner as *p*-chloroazobenzene (**5c**), using *p*-anisidine (8.8 g, 71 mmol) and 4-chloronitrosobenzene (6.8 g, 48 mmol) in 200 mL of acetic acid. Recrystallization from 95% ethanol gave 7.3 g (62%) of 4-chloro-4′-methoxyazobenzene (**5f**); mp 120–121 °C [lit.[27] 121–122 °C].

General Procedure for the Reaction of Isopropylidenecarbene (2) with Azobenzenes 5 and 12. 2-Phenyl-3-isopropylindazole (6a). Method A. To a 100-mL three-necked round-bottom flask equipped with magnetic stirrer, addition funnel, and nitrogen inlet and outlet were added 4.55 g (25 mmol) of azobenzene (**5a**), 70 mL of glyme, and 0.7 g (6.2 mmol) of *t*-BuOK. The solution was cooled to −20 °C with a CCl_4/dry ice bath, and 1.0 g (5.0 mmol) of 2-methyl-1-propenyl triflate (**1**) in 5 mL of glyme was added dropwise. After 1 h gas chromatography (column A, 100 °C) revealed the absence of triflate **1**. The solvent was removed with a rotary evaporator, and the residue was treated with 100 mL of ether. The ether solution was extracted once with water, dried over $MgSO_4$, and filtered, and the solvent was removed under reduced pressure. The residue was chromatographed on a silica column with CCl_4 as eluant to

(21) Huisgen, R.; Eckell, A. *Chem. Ber.* **1977**, *110*, 522, 559.
(22) Haley, N. F. *J. Org. Chem.* **1978**, *43*, 1233.
(23) Kuwajiama, I.; Nakamura, E. *J. Am. Chem. Soc.* **1975**, *97*, 3259.
(24) Stang, P. J.; Treptow, W. *Synthesis* **1980**, 283.
(25) Coleman, G. H.; McCloskey, C. M.; Stuart, F. A. In "Organic Synthesis"; Wiley: New York, 1955; Collect Vol. III, p 668.
(26) Laing, I. G. In "Rodd's Chemistry of Carbon Compounds"; Coffey, S., Ed.; Elsevier: Amsterdam, Netherlands, 1973; Vol. III, C, pp 189–92.
(27) Lichtenberger, J.; Thermet, R. *Bull. Soc. Chim. Fr.* **1951**, 318.

afford 0.50 g (43%) of 2-phenyl-3-isopropylindazole (**6a**), mp 121–122 °C.

Method B. To a 250-mL three-necked round bottom flask equipped with magnetic stirrer, addition funnel, and nitrogen inlet and outlet were added 3.64 g (20 mmol) of azobenzene (**5a**), 80 mL of glyme, and 1.94 g (11.5 mmol) of benzyltrimethylammonium fluoride (BTAF).[23] The solution was cooled to 0 °C with an ice bath, and 2.76 g (10 mmol) of 1-(trimethylsilyl)-2-methyl-1-propenyl triflate (**4**)[5] in 10 mL of glyme was added dropwise. The progress of the reaction was monitored by GC (column A, 240 °C), and after 1 h the ratio of product to azobenzene **5a** was constant. The solvent was removed with a rotary evaporator, and the residue was treated with 150 mL of *n*-pentane. The solution was filtered, and the solvent was removed under reduced pressure. The residue was chromatographed on 150 g of silica gel with 90/10 hexanes/THF as eluant to afford 0.74 g (32%) of 2-phenyl-3-isopropylindazole (**6a**), mp 121–122 °C. The product can be recrystallized from hexanes or 90/10 hexanes/THF.

2-(4-Methylphenyl)-3-isopropyl-5-methylindazole (6b). Method A. 4,4′-Dimethylazobenzene[7] (4.2 g, 20 mmol), *t*-BuOK (1.2 g, 10 mmol), vinyl triflate **1** (2.0 g, 10 mmol), and 150 mL of glyme was reacted at 0 °C for 2 days. After column chromatography on 150 g of silica gel with 90/10 hexanes/THF as eluent 1.0 g (38%) of **5b** is obtained. Physical properties and spectral features are listed in Table I; exact mass found 264.1615 (calcd for $C_{18}H_{20}N_2$ 264.1626).

Preparation of 2-Phenyl-3-isopropyl-5-methoxyindazole (6c) and 2-(4-Methoxyphenyl)-3-isopropylindazole (7c). Method A. A 4.5-g (21-mmol) sample of 4-methoxyazobenzene (**5c**), 0.84 g (7.5 mmol) of *t*-BuOK, 1.0 g (5.0 mmol) of 2-methyl-1-propenyl triflate (**1**), and 125 mL of glyme gave 0.48 g (36%) of a mixture of isomers **6c** and **7c**. Gas chromatography (column A, 226 °C) showed a ratio of 63:37 for **6c** and **7c**. Separation was done by medium-pressure column chromatography with 90/10 hexanes/THF to give **6c** and **7c**. Physical properties and spectral features are listed in Table I; exact mass found for **6c** 266.1428 (calcd for $C_{17}H_{18}N_2$ 266.1419).

Preparation of 2-Phenyl-3-isopropyl-5-chloroindazole (6d) and 2-(4-Chlorophenyl)-3-isopropylindazole (7d). Method A. A 5.4-g (25-mmol) sample of 4-chloroazobenzene (**5d**), 0.62 g (5.5 mmol) of *t*-BuOK, 1.0 g (5.0 mmol) of 2-methyl-1-propenyl triflate (**1**), and 100 mL of glyme gave 0.27 g (20%) of a mixture of isomers **6d** and **7d**. Gas chromatography (column B, 230 °C) showed a ratio of 64:36 for **6d** and **7d**. Separation was done by medium-pressure column chromatography with 90/10 hexanes THF to give **6d** and **7d**. Physical properties and spectral features are listed in Table I; exact mass found for **6d** 270.0897 (calcd for $C_{16}H_{15}N_2Cl$ 270.0897).

Preparation of 2-Phenyl-3-isopropyl-5-fluoroindazole (6e) and 2-(4-Fluorophenyl)-3-isopropylindazole (7e). Method A. A 3.0-g (15-mmol) sample of 4-fluoroazobenzene (**5e**), 0.42 g (3.75 mmol) of *t*-BuOK, 0.61 g (3.0 mmol) of 2-methyl-1-propenyl triflate (**1**), and 100 mL of glyme gave 0.23 g (18%) of amixture of isomers **6e** and **7e**. Gas chromatography (column B, 230 °C) showed a ratio of 53:37 for **6e** and **7e**. Separation was done by medium-pressure column chromatography with 90/10 hexanes/THF to give **6e** and **7e**. **6e**: ^{19}F NMR (CCl_4) δ 123.5; exact mass found 254.1222 (calcd for $C_{16}H_{15}N_2F$ 254.1219). **7e**: ^{19}F NMR (CCl_4) δ 115.8. Physical properties and remaining spectral features for **6e** and **7e** are listed in Table I.

Preparation of 2-(4-Chlorophenyl)-3-isopropyl-5-methoxyindazole (6f) and 2-(4-Methoxyphenyl)-3-isopropyl-5-chloroindazole (7f). Method A. A 2.6-g (10.5-mmol) sample of 4-chloro-4′-methoxyazaobenzene, 0.27 g (2.4 mmol) of *t*-BuOK, 0.43 g (2.1 mmol) of 2-methyl-1-propenyl triflate (**1**), and 100 mL of glyme gave 0.20 g (31%) of a mixture of isomers **6f** and **7f**. Gas chromatography (column A, 220 °C) showed a ratio of 64:36 for **6f** and **7f**. Separation was done by medium-pressure column chromatography with 90/10 hexanes/THF to give **6f** and **7f**. Physical propoerties and spectral features are listed in Table I.

General Procedure for the Preparation of Tetrahydroindazoles 9.[28] **4,5,6,7-Tetrahydro-2-phenyl-3-iropropylindazole (9a).** To a 50-mL round-bottom flask equipped with a magnetic stirrer and a reflux condenser were added 0.5 g (29.5 mmol) of 2-isobutyrylcyclohexanone[29] (**8**) and 0.33 g (29.5 mmol) of phenylhydrazine in 10 mL of ethanol. The reaction was refluxed for 6 h and cooled, and the solvent was remove by using a rotary evaporator. The residue was purified by column chromatography (60–100 mesh silica gel column, eluted with 5/95 THF/hexane) to afford 0.34 g (47%) of **9a**: IR (neat) 2965, 1601, 1510, 1455, 1389, 780, 711 cm^{-1}; NMR (CCl_4) δ 1.17 (d, 6 H, J = 7.6 Hz), 1.5–1.8 (m, 4 H), 2.3–2.7 (m, 4 H), 2.95 (sept, 1 H, J = 7.6 Hz), 7.2–7.4 (m, 5 H).

Preparation of 4,5,6,7-Tetrahydro-2-(4-methoxyphenyl)-3-isopropylindazole (9c). A 1.0-g (60-mmol) sample of 2-isobutyrylcyclohexanone (**8**) and 2.0 g (12 mmol) of 4-(methoxyphenyl)hydrazine hydrochloride gave 0.5 g (32%) of **9c**: IR (neat) 2970, 1590, 1566, 1520, 1468, 1389, 1309, 1255, 1111, 1100, 1050, 1035, 850 cm^{-1}; NMR (CCl_4) δ 1.0k (d, 6 H, J = 6.0 Hz), 1.4–1.8 (m, 4 H), 2.3–2.6 (m, 4 H), 2.79 (sept, 1 H, J = 6.0 Hz), 3.59 (s, 3 H), 6.6 (d, 2 H, J = 6.2 Hz), 7.0 (d, 2 H, J = 6.2 Hz).

Preparation of 4,5,6,7-Tetrahydro-2-(4-chlorophenyl)-3-isopropylindazole (9d). A 0.5-g (29-mmol) sample of 2-isobutyrylcyclohexanone (**8**), 1.0 g (5. mmol) of 4-(chlorophenyl)hydrazine hydrochloride, and 20 mL of ethanol gave 0.33 g (41%) of **9d**: IR (neat) 2965, 1590, 1551, 1490, 1372, 1258, 1190, 1080, 1010, 860, 831 cm^{-1}; NMR (CCl_4) δ 1.15 (d, 6 H, J = 6.1 Hz), 1.4–1.8 (m, 4 H), 2.3–2.3 (m, 4 H), 2.87 (sept, 1 H, J = 6.1 Hz), 7.0–7.3 (m, 4 H).

General Procedure for the Preparation of Indazoles 7 from Tetrahydroindazoles 10.[30] **2-Phenyl-3-isopropylindazole (7a).** To a 50-mL round-bottom flask equipped with a magnetic stirrer and a reflux condenser were added 25 mL of dioxane and 2.27 g (10 mmol) of 2,3-dichloro-5,6-dicyano-1,4-quinone. To this solution was added 0.53 g (2.5 mmol) of 4,5,6,7-tetrahydro-2-phenyl-3-isopropylindazole (**9a**) in 5 mL of dioxane dropwise. The solution was refluxed overnight and cooled, and the solvent was removed by using a rotary evaporator. The residue was purified by column chromatography with CH_2Cl_2 as eluant to afford 0.35 g (60%) of **7a**, mp 121–122 °C. Spectral data confirm the identity to carbene adduct **7a**,

Preparation of 2-(4-Methoxyphenyl)-3-isopropylindazole (7c). A 1.2-g (4.4-mmol) sample of 2,3-dichloro-5,6-dicyano-1,4-quinone, 0.34 g (1.3 mmol) of **10c**, and 25 mL of dioxane gave 0.28 g (59%) of **7c**, mp 130–134 °C. Spectral data confirm the identity to carbene adduct **7c**.

Preparation of 2-(4-Chlorophenyl)-3-isopropylindazole (7d). A 1.14-g (5.0-mmol) sample of 2,3-dichloro-5,6-dicyano-1,4-quinone, 0.34 g (1.3 mmol) of **10d**, and 25 mL of dioxane gave 0.20 g (59%) of **7d**, mp 121–123 °C. Spectral data confirm the identity to carbene adduct **7d**.

Reaction of 3,3′,5,5′-Tetrakis(trifluoromethyl)azobenzene (12a) with Carbene 2. Method A. Preparation of 13a. A 8.5-g (19-mmol) sample of azo compound **12a**, 0.65 g (5.8 mmol) of *t*-BuOK, 1.0 g (5 mmol) of 2-methyl-1-propenyl triflate (**1**), and 200 mL of glyme was reacted according the general procedure described above. Column chromatography, first with hexanes and after removal of all unreacted **12a** with 90/10 hexanes/THF, gave 0.04 g (0.6%) of **13a** and 0.48 g (10%) of **13**. The product can be further recrystallized from hexane. Physical properties and spectral data are listed in Table II.

Method B. Preparation of 1,2,3,4-Tetrakis[3,5-bis(trifluoromethyl)-phenyl]-5-isopropylidenetetrahydrotetrazole (14a). A 5.0-g (11-mmol) sample of 3,3′,5,5′-Tetrakis(trifluoromethyl)azobenzene (**12a**), 1.02 g (6 mmol) of benzyltrimethylammonium fluoride, 1.52 g (5.5 mmol) of 1-(trimethylsilyl)-2-methyl-1-propenyl triflate (**4**), and 150 mL of glyme was reacted according the general procedure described above. By column chromatography on 150 g of silica gel with hexanes as eluent all unreacted **12a** was removed and use of 90/10 hexanes/THF for further chromatography gave 0.8 g (15%) of **14a**. A very pure product was obtained by recrystallization from hexanes. Physical properties and spectral data are listed in Table II. Anal. Calcd for $C_{36}H_{18}F_{24}N_4$: C, 44.92; H, 1.89; N, 5.85. Found: C, 44.88; H, 1.93; N, 5.89.

Conversion of Tetrahydrotetrazole 14a to Compound 13a. A 15-mg (0.06-mmol) sample of tetrahydrotetrazole **14a** was dissolved in 15 mL of THF, and 6 mg (0.6 mmol) of $LiAlH_4$ was added. The solution turned yellow. Reaction progress was checked by TLC, and reaction was found to be complete after 10 min at 50 °c. The reaction mixture was poured on a small silica column, and the organic material was eluted with THF. The solvent was removed with a rotary evaporator, and the residue was treated with 2 mL of boiling hexanes and filtered. Some crystals separated upon cooling. By comparison of the FT-IR of these crystals with the FT-IR of compound **13a** complete identity was found.

Oxidation of 13a To Form Tetrahydrotetrazole 14a. A 26-mg (26-mmol) sample of compound **13a** was dissolved in 20 mL of ether, and 5 mL of dissolved in a 5% solution of sodium hypochlorite was added with stirring. The solution was stirred for 4 h, and TLC showed complete conversion to compound **14a**. The organic phase was extracted with water and dried over Na_2SO_4. Filtration and evaporation of the solvent gave a crystalline residue. The FT-IR of this residue was completely in accord with the FT-IR of **14a**.

Reaction of 4,4′-Bis(trifluoromethyl)azobenzene (12b) with Carbene 2. Method B. Preparation of 1,2,3,4-Tetrakis[4-(trifluoromethyl)-phenyl]-5-isopropylidenetetrahydrotetrazole (14b). A 3.9-g (12.2-mmol)

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sample of **12b**, 1.14 g (6.7 mmol) of benzyltrimethylammonium fluoride, 1.69 g (6.1 mmol) of 1-(trimethylsilyl)-2-methyl-1-propenyl triflate (**4**), and 100 mL of glyme was reacted for 8 h according to the general procedure. Column chromatography on 150 g of silica gel with 50:1 hexanes/THF gave 0.22 g (10%) of **14b**. Recrystallization from 20:1 hexanes/THF gave a very pure product. Physical properties and spectral data are listed in Table II. Anal. Calcd for $C_{32}H_{22}F_{12}N_4$: C, 55.66; H, 3.21; N, 8.11; F, 33.02. Found, C, 55.48; H, 3.29; N, 8.08; F, 33.09.

Preparation of 1-Methyl-2-phenyl-3-isopropylindazolium Triflate (15a). To a solution of 30 mg (0.15 mmol) of 2-phenyl-3-isopropoylindazole (**6a**) in 5 mL of diethyl ether was added 25 mg (0.15 mmol) of methyl trifluormethanesulfonate, and the reaction mixture was stirred for 1 h at room temperature. Gas chromatography revealed the absence of starting indazole, and a white product was formed. The solution was filtered, and the product was washed with ether to yield 50 mg (86%) of indazolium triflate **15a**: mp 154-156 °C; IR (KBr) 1623, 1516, 1470, 1372, 1275, 1229, 1152, 1038, 912, 806, 780, 760, 705, 644 cm^{-1}; ^1H NMR (C_3D_6O) δ 1.61 (d, 6 H, J = 7.4 Hz), 3.35 (sept, 1 H, J = 7.4 Hz), 4.12 (s, 3 H), 7.7-8.8 (m, 9 H); ^{19}F NMR (C_3D_6O) δ 79.3 (s); UV (C_2H_5OH) λ (log ϵ) 217 nm (4.2), 261 (3.9), 268 (4.0), 307 (3.9); mass spectrum, m/z (relative intensity) 252 (20.7), 251 (M^+, 100.0), 250 (42.7), 249 (17.0), 235 (24.7), 209 (23.5), 173 (22.3), 77 (16.5).

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Carcinogenesis by Polycyclic Aromatic Hydrocarbons: A Multilinear Regression on New Type PMO Indices†

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Abstract: A new MCS model of chemical carcinogenicity of polycyclic aromatic hydrocarbons is presented. M stands for metabolism at the M region, C for carbocation formation, and S for size and solubility. Two perturbational MO indices are introduced and discussed together with a size criterion. Thereby, PMO is extended similar to the ω-method in order to differentiate between carbocations and radicals. A three-variable linear regression on carcinogenic potency yields a multiple correlation coefficient r = 0.961 for a representative sample of 26 polycyclic aromatic hydrocarbons. The deviations are within the confidence limits of the experimental Iball index. Predictions are given for some hydrocarbons whose carcinogenic potencies are yet unknown.

1. Introduction

Because of the complexity of chemical carcinogenesis, linear correlations of carcinogenic potency with a single theoretical variable[1-7] are a very crude first step. In the case of polycyclic aromatic hydrocarbons (PAHs), the influence of distinct molecular regions is well established. The experimental evidence[8-13] for the metabolism via epoxide, dihydro diol, and dihydrodiol epoxide to a bay-region carbocation reacting with DNA (Figure 1) clearly points to the pertinent reactivity centers. In addition, molecules containing reactive L regions,[14-16] such as polyacenes, are known for not being carcinogenic. A competition between different regions has been predicted by the Pullmans[14,15] and constitutes a lasting success of the early MO theory of chemical carcinogenesis.

During the last ten years, the theoretical interest has concentrated on the bay-region carbocations[2-7,16-18] that have been assumed to be the ultimate carcinogens. However, the rank correlations between the MO theoretical stability of such carbocations and carcinogenicity[2-5,7] give rise to a serious number of "false positives".[6,13,16]

It will be shown that one main reason for the exceptions is that the indices used so far are inadequate to characterize the formation of the bay-region carbocation. They are unable to distinguish between the formation of a radical and that of carbocation. Such a distinction is necessary for an improved correlation with experimental facts. It is possible to account for the differences between radicals and ions, e.g., by the Pariser-Parr-Pople approximation[19-21] and—as shown below—even by an improved and extended[22] perturbational MO (PMO) method. In this article, I present a linear correlation with three independent variables yielding a good correlation with experimental Iball indices of carcinogenicity.[23] The exceptions mentioned in earlier papers[6,13,24,33] disappear.

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